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Full Title
Interventional, randomised, double-blind, placebo-controlled, active reference (fluoxetine), fixed-dose study of vortioxetine in paediatric patients aged 7 to 11 years, with Major depressive disorder (MDD)

Short Title
12709A Protocol Edition 4.0

Study Number 12709A

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Clinical Study Protocol

Interventional, randomised, double-blind, placebo-controlled, active reference (fluoxetine), fixed-dose study of vortioxetine in paediatric patients aged 7 to 11 years, with Major depressive disorder (MDD)

Vortioxetine

Study No.:	12709A
EudraCT No./IND:	2008-005353-38/ 112581
Sponsor:	H. Lundbeck A/S (Lundbeck) 2500 Valby (Copenhagen), Denmark
Edition No.:	4.0 (including PA03) (the version No. in the footer is the system version No.)
Date of edition:	21 August 2018
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Synopsis – Study 12709A

Sponsor H. Lundbeck A/S.	**Investigational Medicinal Product** Vortioxetine	**EudraCT/IND No.** 2008-005353-38/ 112581

Title of Study

Interventional, randomised, double-blind, placebo-controlled, active reference (fluoxetine), fixed-dose study of vortioxetine in paediatric patients aged 7 to 11 years, with Major depressive disorder (MDD)

Study Sites and Number of Patients Planned

Approximately 100 sites are planned in approximately 15 countries worldwide (specialists, mainly outpatient clinics) with patients from the European Union, Europe outside the European Union, North America, and other geographical regions.

Approximately 600 patients are planned for enrolment to the 4-week treatment with standardised brief psychosocial intervention (BPI) and placebo period (Phase A). At the end of Phase A, a total of 438 patients with incomplete improvement are planned to be randomised to the 8 week double-blind Phase B.

Objectives

- Primary objective:
  - to evaluate the efficacy of vortioxetine 10 mg/day and 20 mg/day versus placebo after 8 weeks of treatment on depressive symptoms in children with a DSM-5™ diagnosis of MDD.
- Secondary objectives:
  - to evaluate the efficacy of vortioxetine 10 mg/day and 20 mg/day versus placebo during the 8 weeks of treatment on:
    - global clinical impression
    - functionality
    - health-related quality of life
  - to assess pharmacokinetics of vortioxetine in paediatric patients, aged 7 to 11 years using population pharmacokinetic approach
- Exploratory objectives:
  - to explore the efficacy of vortioxetine 10 mg/day and 20 mg/day versus placebo on co-morbid symptoms
- Safety objectives:
  - to evaluate the safety and tolerability of vortioxetine 10 mg/day and 20 mg/day versus placebo in children with a DSM-5™ diagnosis of MDD

Study Methodology

- This is an interventional, multi-national, multi-site, randomised, two-phase, single- and double-blind, parallel-group, placebo-controlled, active-reference (fluoxetine), fixed-dose study.
- An interim analysis to potentially stop the study early for either efficacy or futility will be performed when at least 240 randomized patients have either completed or been withdrawn from the study.
- If the study continues after the interim analysis, enrolment to the fluoxetine arm will be stopped and the study will continue as a 3-arm study.
- The screening period will be 5 to 15 days followed by a 4-week single-blind period (Phase A) of treatment with standardised brief psychosocial intervention and single-blind (patients and parents) placebo. Patients who demonstrate an incomplete improvement of depressive symptoms at the end of Week 4 will be randomised to a double-blind, 8-week treatment period (Phase B) as follows: Prior to interim analysis (Study part 1), at least 240 patients will be randomized in a 1:1:1:1 ratio to vortioxetine 10 mg/day, vortioxetine 20 mg/day, fluoxetine 20 mg/day, or placebo. If the study continues after interim analysis (Study part 2), patients will be randomized in a 1:1:1 ratio to vortioxetine 10 mg/day, vortioxetine 20 mg/day, or placebo. A total of 438 patients are planned to be randomised to Phase B, provided that the study continues after the interim analysis. Patients and parents are blinded to the time point of randomisation to Phase B. There will be 2 baselines in this study: Baseline A (Week 0) of the 4 week single-blind Phase A and Baseline B (week 4) of the 8 week double-blind Phase B.
- Incomplete improvement in depressive symptoms is defined as patients demonstrating a <40% reduction from Baseline A on the Children depression rating scale revised version (CDRS-R), and with a (CDRS-R) ≥40 total score and confirmed by a Parent Global Assessment – Global Improvement (PGA) value of >2.
- Randomisation will be done blinded at the end of Phase A (Week 4) using an Interactive Voice/Web Response system (IVRS/IWRS).
- Patients participating in Phase B will be asked to come back to the study site for a safety follow up 4 weeks after early withdrawal or completion. This procedure will not apply for patients entering in an extension study.
- Patients randomised to the 10 mg/day vortioxetine group will receive a lower initial dose (5 mg/day for 2 days) prior to receiving 10 mg/day. Patients randomised to the 20 mg/day vortioxetine group will receive a lower initial dose (5 mg/day for 2 days followed by 10 mg/day for 2 days and 15 mg/day for 2 days) prior to receiving 20 mg/day. Patients randomised to the fluoxetine 20 mg/day group will receive a lower initial dose (10 mg/day for 6 days) prior to receiving 20 mg/day.
- Based on tolerability the dose may be reduced at Week 8 (Visit 10 = Week 4 of Phase B). For patients randomised to vortioxetine the reduction will be by 5 mg/day and for fluoxetine 10 mg/day. No dose increase will be allowed.
- Patients who do not fulfil the criteria of incomplete improvement in Phase A at Week 3 will be withdrawn from the study before Week 4. Patients who do not fulfil the criteria of incomplete improvement at week 4 will be withdrawn from the study and not participate in the double-blind Phase B of the study. No specific study related follow-up is required for these patients. However as rescue procedure, they may receive up to 4 outpatient visits to the study site for consultations over a two-month period.
- Patients will receive 5 sessions of standardised brief psychosocial intervention at Week 1, 2, 3, 5 and 8.
- Supportive psycho-educative material will be handed out to patients and families at the Screening Visit.
- If the study is terminated early based on the results of interim analysis, patients ongoing in the study Phase B should complete the study according to the protocol. After completion of the phase B, these patients may be eligible to enter an open-label extension study. Patients ongoing in the study phase A at the early termination of the study will be offered treatment at the discretion of the investigator in line with clinical practice. As rescue procedure, they may receive up to 4 outpatient visits to the study site for consultations over a two-month period.
- If the decision is to continue the study, patients ongoing in the study Phase B should complete their originally allocated treatment according to the protocol. Patients ongoing in the study phase A should complete this phase according to the protocol. Those eligible for the part B will be randomized according to the new randomization scheme, i.e., in a 1:1:1 ratio to vortioxetine 10 mg/day, vortioxetine 20 mg/day, or placebo, which will be implemented as soon as the decision to continue the study is taken.

Study Methodology continued

- The study design is presented in Panel 1 and the scheduled assessments are summarised in Panel 2.
- Efficacy and safety measures will be assessed at relevant time points during the study summarised in Panel 2.

Target Patient Population

- The patient has Major depressive disorder (MDD), diagnosed according to DSM-5™.
- The patient has a CDRS-R total score ≥45 at the Screening Visit and the Baseline A Visit (Week 0).
- The patient has a Clinical Global Impression – Severity of Illness (CGI-S) score ≥4 at the Screening Visit and the Baseline A Visit (Week 0).
- The patient is a boy or girl, aged ≥7 and <12 years at Screening Visit.

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

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

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

Efficacy Assessments

- Assessment of depressive symptoms:
  - Investigator rated
    - Children depression rating scale revised version (CDRS-R)
  - Patient and parent rated
    - General Behaviour Inventory (GBI), using the 10-item depression subscale
  - Parent rated
    - Parent Global Assessment – Global Improvement (PGA)
- Assessment of Global Impression:
  - Investigator rated
    - Clinical Global Impression Scale – Global Improvement (CGI-I)
    - Clinical Global Impression Scale – Severity of Illness (CGI-S)
- Assessment of functionality:
  - Investigator rated
    - Children's Global Assessment Scale (CGAS)
  - Patient rated
    - The PedsQL Present Functioning Visual Analogue Scales (PedsQL VAS)
- Assessment of health-related quality of life:
  - Patient rated
    - Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)

Exploratory Assessments

- Assessment of co-morbid symptoms:
  - Patient rated
    - Multidimensional Anxiety Scale for Children short version (MASC-10)

Safety Assessments

- Adverse events (AEs)
- Paediatric Adverse Event Rating Scale (PAERS)
- Clinical safety laboratory tests
- Vital signs
- Weight/Height
- Electrocardiograms (ECGs)
- Physical examinations incl. Tanner scoring
- Columbia Suicide Severity Rating Scale (C-SSRS)
- General Behaviour Inventory (GBI), using the 10-item mania subscale

Endpoints

This section refers to the 8 week double-blind phase (Phase B) measuring changes from Baseline B Visit (Week 4) after/during 8 weeks of treatment (Week 12 visit). Baseline refers to Baseline B Visit.

Primary endpoints:

- depressive symptoms:
  - change from Baseline B in the CDRS-R total score after 8 weeks of treatment

- Secondary endpoints:
  - depressive symptoms:
    - change from Baseline B in the CDRS-R total score during the 8 weeks of treatment
    - CDRS-R response (defined as >50% reduction in the CDRS-R total score (subtracted 17 points) from Baseline B) during the 8 weeks treatment period.
    - remission over the 8 week treatment period (defined as CDRS-R ≤28), at each visit assessed
    - change from Baseline B in the General Behaviour Inventory (GBI), using the 10-item depression subscale, during the 8 weeks of treatment
    - score in the PGA during the 8 weeks treatment period
  - Global Clinical Impression:
    - change from Baseline B in the CGI-S score during the 8 weeks treatment period
    - score in the CGI-I during the 8 weeks treatment period
    - remission in the CGI-S score (defined as a CGI-S score of 1or 2) during the 8 week treatment period, at each visit assessed
    - response in the CGI-I score (defined as a CGI-I score of 1or 2) during the 8 week treatment period
  - functionality:
    - change from Baseline B in the CGAS score during the 8 weeks treatment period
    - change from Baseline B in the PedsQL VAS score during the 8 weeks treatment period
  - health-related quality of life:
    - change from Baseline B in the PQ-LES-Q scores during the 8 weeks treatment period
  - pharmacokinetics:
    - pharmacokinetic parameters for vortioxetine
- Exploratory endpoint:
  - co-morbid symptoms:
    - change from Baseline B in the MASC-10 score during the 8 weeks treatment period
- Safety endpoints during the 8 weeks treatment period:
  - adverse events (AEs)
  - tolerability will be assessed using the PAERS
  - absolute values and changes from Baseline B in clinical safety laboratory tests, vital signs, weight, height, and ECG parameters
  - potentially clinically significant clinical safety laboratory test values, vital signs, weight, and ECG parameter values
  - C-SSRS categorisation based on C-CASA definitions (1, 2, 3, 4, and 7)
  - GBI using the 10-item mania subscales (patient and parental versions)

Statistical Methodology

- The following analysis sets will be used to analyse and present the data:
  - *all-patients-enrolled* (APES) – all patients enrolled to the 4-week Single-blind period (Phase A) who received at least one dose of IMP
  - *all-patients-randomised Phase B* (APRS) – all patients randomised to the double-blind, 8-week treatment period (Phase B)
  - *all-patients-treated set Phase B* (APTS) – all patients randomised to the double-blind, 8-week treatment period (Phase B) who took at least one dose of double-blind IMP
  - *full-analysis set Phase B* (FAS) – all patients in the APTS who had a valid Baseline B assessment and at least one valid post-Baseline B assessment of the CDRS-R total score.
  - The efficacy analysis will be based on the FAS
- Primary analysis:
  - For the primary endpoint (change from Baseline B in the CDRS-R total score to Week 8 in phase B (Week 12)), comparisons of the pooled doses of vortioxetine 10 and 20 mg/day versus placebo will be made using Mixed Model Repeated Measurements (MMRM) with freely varying mean and covariance structure and with country as a fixed factor and Baseline B CDRS-R score as a covariate interacting with visit. Treatment (vortioxetine 10 mg/day, vortioxetine 20 mg/day, fluoxetine, and placebo) is included as a fixed factor interacting with visit. For the primary endpoint a contrast test with weights 0.5, 0.5, 0, and -1, respectively, to estimate the average effect of the pooled doses of vortioxetine against placebo, based on the LSMeans for the treatment by visit interaction at Week 8 in phase B (Week 12) will be used. This will be evaluated at a one-sided 2.5% significance level.
- Key Secondary analyses:
  - Using the same model as in the primary analysis an evaluation of the separate comparisons of vortioxetine 10 mg/day and vortioxetine 20 mg/day versus placebo will be made. These will be estimated based on LSMeans for the treatment by visit interaction at Week 8 in phase B (Week 12). Both of the comparisons will be evaluated at a one-sided 2.5% significance level.
- Testing strategy for multiplicity controlled analyses:
  - Statistical significance can be claimed on the individual doses only if significance is claimed for the pooled vortioxetine doses. The multiplicity control for the primary and key secondary analyses is kept due to the closed testing principle.
  - To further account for the sequential approach, including one interim analysis with stopping rules for efficacy and futility, an error-spending approach based on Kim & DeMets method will be applied on the outcome from the MMRM model.
- Sensitivity analyses of the primary endpoint:
  - The primary endpoint will also be analysed using an analysis of covariance (ANCOVA, OC and last observation carried forward [LOCF]) as sensitivity analysis. The Missing at Random assumption behind the MMRM model will be investigated.
  - A sensitivity analysis investigating the impact of the study methodological changes will be performed if the study is not stopped at interim analysis. This will be done by adding a factor to the primary analysis indicating whether the individual patient was enrolled prior to the change in study design or after.
- Analyses of other efficacy endpoints:
  - For continuous endpoints, the same methodology as the primary analysis described for the primary endpoint will be used. In addition ANCOVA will be performed (OC and LOCF).
  - For dichotomous endpoints, such as response and remission, logistic regression with treatment as a factor and the baseline score as a covariate will be used. This will be done based on OC, LOCF and NRI.
  - The safety analyses will be based on the APES and the APTS.
- Analyses of safety endpoints:
  - Adverse events, PAERS scores, clinical safety laboratory tests, vital signs, weight/BMI, ECG parameters, physical examinations, GBI scores (using the 10-item mania subscale), and C-SSRS scores will be summarised using descriptive statistics. Adverse events and other safety endpoints will be reported separately for Phase A and Phase B.

Statistical Methodology continued

- A DMC will monitor safety data at regular intervals to be specified in the Data Monitoring Committee Charter.
- Patient disposition and demographics will be summarised using descriptive statistics.
- An interim analysis for both efficacy and futility is planned to be conducted when at least 240 have been randomized and completed the Week 12 visit or been withdrawn from the study. Interim analysis will be performed by an independent biostatistician as pre-specified in an interim statistical analysis plan and a charter. Only the decision to continue or terminate the study will be communicated to the Sponsor, without further details about the results.
- To ensure that the study is sufficiently powered an estimate of the variability of the primary endpoint and the withdrawal rate will be derived. The analysis will be performed prior to the interim analysis and will be based on blinded and pooled data from all groups. Based on these estimates the power calculation will be updated and adequate actions will be taken if the study has lost power.
- Patient disposition and demographics will be summarised using descriptive statistics.

Pharmacokinetic Analysis

Sparse PK samples (2) will be collected to measure vortioxetine and fluoxetine plasma concentration; however the population PK analysis will only be conducted for vortioxetine. Plasma concentrations of fluoxetine will be listed. The population PK of vortioxetine will be assessed by means of nonlinear mixed effect modelling and the results from the analysis will be reported in a separate population PK report.

Sample Size Considerations

To obtain a power of 85%, with a one-sided significance level of 2.5% and an expected effect size of 4 for each vortioxetine dose, and a standard deviation of 11 for the change from baseline for each dose, 102 patients need to be included in a non-sequential trial. To maintain the power at 85%, the sample size needs to be increased for the loss of power due to the sequential approach. As a result, then taking a drop-out rate of 15% in Phase B into account, 126 randomized patients per arm will be required. In total, 378 randomised patients are required in the final analysis if the study continues after the interim analysis, and in addition approximately 60 patients will be randomised to the fluoxetine group (Study part 1), which means a total of 438 randomised patients.

More details are provided in the statistical analysis plan.

Ethical Rationale for Study and Study Design

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

As outlined in the EMA *Assessment of the Paediatric Needs* in psychiatry there is a therapeutic need in the paediatric population of depressed patients. Only one antidepressant, fluoxetine, is currently approved in Europe for the treatment of MDD in children and adolescents. In the US only fluoxetine is approved for children and fluoxetine and escitalopram for the adolescent population. Development of a new antidepressant will increase and strengthen the pharmacological treatment options for this patient population. This study is part of the agreed EMA *Paediatric Investigational Plan* (PIP) for vortioxetine, and the *US Paediatric Research Equity Act* (PREA) with the purpose to investigate the anti-depressive effect of vortioxetine in MDD patients aged 7 to 11 years. It is the expectation that the investigation plan will provide positive efficacy data, with a favourable safety and tolerability profile, and therefore demonstrate a positive benefit-risk ratio for the use of vortioxetine in the paediatric population.

Vortioxetine is approved in the US, EU and a number of other countries for the treatment of MDD in the adult population. The evaluation of the safety and tolerability of vortioxetine is based on data from a large clinical development programme in adult and elderly patients. In the overall clinical development programme treatment with vortioxetine at the therapeutic doses (5-20 mg/day) was safe and well tolerated. The approved recommended dose range of 5-20 mg/day for adults was evaluated in a pharmacokinetic and tolerability study performed in the paediatric population (aged 7 to 11 years) designed to guide the choice of doses to be used in the planned paediatric investigation plan. Hence the chosen doses of vortioxetine (10 and 20 mg/day) for this study is based on the results from the paediatric pharmacokinetic and tolerability study and the knowledge from the adult studies. As the sole antidepressant approved both in children and adolescents for MDD in EU and US, fluoxetine has been selected as comparator to provide evidence of assay sensitivity.

The presence of a high placebo response rate is known to be a confounding factor in antidepressant studies, particularly in those enrolling children and adolescents. The recent studies of duloxetine in the treatment of paediatric patients with MDD were failed as neither duloxetine nor the active control (fluoxetine, with known efficacy in children and adolescents with MDD), were statistically significantly different from placebo on the primary outcome measure.

The present study is designed with the aim to lower the placebo response and includes a single-blind phase (Phase A) where patients who respond to standardised brief psychosocial intervention will not be eligible for entering the double-blind IMP treatment phase (Phase B). Furthermore patients and parents are blinded to the time point of randomisation to the double-blind phase in order to lower expectations. This study will permit the investigation of the efficacy and safety of a new potential treatment of MDD in paediatric patients and the inclusion of a placebo group has major scientific importance in this evaluation to ensure adequate evaluation of efficacy as well as distinguishing disease manifestations from adverse reactions of the compound. The choice of the double-blind 8 week study duration is based on previous experience with positive studies and European guidelines.

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

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

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

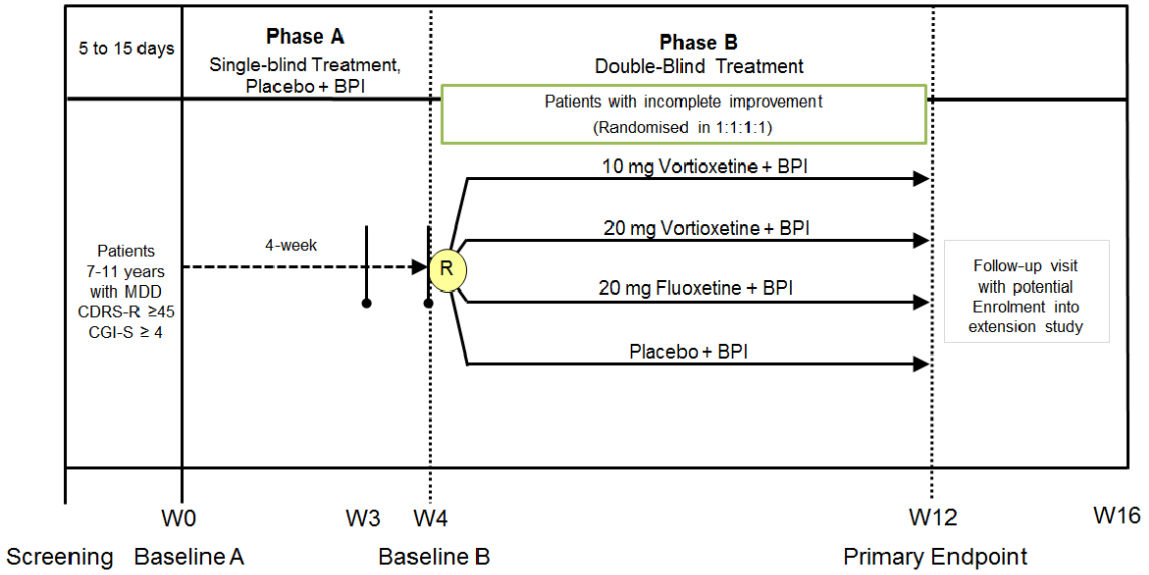
The selection criteria exclude the participation of patients at significant risk of suicide, and patients becoming at significant suicidal risk during the study will be withdrawn. Throughout the study, potential suicidal risk will be assessed both by rating scale (The Columbia-Suicide Severity Rating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

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

Due to challenges with recruiting paediatric patients into clinical research, study design modifications have been made in agreement with the regulatory Authorities in Europe and US to reduce the size of the study. These modifications are considered ethically justified as they prevent unnecessary exposure of paediatric subjects to experimental treatments.

Panel 1 Study Design

Study part 1:
Applicable prior to interim analysis

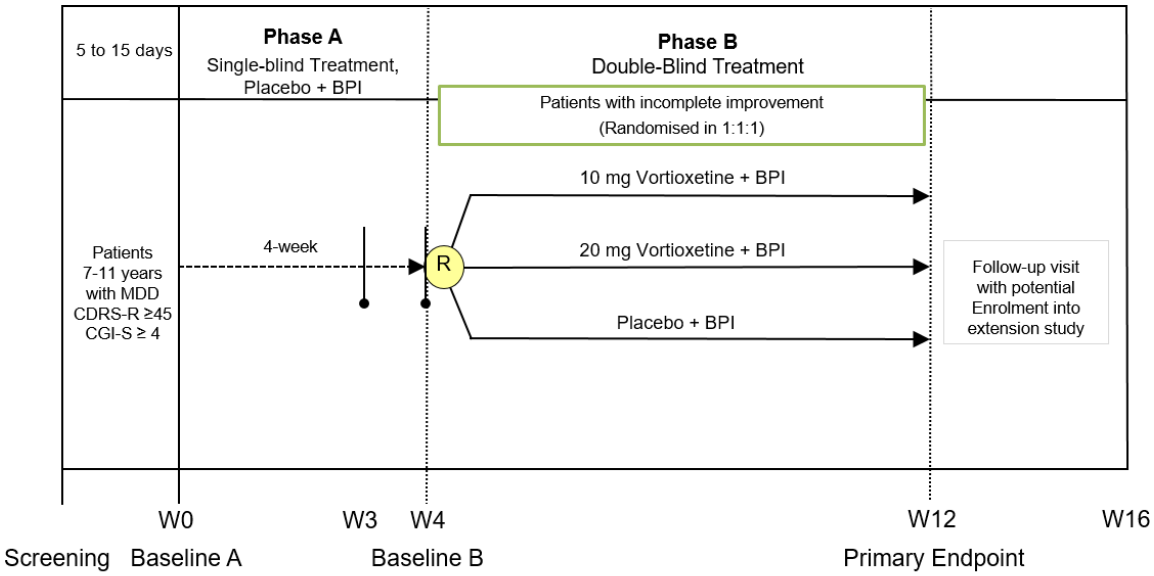


= Patients improving significantly at Week 3 (Phase A) will be excluded before Week 4 (Phase A); patients improving at week 4 (Phase A) will not be randomized to the double-blind Phase B of the study. These patients may receive up to 4 outpatient visits to the study site for consultations over a two-month period.

R = Randomization BPI = Brief Psychosocial Intervention

Study part 2:

Applicable after interim analysis, if the study continues



= Patients improving significantly at Week 3 (Phase A) will be excluded before Week 4 (Phase A); patients improving at week 4 (Phase A) will not be randomized to the double-blind Phase B of the study. These patients may receive up to 4 outpatient visits to the study site for consultations over a two-month period.

R = Randomization BPI = Brief Psychosocial Intervention

Panel 2 Study Procedures and Assessments

		Phase A					Phase B						
		Single-blind Treatment Period					Double-blind Treatment Period						
Visit	**Screening**	**Baseline (Phase A)**				**Baseline (Phase B)**						**Completion /Withdrawal[a]**	**Safety Follow-up[b]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Day/End of Week	**d-5/d-15**	**0**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W10**	**W12**	**W16**
Visit Window[c] (days relative to nominal visit)			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**
Screening/Baseline Procedures and Assessments													
Signed informed assents/consents	√												
Diagnosis (DSM-5™)	√												
K-SADS-PL[d]	√												
Disease-specific history	√												
Relevant history (social, medical, psychiatric, neurological)	√												
History of stimulant medication, if any	√												
Demographics (age, sex, race)	√												
Smoking, alcohol consumption	√												
Family psychiatric history	√												
Traumatic life events	√												
Pregnancy test[e]	√											√[f]	
Inclusion/exclusion criteria	√	√											
Randomisation to Phase B						√							
BPI			√	√	√		√			√			
Efficacy Assessments													
CDRS-R	√	√		√	√	√		√		√	√	√	
CGI-S	√	√	√	√	√	√	√	√	√	√	√	√	
CGI-I			√	√	√	√	√	√	√	√	√	√	
PGA (PRO)[g]				√	√	√		√		√	√	√	
GBI (depression subscale)	√	√		√		√		√		√	√	√[f]	
CGAS		√				√				√		√[f]	
PedsQL VAS (PRO)		√				√				√		√[f]	
PQ-LES-Q (PRO)		√				√				√		√[f]	

		Phase A					Phase B						
		Single-blind Treatment Period					Double-blind Treatment Period						
Visit	**Screening**	**Baseline (Phase A)**				**Baseline (Phase B)**						**Completion /Withdrawal[a]**	**Safety Follow-up[b]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Day/End of Week	**d-5/d-15**	**0**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W10**	**W12**	**W16**
Visit Window[c] (days relative to nominal visit)			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**
Exploratory Assessments													
MASC-10 (PRO)		√				√				√		√[f]	
Vortioxetine and Fluoxetine Quantification													
Blood sampling vortioxetine and fluoxetine quantification										√		√[f]	
Translational Medicine Assessments[h]													
Blood sampling for gene expression profiling						√				√		√[f]	
Blood sampling for metabolomics/proteomics						√				√		√[f]	
Blood sampling for pharmacogenetics (optional)	√												
Safety Assessments													
Adverse events[i]	√	√	√	√	√	√	√	√	√	√	√	√	√[j]
Blood and urine sampling for clinical safety laboratory tests	√					√				√		√[f]	
Vital signs	√	√	√	√	√	√	√	√	√	√	√	√	
ECGs	√					√				√		√[f]	
Weight and height	√					√				√		√[f]	
Examinations (physical and neurological)	√											√[f]	
Tanner score	√												
PAERS	√	√	√	√	√	√	√	√	√	√	√	√[f]	
C-SSRS	√	√	√	√	√	√	√	√	√	√	√	√	
GBI (mania subscale)	√	√		√		√		√		√	√	√[f]	
Other Study Procedures													
IMP dispensed		√	√	√	√	√	√	√	√	√	√		
Possible change in IMP dose										√[k]			
IMP returned and IMP accountability			√	√	√	√	√	√	√	√	√	√	
Recent and concomitant	√	√	√	√	√	√	√	√	√	√	√	√	

		Phase A					Phase B						
		Single-blind Treatment Period					Double-blind Treatment Period						
Visit	**Screening**	**Baseline (Phase A)**				**Baseline (Phase B)**						**Completion /Withdrawal[a]**	**Safety Follow-up[b]**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Day/End of Week	**d-5/d-15**	**0**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W10**	**W12**	**W16**
Visit Window[c] (days relative to nominal visit)			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**
medication													

a. This visit should take place as soon as possible after the patient withdraws from the study. Any visit during Phase A, can be converted in to a withdrawal visit on the day of the visit. The BPI is optional if a visit during Phase A is converted into a withdrawal visit.
b. This can be a telephone contact, unless an SAE has occurred since the last visit or 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). All enrolled patients should have a safety follow-up visit unless they continue into the extension study.
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 randomisation/baselines.
d. The Kiddie-Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime version (K-SADS-PL) will be used to confirmed diagnosis of Major depressive disorder (MDD) and to assess possible psychiatric co-morbidities.
e. If the patient is a female subject of childbearing potential (defined as females aged ≥10 year's 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 screening and if the patient has completed or withdrawn in Phase B.
f. Should only be performed if the patient has completed or withdrawn in Phase B.
g. The PGA assessment should be in reference to Baseline A.
h. Samples will be collected at the designated time points. Any results of the Translational Medicine Assessments will not be available at the time of reporting and will consequently not be part of the actual report of the study.
i. Pre-treatment adverse events (before IMP intake i.e. before Baseline B) must be recorded on the *Adverse Event Form* in the eCRF. Adverse events from open questioning in addition to all spontaneously reported adverse events must be recorded on the *Adverse Event Form* in the eCRF. If the adverse event is an SAE, the *Serious Adverse Event Report Form* must also be completed. For practical reasons, questioning for adverse events could follow vital sign assessments. In addition, the tolerability will also be assessed using the Paediatric Adverse Event Rating Scale (PAERS). Application of this scale should follow after the open, non-leading question for any adverse events.
j. Only for adverse events on-going at Completion/Withdrawal and new SAEs.
k. The vortioxetine dose may be down-titrated with 5mg/day based on poor tolerability, only one down-titration is allowed. No up-titration will be allowed. The fluoxetine dose may be down-titrated to 10 mg/day based on poor tolerability only one down-titration is allowed (Only applicable during Study part 1). No up-titration will be allowed.

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List of Abbreviations and Definitions of Terms

γGT	γ-glutamyl transferase
AIDS	Acquired Immune Deficiency Syndrome
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	alkaline phosphatase
APES	All-patients-enrolled set
APRS	all-patients-randomised set
APTS	all-patients-treated set
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BMI	body mass index
BP	blood pressure
BPI	Brief Psychosocial Intervention
bpm	beats per minute
BUN	blood urea nitrogen
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CDRS-R	Children Depression Rating Scale Revised version
CGAS	Children's Global Assessment Scale
CGI-I	Clinical Global Impression – Global Improvement
CGI-S	Clinical Global Impression – Severity of Illness
CHMP	Committee for Medicinal Products for Human Use (European Union)
C_{max}	maximum observed concentration
CRA	clinical research associate
CRF	case report form
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450 isoenzyme
DMC	Data Monitoring Committee
DO	Doctor of osteopathic
DSM-5™	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSM-IV-TR™	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	full-analysis set
FDA	United States Food and Drug Administration
GAD	Generalized Anxiety Disorder

GBI	General Behaviour Inventory
GPV	Division of Global Pharmacovigilance, H. Lundbeck A/S
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
IND	Investigational New Drug Application
INR	international normalised ratio of prothrombin time
IRB	institutional review board
IVRS	interactive voice response system
IWRS	interactive web response system
K-SADS_PL	Kiddie-Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime version
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LOCF	last observation carried forward
Lu	Lundbeck
MADRS	Montgomery and Åsberg Depression Rating Scale
MASC-10	Multidimensional Anxiety Scale for Children short version
MedDRA	Medical Dictionary for Regulatory Activities
MDD	Major depression disorder
MMRM	mixed model for repeated measurements
mRNA	messenger ribonucleic acid
NA	not applicable
NICE	National Institute for Health and Care Excellence
NOAEL	no-observed-adverse-effect level
OC	observed cases
OCD	Obsessive Compulsory Disorder
PCR	polymerase chain reaction
PCS	potentially clinically significant
PAERS	Paediatric Adverse Event Rating Scale
PedsQL™ VAS	PedsQL Present Functioning Visual Analogue Scales
PGA	Parent Global Assessment – Global Improvement

PIP	Paediatric Investigational Plan
PK	pharmacokinetic(s)
PQ-LES-Q	Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire
PR	specific ECG interval describing atrioventricular conduction
PREA	US Paediatric Research Equity Act
PRO	patient-reported outcome
PTSD	Post-traumatic Stress Disorder
QP	qualified person
qPCR	quantitative polymerase chain reaction
QRS	specific ECG interval describing ventricular depolarisation
QT	specific ECG interval describing ventricular depolarisation/repolarisation
QT_c	heart-rate corrected QT interval
RR	specific ECG interval describing the ventricular depolarisation/repolarisation cycle
SAE	serious adverse event
SCC	Specialist Clinical Care
SD	standard deviation
SERT	serotonin (5-HT) transporter
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	apparent elimination half-life
TEAE	treatment-emergent adverse event
TMF	trial master file
TSH	thyroid stimulating hormone
WHO	World Health Organization

1 Introduction

1.1 Background

1.1.1 Overview

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

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

Signs and symptoms of MDD are similar to the adult population, but depressive disorders meeting the diagnostic criteria rarely is present before the age of seven years.[8,9] The clinical picture may differ according to age at presentation. Children may have mood liability, irritability, low frustration tolerance, somatic complaints, and/or social withdrawal instead of verbalising feelings of depression, whilst adolescents are more likely than children to complain of feelings of hopelessness/helplessness, lack of energy and to have a higher rate of suicidal thoughts.[10,11] For this reason separate studies are to be conducted in children and adolescents.[9]

The aim of this study is to evaluate the efficacy of vortioxetine 10 mg/day and 20 mg/day versus placebo after 8 weeks of treatment on 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.*[12]

For information on the reference compound fluoxetine please refer to the *Summary of Product Characteristics (SmPC)/Prescribing Information.*

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.[13]

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

1.1.3 Clinical Data

1.1.3.1 Pharmacokinetics

In adults, vortioxetine has shown to be a compound with slow absorption, large volume of distribution and medium clearance. Vortioxetine is slowly, but well absorbed after oral administration and the peak plasma concentration is reached within 7 to 11 hours. Following multiple dosing of 5, 10, or 20 mg/day, mean C_{max} values of 9 to 33 ng/mL were observed. The absolute bioavailability is 75%. No effect of food on the pharmacokinetics was observed. The mean volume of distribution (V_{ss}) is 2,600 L, indicating extensive extravascular distribution. Vortioxetine is highly bound to plasma proteins (98 to 99%) and the binding appears to be independent of vortioxetine plasma concentrations. Vortioxetine is extensively metabolised in the liver, primarily through oxidation catalysed by CYP2D6 and to a minor extent CYP3A4/5 and CYP2C9, and subsequent glucuronic acid conjugation. No inhibitory or inducing effect of vortioxetine was observed in the drug-drug interaction studies for the CYP isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5. Vortioxetine is a poor P-gp substrate and inhibitor. The major metabolite (Lu AA34443) of vortioxetine is pharmacologically inactive. The mean elimination half-life and oral clearance are 66 hours and 33 L/h, respectively. The pharmacokinetics is linear and time independent in the dose range studied (2.5 to 60 mg/day).[12]

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

children, but data suggests that the doses tested (5 to 20mg/day vortioxetine) and the up-titration scheme employed in this study are appropriate for the paediatric population.

1.1.3.2 Efficacy

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

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

1.1.3.3 Safety

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

The tolerability of vortioxetine in multiple oral doses of 5 to 20 mg/day was also evaluated in an open label study among children and adolescent patients (aged 7 to 17 years) with a DSM-IV-TR™ diagnosis of depressive or anxiety disorder. The purpose of this uncontrolled, open-label study was to assess the safety, tolerability, and pharmacokinetics of vortioxetine in children and adolescents with depressive or anxiety disorder and to provide supportive information for its dose regimen in paediatric efficacy and safety studies. In total 24 children and 24 adolescents received vortioxetine. Based on the data from this study, no concerns were raised on the safety and tolerability profile of vortioxetine among paediatric patients with depression or anxiety. Vortioxetine was safe and well tolerated following 14 days of dosing as well as during an initial up-titration period. Overall, the adverse event profile in adolescents and children appeared similar to that of the adult population. Nausea and headache were the TEAEs with the overall highest incidence in this study, 11 (Nausea) and 12 (headache) patients. Nausea is also the most common TEAE in studies with adult patients, with an

incidence of approximately 20 to 30% following 5 to 20 mg vortioxetine. Other common TEAEs were sedation, abdominal pain upper, fatigue, and vomiting. There was no apparent relationship between dose and the incidence of these adverse events.

1.2 Rationale for the Study

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

As outlined in the EMA *Assessment of the Paediatric Needs in psychiatry* there is a therapeutic need in the paediatric population of depressed patients.[14] Although several acute treatment studies of antidepressants have been completed in the MDD patient population, only two antidepressants have shown replicate efficacy in two or more trials, and have received regulatory approval for the treatment of MDD in paediatric patients. Fluoxetine in the treatment of children and adolescents with MDD,[15,16] and escitalopram in the treatment of adolescents with MDD.[17,18]

Specific studies are necessary in the paediatric population and separate studies should generally be conducted in children and adolescents.[19] This study is part of the agreed EMA *Paediatric Investigational Plan (PIP)* for vortioxetine and the US *Pediatric Research Equity Act (PREA)* with the purpose to investigate the antidepressive effect of vortioxetine in MDD patients aged 7 to 11 years. It is the expectation that the investigation plan will provide positive efficacy data, with a favourable safety and tolerability profile, and therefore demonstrate a positive benefit-risk ratio for the use of vortioxetine in the paediatric population.

2 Objectives

- Primary objective:
  - to evaluate the efficacy of vortioxetine 10 mg/day and 20 mg/day versus placebo after 8 weeks of treatment on depressive symptoms in children with a DSM-5™ diagnosis of MDD.
- Secondary objectives:
  - to evaluate the efficacy of vortioxetine 10 mg/day and 20 mg/day versus placebo during the 8 weeks of treatment on:
    - global clinical impression
    - functionality
    - health-related quality of life
  - to assess pharmacokinetics of vortioxetine in paediatric patients, aged 7 to 11 years using population pharmacokinetic approach
- Exploratory objectives:
  - to explore the efficacy of vortioxetine 10 mg/day and 20 mg/day *versus* placebo on co-morbid symptoms

- Safety objectives:

– to evaluate the safety and tolerability of vortioxetine 10 mg/day and 20 mg/day *versus* placebo in children with a DSM-5™ diagnosis of MDD

3 Study Design

3.1 Overview of the Study Design

This study has been designed in accordance with the *Declaration of Helsinki.*[20]

This is an interventional, multi-national, multi-site, randomised, two- phase, single- and double-blind, parallel-group, placebo-controlled, active reference (fluoxetine), fixed-dose study.

The study was designed as a 4-arm study, with two doses of vortioxetine (10 and 20 mg), placebo, and fluoxetine (20 mg, included as an active reference). Due to recruitment difficulties, the study design was amended (Protocol Amendment PA3) focusing on the main objective of the study, as follows:

An interim analysis to potentially stop the study early for either efficacy or futility will be performed when at least 240 randomized patients have either completed or been withdrawn from the study. If the study continues after the interim analysis, enrolment to the fluoxetine arm will be stopped and the study will continue as a 3-arm study.

In addition, the testing strategy for the primary analysis is changed to allow reduction in sample size while maintaining the same statistical power.

This study will be conducted in compliance with the protocol, *Good Clinical Practice*,[21] and applicable regulatory requirements.

An overview of the study is presented in Panel 1.

The study will consist of a screening period of 5-15 days and will consist of two phases (Phase A and Phase B) after this screening period.

Phase A is a single blind 4-weeks period where patients (and parents) are blinded and receive placebo + Brief Psychosocial Intervention (BPI). If not responding to BPI/placebo then patients are randomised into Phase B.

Phase B is a double-blind 8-weeks period where patients and investigators are blinded. In this phase all patients continue to receive BPI in addition their randomized treatment, which can be either placebo, vortioxetine 10 mg, vortioxetine 20 mg, or fluoxetine 20 mg (fluoxetine only in the part 1 of the study, prior to interim analysis).

The patient is a boy or a girl, aged ≥7 and <12 at Screening Visit with a diagnosis of MDD according to DSM-5™ Criteria and a CDRS-R score ≥45 and a CGI-S score ≥4 at the Screening Visit and the Baseline A Visit (Week 0).

Approximately 600 patients are planned for enrolment to the 4-week treatment with standardised brief psychosocial intervention and single-blind placebo period (Phase A). At the end of Phase A (Baseline B) patients with incomplete improvement are to be randomised to the 8 week double-blind Phase B as follows:

Study part 1: Prior to the interim analysis, at least 240 patients will be randomized in a 1:1:1:1 ratio to vortioxetine 10 mg, vortioxetine 20 mg, fluoxetine 20 mg, or placebo.

Study part 2: If the study continues after interim analysis, patients will be randomized in a 1:1:1 ratio to vortioxetine 10 mg, vortioxetine 20 mg, or placebo.

In total, 438 patients will be randomised if the study continues after interim analysis, with approximately 126 patients in each of the vortioxetine and placebo groups, and approximately 60 patients in the fluoxetine group.

Incomplete improvement in depressive symptoms is defined as a <40% reduction from Baseline A on the Children depression rating scale revised version (CDRS-R), and with a (CDRS-R) ≥40 total score and confirmed by a Parent Global Assessment- Global Improvement (PGA) value of >2.

Patients who do not fulfil the criteria of incomplete improvement in Phase A at Week 3 will be withdrawn from the study before Week 4. Patients who do not fulfil the criteria of incomplete improvement at week 4 will be withdrawn from the study and not participate in the double-blind Phase B of the study. No specific study related follow-up is required for these patients. However as rescue procedure, they may receive up to 4 outpatient visits to the study site for consultations over a two-month period.

Patients will receive 5 sessions of standardised brief psychosocial intervention at Weeks 1, 2, 3, 5 and 8.

Interim analysis will be performed by an independent biostatistician as pre-specified in a charter. Only the decision to continue or terminate the study will be communicated to the Sponsor, without further details about the results.

If the decision is to terminate the study early, patients ongoing in the study Phase B should complete the study according to the protocol. After completion of the phase B, these patients may be eligible to enter an open-label extension study. Patients ongoing in the study phase A at the early termination of the study will be offered treatment at the discretion of the investigator in line with clinical practice. As rescue procedure, they may receive up to 4 outpatient visits to the study site for consultations over a two-month period.

If the decision is to continue the study, patients ongoing in the study Phase B should complete their originally allocated treatment according to the protocol. Patients ongoing in the study

phase A should complete this phase according to the protocol. Those eligible for the part B will be randomized according to the new randomization scheme, i.e., in a 1:1:1 ratio to vortioxetine 10 mg/day, vortioxetine 20 mg/day, or placebo, which will be implemented as soon as the decision to continue the study is taken.

An independent Data Monitoring Committee will be established in order to review the safety and tolerability data throughout the study.

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

3.2 Rationale for the Study Design

The proposed Study 12709A is a randomised, two-phase single- and double-blind, fixed-dose study with the primary objective to evaluate the efficacy of vortioxetine 10 mg/day and 20 mg/day versus placebo after 8 weeks of treatment on depressive symptoms in children with a DSM-5™ diagnosis of MDD. Secondary objectives are to evaluate the efficacy of vortioxetine 10 mg/day and 20 mg/day *versus* placebo during the 8 weeks of treatment on global clinical impression, functionality, health-related quality of life and to confirm the population pharmacokinetics of vortioxetine in paediatric patients, aged 7 to 11 years. In addition the efficacy of vortioxetine 10 mg/day and 20 mg/day versus placebo on co-morbid symptoms will be explored.

In the overall adult clinical development programme treatment with vortioxetine at the therapeutic doses (5-20 mg/day) was safe and well tolerated. It has been suggested that a failure to conduct and use information from appropriately designed preliminary pharmacokinetic and dose-finding studies has contributed to the failure of several large scale antidepressant studies in the paediatric MDD population.[22] The chosen doses of vortioxetine (10 and 20 mg/day) for this study is based on the knowledge from the clinical development programme in adult patients and from the paediatric pharmacokinetic and tolerability study performed in the paediatric population (aged 7 to 11 years) designed to guide the choice of doses to be used in the planned paediatric investigation plan.

The presence of a high placebo response rate is known to be a confounding factor in antidepressant studies, particularly in those enrolling children and adolescents. The recent studies of duloxetine in the treatment of paediatric patients with major depressive disorder (MDD) were failed as neither duloxetine nor the active control (fluoxetine, with known efficacy in children and adolescents with MDD), were statistically significantly different from placebo on the primary outcome measure.[23,24]

The present study is designed with the aim to lower the placebo response and includes a single-blind phase (Phase A) where patients who respond to standardised brief psychosocial intervention and/or placebo will not be eligible for entering the double-blind IMP treatment Phase (Phase B). Furthermore patients and parents are blinded to the time point of randomisation to the double-blind phase in order to lower expectations.

The choice of the double-blind 8 week study duration is based on previous experience with positive studies and European guidelines.[19] The 4-week single-blind period (Phase A) of treatment with standardised brief psychosocial intervention and single-blind (patients and parents) placebo run-in phase is in alignment with the new *Guideline on clinical investigation of medicinal products in the treatment of depression*[19] and consistent with *the NICE treatment guideline*.[25] Studies should include only patients with insufficient response to psychotherapy and all subjects should receive psychosocial interventions throughout the trials.[19] For this reason patients who respond to placebo and or standardised brief psychosocial intervention received during the 4-week single blind period will not be included in the 8 week double blind treatment period.

To standardise the psychosocial intervention, a brief psycho social intervention program (BPI) is developed for this study The BPI arises from the Specialist Clinical Care (SCC) programme and has its origins in the work of the ADAPT[26] RCT team in order to implement high quality psychosocial intervention in the study. It is a pragmatic synthesis of clinical practice that results in good quality specialised psychosocial care for depressed children and adolescents. A detailed description of key elements of comprehensive BPI case management is provided in a manual that will be delivered to the site.

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

The Parent Global Assessment- Global Improvement (PGA) is used as a secondary efficacy measure of the antidepressant effect symptoms and to confirm incomplete improvement in depressive symptoms. The PGA has been used receptively and successfully in studies in ADHD. The General Behavior Inventory 10-Item Depression Scale[27] will also be used to assess depressive symptoms. The GBI 10- item version has been shown to discriminate between diagnostic groups using youth self-report.[27, 28] The CGI-S and CGI-I are used for assessing disorder severity and improvement.[29]

The Children's Global Assessment Scale (CGAS) and the PedsQL Present Functioning Visual Analogue Scales (PedsQL™ VAS) will be used to assess functionality and the Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q)[30] will be used to assess health-related quality of life. Children and adolescents with MDD are at high risk of having severe difficulties in various domains of functioning and in quality of life.[1,31]
Both the CGAS, PedsQL™ VAS and PQ-LES-Q are validated scales appropriate for use in children and adolescents with psychiatric disorders. [31,32]

The primary objective of this study is to demonstrate the superiority of vortioxetine versus placebo. In view of the recruitment difficulties experienced in the study, is it important to limit the size of the study while still ensuring that the main study objective can be addressed. The following modifications to the study design have been agreed with the regulatory

authorities in Europe (EMA/PDCO) and US FDA as a mean of optimising the ongoing paediatric vortioxetine studies to allow for their timely completion:

- The testing strategy for the primary analysis is changed to a comparison of the pooled doses to placebo, to allow reduction in sample size while maintaining the same statistical power. The rationale for testing the pooled doses is that, under the design assumption of a similar effect for the vortioxetine doses, this strategy is more powerful than testing the doses separately and therefore allows for a smaller sample size (126 patients per group as compared 150 patients per group). Importantly, the proposed testing strategy will still allow for subsequent multiplicity-controlled testing of each dose individually based on a closed testing procedure.

- An interim analysis for efficacy or futility will be conducted based on the primary outcome data from at least 240 patients, to allow for early termination of the study if there is sufficient evidence of an effect of vortioxetine, or a clear lack thereof. If the results of the interim analysis meet neither the efficacy nor the futility criteria, the study will continue until the planned 438 patients have been randomized.

- Recruitment to the fluoxetine group will stop after the interim analysis, if the study has to continue (Study part 2). Comparison to fluoxetine is not the primary objective and assay sensitivity can still be evaluated with reasonable precision based on the available data in the fluoxetine group.

4 Ethics

4.1 Ethical Rationale

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

The risks associated with the study are considered, well controlled by cautionary measures in the study design, and well balanced with the potential benefits of the treatment. Vortioxetine is approved in the US, EU and a number of other countries for the treatment of MDD in the adult population. The evaluation of the safety and tolerability of vortioxetine is based on data from a large clinical development programme in adult and elderly patients. In the overall clinical development programme treatment with vortioxetine at the therapeutic doses (5-20 mg/day) was safe and well tolerated. The approved recommended dose range of 5-20 mg/day for adults was evaluated in a pharmacokinetic and tolerability study performed in the paediatric population (aged 7 to 11 years) designed to guide the choice of doses to be used in the planned paediatric investigation plan. Hence the chosen doses of vortioxetine (10 and 20 mg/day) for this study is based on the results from the paediatric pharmacokinetic and tolerability study and the knowledge from the adult studies. As the sole antidepressant

approved both in children and adolescents for MDD in EU and US, fluoxetine has been selected as comparator to provide evidence of assay sensitivity.

This study will permit the investigation of the efficacy and safety of a new potential treatment of MDD in paediatric patients and the inclusion of a placebo group has major scientific importance in this evaluation to ensure adequate evaluation of efficacy as well as distinguishing disease manifestations from adverse reactions of the compound. The patients will be asked to attend the investigational clinic at regular intervals to ensure an adequate follow-up. All visits will be performed on an outpatient basis at the clinic, other than the follow-up visit that can be a phone call. In order to minimize potential pain, distress, and fear, patients will be seen in facilities which will be appropriate for childcare. The study personnel who interact with the patients will be experienced health care professionals (physicians with paediatric qualification, qualified paediatric nurses or psychologists) and their education, training and experience will be documented. Age-appropriate explanations will be given to the child prior to any investigation or procedure, in order to decrease anxiety and anticipation of pain. Potentially painful procedures such as venipuncture will be minimized with the use of topical anaesthesia. Blood sampling will be limited to the minimum required for obtaining valid data for evaluation. The number of blood samples and visits has been carefully evaluated against the value for the overall objectives of the study.

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

The key ethical dilemma in placebo-controlled studies lies in avoiding exposing children to unnecessary risk versus meeting the need for adequate information to guide clinical care. In view of this, as well as the challenges with recruiting paediatric patients into clinical research, study design modifications have been made in agreement with the Regulatory Authorities in Europe and US to reduce the size of the study. These modifications are considered ethically justified as they prevent unnecessary exposure of paediatric subjects to experimental treatments. In particular, implementation of an interim analysis ensures that the study is not continued unnecessarily, thereby avoiding that the enrolled children are put at unnecessary risk of receiving placebo or an inefficacious treatment. This may also enable children not participating in the study to get earlier access to the superior treatment.

In accordance with *Good Clinical Practice*[21] qualified medical personnel at Lundbeck or a delegate specify will be readily available to advise on study-related medical questions. Medical monitoring will be performed throughout the study. Safety data will be reviewed regularly by the Lundbeck Vortioxetine Safety Committee to ensure that prompt action is taken, if needed, to maximise patient safety.

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

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

In accordance with *Good Clinical Practice*,[21] the investigator will be responsible for all study-related medical decisions.

4.2 Informed Assent/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 parents/legal representative.

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 Assents/Consents Forms* have been signed.

Minors are dependent on their legal representative(s) (typically their parent[s]) to assume responsibility for their participation in clinical studies.[33]

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 assents/consents, the investigator or a designee must explain to the patients and their legal representatives the aims, methods, and potential hazards of the study and any discomfort it may entail. The patients and their legal representatives must be informed that their participation in the study is voluntary and that they are free to withdraw from the study at any time without justifying their decision. The patients and their legal representatives must be informed of the possibility of withdrawing assents/consents (section 8.5).

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

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

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

The blood samples for exploratory biomarker analysis may be shared with academic or public institutions and companies; however, Lundbeck will retain full control of the samples and their use in accordance with the information in the *Patient Information Sheet* and a material transfer agreement.

4.3 Personal Data Protection

The data collected in this study will be processed in accordance with the specifications outlined in the European Union legislation[34] 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 Independent Ethics Committees (IECs) and Institutional Review Boards (IRBs)

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

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

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

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

4.5 Regulatory Approval/Notification Requirements

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

5 Study Population

5.1 Numbers of Patients and Sites

Planned countries and regions:

Patients from the European Union, Europe outside the European Union, North America and other geographical regions.

Planned number of patients:

to be screened (approximately):	800
to be enrolled (approximately):	600
to be randomised:	438

Planned number of:

study sites (approximately):	100

5.2 Patient Recruitment

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

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

5.3 Selection Criteria

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 A Visit and none of the exclusion criteria at the Screening Visit and Baseline A Visit are eligible to participate in this study.

Patients with incomplete improvement of depressive symptoms in Phase A who meet the specific inclusion criteria at Baseline B (Week 4) visit are eligible to continue in Phase B of this study.

Inclusion Criteria Phase A

1. The patient is a boy or girl, aged ≥7 and <12years at screening (patients who turn 12 years during the study will be allowed to continue in the study).
2. The patient is capable of communicating with the site personnel.
3. The patient is able to understand the *Informed Assent Form* and parent(s)/legal representative(s) are able to read and understand the *Informed Consent Form*.

4. The patient has provided assent to participation and parent(s)/legal representative (s) signed the *Informed Consent Form*.
5. The patient and parent(s)/ legal representative (s) is willing and able to attend study appointments within the specified time windows.
6. The patient is an outpatient consulting a clinician.
7. 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.
8. The patient has a CDRS-R total score ≥45 at the Screening Visit and at the Baseline A Visit (Week 0).
9. The patient has a CGI-S score ≥4 at the Screening Visit and at the Baseline A Visit (Week 0).
10. Contraception criterion, if applicable: The patient, if a girl who is sexually active and of childbearing potential (defined as girls aged ≥10 years old and younger girls who, at the discretion of the investigator, are deemed to be of reproductive potential), must use adequate contraception from the Screening Visit to 30 days following the last dose of IMP.
11. Contraception criterion, if applicable: The patient, if a boy, who is sexually active, must use adequate contraception from the Screening Visit to 30 days following the last dose of IMP.
12. The patient, if a girl aged ≥10 years old, or if a younger girl who, at the discretion of the investigator, was deemed to be of reproductive potential, must have a confirmed negative urine pregnancy test at the Screening Visit.

Inclusion Criteria for participation in Phase B

1. The patient has a CDRS-R total score ≥40 at the Week 3 visit and Week 4 visit.
2. The patient has a decrease of the CDRS-R value (subtracted 17 to avoid flooring effect) compared to Baseline A < 40% at the Week 3 visit and Week 4 visit.
3. The patient has a PGA value of >2 at the Week 3 visit and Week 4 visit.

Exclusion Criteria

1. The patient has previously been enrolled in this study.
2. The patient has participated in a clinical study <30 days prior to the Screening Visit.
3. 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.
4. The patient has previously participated in a study with vortioxetine.
5. The patient is under forced treatment.
6. The patient is pregnant or breast-feeding.
7. The patient receives on-going current psychotherapy that is planned to be intensified. Interpersonal psychotherapy (IPT) or cognitive behavioural therapy (CBT) are not allowed.

8. The patient has a history of severe drug allergy or hypersensitivity, or known hypersensitivity to any of the IMP(s) or their excipients.
9. The patient has hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrose-isomaltase insufficiency.
10. The patient has any current psychiatric disorder (DSM-5™ criteria), 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).
11. The patient suffers from intellectual disability, organic mental disorders, or mental disorders due to a general medical condition (DSM-5™ criteria).
12. The patient has a known intellectual disability (as suggested by a known IQ <70), or, clinical evidence or known social or school history indicative of intellectual disability.
13. 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.
14. 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.
15. The patient has an attention-deficit/hyperactivity disorder (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 A visit.
16. The patient has a known first degree relative with a history of Bipolar Disorder.
17. The patient is unable to swallow capsules.
18. The patient has a history of cancer that has not been in remission for >5 years prior to the first dose of IMP.
19. The patient has or has had one or more of the following conditions that is/are considered clinically relevant in the context of the study:
    - neurological disorder
    - other psychiatric disorder
    - cardiovascular disease
    - seizure disorder or encephalopathy
    - congestive heart failure
    - cardiac hypertrophy
    - arrhythmia
    - bradycardia (pulse <50 bpm)
    - respiratory disease
    - hepatic impairment or renal insufficiency
    - metabolic disorder
    - endocrinological disorder
    - gastrointestinal disorder
    - haematological disorder
    - infectious disorder
    - any clinically significant immunological condition
    - dermatological disorder

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

20. The patient takes or has taken disallowed recent or concomitant medication (specified in Appendix II) or it is anticipated that the patient will require treatment with at least one of the disallowed concomitant medications during the study.
21. The patient has clinically significant abnormal vital signs at the Screening Visit.
22. 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:
    - a serum creatinine value >1.5 times the upper limit of the reference range
    - a serum total bilirubin value >1.5 times the upper limit of the reference range
    - a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2 times the upper limit of the reference range
23. The patient has an abnormal thyroid stimulating hormone (TSH) level. Patients with thyroid disease may be enrolled in the study provided they are stable and euthyroid.
24. The patient has, at the Screening Visit:
    - an abnormal ECG that is, in the investigator's opinion, clinically significant
    - a QTcF interval >450 ms (based on the Fridericia correction where QTcF = QT/RR0.33)
25. The patient has a disease or takes medication that could, in the investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with the conduct or interpretation of the study.
26. The patient is, in the investigator's opinion, unlikely to comply with the protocol or is unsuitable for any reason.
27. The patient has 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 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 investigator considers it, for safety, lack of efficacy, and/or study compliance reasons, in the best interests of the patient that he or she be withdrawn
- the patient did not take IMP on the assigned dose level for 6 consecutive days
- the patient has been randomised in error
- any site personnel break the randomisation 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

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

Patients who withdraw will not be replaced.

6 Investigational Medicinal Products

6.1 Treatment Regimen

The screening period will be 5 to 15 days followed by a 4-week single-blind period (Phase A) of treatment with standardised brief psychosocial intervention and placebo. Patients who demonstrate an incomplete improvement of depressive symptoms at the end of Week 4 will be randomised to a double-blind, 8-week treatment period (Phase B) as follows:

Study part 1: Prior to the interim analysis, at least 240 patients will be randomized in a 1:1:1:1 ratio to vortioxetine 10 mg/day, vortioxetine 20 mg/day, fluoxetine 20 mg/day, or placebo.

Study part 2: If the study continues after interim analysis, patients will be randomized in a 1:1:1 ratio to vortioxetine 10 mg/day, vortioxetine 20 mg/day, or placebo.

In total, 438 patients will be randomised if the study continues after interim analysis, with approximately 126 patients in each of the vortioxetine and placebo groups, and approximately 60 patients in the fluoxetine group.

Patients randomised to the 10 mg/day vortioxetine group will receive a lower initial dose (5 mg/day for 2 days) prior to receiving 10 mg/day. Patients randomised to the 20 mg/day vortioxetine group will receive a lower initial dose (5 mg/day for 2 days followed by 10 mg/day for 2 days and 15 mg/day for 2 days) prior to receiving 20 mg/day. Patients randomised to the fluoxetine 20 mg/day group will receive a lower initial dose (10 mg/day for 6 days) prior to receiving 20 mg/day (Only applicable during Study part 1).

Based on tolerability the dose may be reduced at Week 8 (Visit 10 = week 4 of Phase B). For patients randomised to vortioxetine the reduction will be by 5 mg/day and for fluoxetine 10 mg/day (Only applicable during Study part 1). No dose increase will be allowed.

The dose titration schedules are presented in Panel 3.

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

Panel 3 Dose Titration Schedules

Study part 1: Applicable prior to interim analysis

Visit	Patients will take 1 capsule per day Treatment Group			
	Vortioxetine 10 mg	**Vortioxetine 20 mg**	**Fluoxetine 20 mg**	**Placebo**
2-5	Placebo	Placebo	Placebo	Placebo
6	Up-titration	Up-titration	Up-titration	Placebo
7-9	10 mg	20 mg	20 mg	Placebo
10-12	10 mg or 5 mg*	20 mg or 15 mg*	20 mg or 10 mg*	Placebo

* Down-titration

Study part 2: Applicable after interim analysis (if the study continues)

Visit	Patients will take 1 capsule per day Treatment Group		
	Vortioxetine 10 mg	**Vortioxetine 20 mg**	**Placebo**
2-5	Placebo	Placebo	Placebo
6	Up-titration	Up-titration	Placebo
7-9	10 mg	20 mg	Placebo
10-12	10 mg or 5 mg*	20 mg or 15 mg*	Placebo

* Down-titration

6.2 IMPs, Formulations, and Strengths

The IMPs supplied by Lundbeck in this study are:

- Vortioxetine – 5 mg, 10 mg, 15 mg and 20 mg encapsulated tablets
- Fluoxetine – 10 mg and 20 mg encapsulated tablets or encapsulated capsules
- Placebo – encapsulated tablets

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.

The IMP will be provided in 1-week wallet cards, containing 10 capsules.

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

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

The IMPs will be identified using a unique IMP number.

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

6.4 Method of Assigning Patients to Treatment

An Interactive Voice Response System (IVRS/IWRS) will be used in this study. The patients will be assigned a screening number by the IVRS/IXRS system, and that number will be used to identify them throughout the study.

When a patient is to be randomised, the investigator will contact the IVRS/IWRS. The IVRS/IWRS will allocate the patient to a treatment group during the call and assign the patient a randomisation number in accordance with the specifications from the Department of Biostatistics, H. Lundbeck A/S, and then follow up by fax, e-mail, or the web (depending on availability or preference at the site).

6.5 IMP Accountability

The IMP(s) must be tracked at each site using two logs:

- a site-specific log to track the complete inventory (that is, what is shipped between the site and Lundbeck)
- a patient-specific log to track what is dispensed to and returned by the patient

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

6.6 Unblinding Procedures

GPV, and the investigator or the pharmacist (if applicable) will have access to the details of the double-blind treatment for each patient. Access to these details will be via IVRS/IWRS.

The IVRS/IWRS unblinding procedure is described in the *IVRS User Guide*.

The investigator may only break the code if knowledge of the IMP is necessary to provide optimal treatment to the patient in an emergency situation. If possible, the investigator must consult the CRA before breaking the code. The investigator must record the date, time, and reason for breaking the code on the *Completion/Withdrawal Form* (this corresponds to the Completion/Withdrawal Visit, as the patient must be immediately withdrawn from the study) and sign the form. If the emergency situation was an adverse event, it must be recorded on an *Adverse Event Form*. The CRA must be notified immediately.

The IVRS/IWRS will also 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 e-mail, depending on availability/preference.

6.7 Post-study Access to IMP

After completion of the study or withdrawal from the study, the patient must be treated in accordance with normal practice.

No IMP will be provided by Lundbeck.

7 Concomitant Medication

Concomitant medication is any medication other than the IMPs that are taken during the study, including the Screening Period.

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

Details of all concomitant medication (prescription and over-the-counter) taken <3 months prior to the Screening Visit must be recorded in the eCRF at the first visit. Any changes (including reason for changes) in concomitant medication must be recorded at each subsequent visit. For any concomitant medication initiated or for which the dose has changed due to a new disorder or worsening of a concurrent disorder, the disorder must be recorded as an adverse event.

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

8 Study Visit Plan

8.1 Overview

An overview of the procedures and assessments to be conducted during the study and their timing is presented in Panel 2. Further details are in chapter 9.
After completing or withdrawing from the study, the patient must be treated in accordance with usual clinical practice. However, this will not apply for patients entering in an extension study.

8.2 Screening Visit (Visit 1)

Screening Visit takes place between Day –5 and Day –15 prior to Baseline A.

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 at Lundbeck, provided the Medical Monitor accepts the rationale provided for the extension.

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 begin before any Baseline A assessment is done and must comply with the required washout periods in Appendix II. Baseline A assessment is described in Panel 2.

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 by the site and transmitted to the Contract Research Organisation (CRO) for their review. A confirmation that the patient can continue further with the study procedures is required before randomization.

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 patients with a *complete* Screening Visit and who fail to attend the Baseline A 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.

Authorisation for re-screening may only be granted by the sponsor's medical expert/CRO 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 legal representative (if applicable) and 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 authorised by the sponsor's medical expert or state who
- 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 Phase A (Visit 2 to 5)

Phase A starts with Baseline A (Week 0) for the 4 week single-blind phase.

Patients eligible for entering phase A will receive BPI at Week 1, 2 and 3 (visit 3, 4 and 5) and placebo. Patients who do not fulfil the criteria of incomplete improvement in Phase A at Week 3 will be withdrawn from the study before Week 4. Patients who do not fulfil the criteria of incomplete improvement at week 4 will be withdrawn from the study and not participate in the double-blind Phase B of the study. No specific study related follow-up is required for these patients. However, as rescue procedure, they may benefit from up to four outpatient visits to the study site for consultations over a two-month period.

8.4 Phase B (Visit 6 to 12)

Phase B starts with Baseline B (Week 4) for the 8 week double-blind phase.

The patients eligible for Phase B will be randomised at visit 6 (week 4) to one of the four treatment arms and receive BPI at Visit 7 and 10.

8.5 Withdrawal Visit (Visit 12)

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

No new information will be collected from patients who withdraw, except information collected in relation to the scheduled Withdrawal Visit or needed for the follow-up of adverse events (section 11.5).

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

For a patient and/or his or her legal representative who withdraw assent/consent:

- if the patient and/or his or her legal representative withdraw assent/consent during a visit and then agrees to it being the final visit, the investigator will complete the visit as a Withdrawal Visit and all the data collected up to and including this visit will be used
- if the patient and/or his or her legal representative withdraw assent/consent during a telephone conversation, the investigator will ask the patient if he or she will attend a Withdrawal Visit. If the patient:
  - agrees to attend a Withdrawal Visit, all the data collected up to and including this visit will be used
  - refuses to attend a Withdrawal Visit, the investigator should attempt to follow the patient's safety and future treatment; any information collected will only be recorded in the patient's medical record
- if the patient and/or his or her legal representative explicitly request that his or her data collected from the time of withdrawal of assent/consent onwards not be used, this will be respected

8.6 Safety Follow-up Visit/Contact (Visit 13)

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

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

For adverse events that were on-going 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 on-going at the safety follow-up, the stop date must be recorded as "on-going". SAEs must be followed until resolution or the outcome is known.

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

Patients who withdrew due to elevated AST or ALT values (see section 5.4) should be followed until the values normalise or stabilise or a diagnosis or a reasonable explanation has been established (see section 11.5).

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

8.7 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 on-going in the study.

9 Brief Psychological intervention (BPI)

The patients will receive treatment with standardised brief psychosocial intervention during the study. The treatment will be spread across 5 sessions. There will be 3 sessions in Phase A (Weeks 1, 2 and 3), followed by 2 sessions in Phase B (Weeks 5 and 8). BPI for depression[35] is a comprehensive package of specialist care for children and adolescents with depression. It arises from the practise and formulation of a Specialist Clinical Care (SCC) programme and has its origins in the work of the ADAPT RCT[26] team. It comprises: assessment, formulation, case management, achieving engagement with the young person and their parents, planning and delivery of treatment. It is structured around core clinical skills, key elements known to counter depressive tendencies, psycho-education & liaison and multi-systemic formulation (biological, psychological and social elements). A detailed description of key elements of BPI case management is provided in a manual that will be delivered to the site. The manual is intended as a guide to practice, not a session-by-session prescription. It is expected across the treatment period that due consideration is given to all elements described in the manual. The clinician is directed to use their clinical discretion to decide in which session to apply which element of BPI. Session length for BPI will be up to 30 minutes. The BPI session should be performed after assessment of efficacy scales.

10 Assessments

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

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

10.1 Screening and Baseline Procedures and Assessments

10.1.1 Demographics and Other Baseline Characteristics

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

At the Screening Visit, 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
- Smoking, and alcohol consumption habits
- Family psychiatric history
- Traumatic life events
- Height, weight
- Puberty status (Tanner scoring)
- Source of the recruitment: advertisement or other

10.1.2 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.

Detailed instruction 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 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.

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

The K-SADS-PL[36] is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents. The K-SADS-PL is 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).

10.1.4 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 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 authorised 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.

10.2 Efficacy Assessments

10.2.1 Clinician rated Scales

10.2.1.1 Use of Clinician-rated Scales

The following assessment tools will be used:
- CDRS-R – assessing depressive symptoms
- CGI – assessing global impression
- CGAS - assessing functionality

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

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

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

The CDRS-R[37] is a clinician-rated scale to measure the severity of depression of children and adolescents. The CDRS-R consists of 17 items: 14 items rate verbal observations, and three items rate nonverbal observations (tempo of language, hypoactivity, and nonverbal expression of depressed affect). Depression symptoms are rated on a 5-point scale from 1 to 5 for the

verbal observations, and a 7-point scale from 1 to 7 for the nonverbal observations. The total score ranges from 17 (normal) to 113 (severe depression). The CDRS-R can be administered by a clinician after a training session. It takes approximately 20 to 30 minutes to administer and rate the CDRS-R.

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

The CGI[29] 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 Baseline A 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.

10.2.1.4 Children's Global Assessment Scale (CGAS)

The CGAS[38] is a clinician-rated global scale to measure the lowest level of functioning for a child (4 to 16 years) during a specified time period. The CGAS contains behaviourally-oriented descriptors at each anchor point that depict behaviours and life situations applicable to a child. The items range in value from 1 (most functionally impaired child) to 100 (the healthiest). A total score above 70 indicates normal function. The CGAS can be administered by a clinician after a training session. It takes approximately 2 minutes to administer CGAS.

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

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

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

Any exceptions must be discussed and approved by Lundbeck.

Only raters who have been certified in a study-specific Rater Certification Programme will be authorised 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.

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 Scales vendor(s).

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.

10.2.2 Patient and/or Parent Reported Outcomes (PROs)

10.2.2.1 Use of PROs

The following PROs will be used:

- GBI – assessing depressive symptoms
- PGA – assessing depressive symptoms
- PedsQL VAS – assessing functionality
- PQ-LES-Q – assessing health-related quality of life

The GBI, PGA, PedsQL VAS and PQ-LES-Q 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.

10.2.2.1.1 General Behavior Inventory (GBI) 10-Item Depression Scale

The GBI 10-item depression scale[39] is a parent- and subject-rated scale designed to screen for depressive symptoms in children and adolescents. The ten depression 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 depression scale.

10.2.2.1.2 Parent Global Assessment – Global Improvement (PGA)

The PGA[40] is a parent- rated variation of the CGI-I to evaluate the severity of the child's symptoms. The PGA reflects assessments of change from Baseline A symptoms using a 7

point scale ranging from 1 (very much improved) to 7 (very much worse). It takes 1 to 2 minutes to score the PGA.

10.2.2.1.3 The PedsQL Present Functioning Visual Analogue Scales (PedsQL™ VAS)

The PedsQL™ VAS[41] is designed to measure at-that-moment functioning in children and adolescents. The PedsQL VAS consists of 6 domains: anxiety, sadness, anger, worry, fatigue and pain using visual analogue scales. The functionality for each domain is measured on a 10 cm line with a happy face at one end and a sad face at the other. The patients are asked to mark on the line how they feel. The total score is the average of all 6 items, and the emotional distress summary score is the mean of the anxiety, sadness, anger, and worry items. It takes 2 to 5 minutes to administer and rate the PedsQL VAS.

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

The PQ-LES-Q[42] 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 1-14 assess the degree of satisfaction experienced by subjects 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 1-14 is 14 to 70, with higher scores indicating greater satisfaction. It takes 5 to 10 minutes to complete the scale.

10.3 Blood Sampling for Vortioxetine and Fluoxetine Quantification

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

The blood samples will be analysed for vortioxetine and fluoxetine using methods validated in accordance with the EMA *Guideline on Bioanalytical Method Validation*[43] and the FDA *Guidance for Industry*.[44] A bioanalytical protocol will be prepared by Lundbeck before the plasma samples are analysed.

Selected samples will be subjected to incurred sample re-analysis (ISR) for fluoxetine as part of the in-study method validation of the applied bioanalytical method. PK results and ISR results will be clearly distinguished from each other in the bioanalytical study report that will be prepared by the Department of Bioanalysis, H. Lundbeck A/S.

10.4 Safety Assessments

10.4.1 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. Adverse events (including worsening of concurrent disorders, new disorders, and pregnancies) either observed by the investigator or reported spontaneously by the patient will be recorded, and the investigator will assess the seriousness and the intensity of the adverse event and its relationship to the IMP. Results from relevant tests and examinations, such as clinical safety laboratory tests, vital signs, and ECGs, or their corresponding conditions will also be recorded as adverse events if considered by the investigator to be clinically significant.

See chapter 11 for further information on adverse events.

10.4.2 Clinical Safety Laboratory Tests

The clinical safety laboratory tests are listed in Panel 4.

Panel 4 Clinical Safety Laboratory Tests

Haematology	**Lipids**[a]	**Infection**[c]
B-haemoglobin	S-cholesterol (total) (non fasting)	S-C-reactive protein (CRP)
B-erythrocyte count	S-triglycerides (non fasting)	**Urine**[d]
B-haematocrit	S-low density lipoprotein (LDL)	U-protein (dipstick)
B-total leucocyte count	S-high density lipoprotein (HDL)	U-glucose (dipstick)
B-neutrophils (% of total leucocytes)	**Electrolytes**[a]	U-blood (dipstick)
B-eosinophils (% of total leucocytes)	S-sodium	U-ketones (dipstick)
B-basophils (% of total leucocytes)	S-potassium	**Pregnancy**[e] **(women only)**
B-lymphocytes (% of total leucocytes)	S-calcium (total)	U-hCG
B-monocytes (% of total leucocytes)	**Endocrine and Metabolic**[a]	B-hCG (confirmatory for positive urine test only)
B-thrombocyte count	S-albumin	
Liver[a]	S-glucose (non fasting)	
S-total bilirubin	S-TSH[b]	
S-conjugated bilirubin	**Kidney**[a]	
S-alkaline phosphatase (AP)	S-creatinine	
S-alanine aminotransferase (ALT)	S-urea nitrogen (BUN)	
S-aspartate aminotransferase (AST)	**Serology**[c]	
S-lactate dehydrogenase (LDH)	S-HBsAg	
S-γ-glutamyl transferase (γGT)	S-anti HCV	
B – blood; P – plasma; S – serum; U – urine		

a Clinical chemistry
b Performed only at the Screening/washout visit in order to exclude patients with depression symptoms due to a thyroid dysfunction.
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.
e 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 of the *Clinical Study Synopsis*. The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual*.

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

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

The investigator must review (initial and date) the results of the clinical safety laboratory tests as soon as possible after receipt of those results. Out-of-range values must be interpreted by the investigator as “not clinically significant” or “clinically significant” with a comment concerning the planned follow-up. Tests for clinically significant out-of-range values must be

repeated, or an appropriate clinical follow-up must be arranged by the investigator and documented on the laboratory report, until the value has stabilised or until the value has returned to a clinically acceptable value (regardless of relationship to IMP). Any value that is out-of-range at the Completion or Withdrawal Visit and judged clinically significant must be followed according to accepted medical standards for up to 30 days or until the value normalises or stabilises or a diagnosis or reasonable explanation has been established. Any out-of-range values followed after the last protocol-specified contact with the patient will be documented in the patient's medical record.

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

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

10.4.3 Vital Signs

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

Vital signs should be assessed prior to blood sampling.

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

10.4.4 Height and Weight

Height will be measured with a stadiometer, without shoes.

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

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

10.4.5 Electrocardiograms (ECGs)

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

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

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

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

10.4.6 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.

The physical examination must, at a minimum, include an examination of appearance, extremities, skin, head, neck, eyes, ears, nose, throat, lungs, chest, heart, abdomen and musculoskeletal system. The examination at the Screening Visit will be considered the baseline physical examination.

The neurological examination must be performed by a physician.

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

10.4.7 Tanner evaluating

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

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

For 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 at Screening Visit.

10.4.8 Assessment Tools

The Paediatric Adverse Event Rating Scale (PAERS), The Columbia-Suicide Severity Rating Scale (C-SSRS) and GBI mania, will be used for evaluation of tolerability and safety.

The PAERS, C-SSRS, and GBI will be administered in the local language. Only the scales provided for this Lundbeck study should be used.

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

10.4.9 Paediatric Adverse Event Rating Scale (PAERS)

The PAERS[45] is a clinician-rated scale designed and validated to assess adverse events occurring in paediatric patients who are treated with psychotropic medication in clinical studies.

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

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

The PAERS must be applied after the non-leading, open questions on any adverse events (see section 10.4). As this recording of adverse events should precede the use of the PAERS, the numbers of adverse events captured by these two methods potentially differ.

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

The C-SSRS[46] 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.

10.4.11 General Behavior Inventory (GBI) 10-Item Mania Scale

The GBI 10-item mania scale[47] is a parent- and subject-rated scale designed to screen for manic symptoms in children and adolescents. The 10 items are rated on a scale from 0 (*never or hardly ever*) to 3 (*very often or almost constantly*). The total score ranges from 0 to 30 points, with high scores indicating greater pathology. It takes approximately 5 minutes to complete the GBI 10-item mania scale.

10.4.12 Rater Qualification and Certification

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

Only raters who have been certified in a study-specific Rater Certification Programme will be authorised 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 process.

10.5 Exploratory Assessments

10.5.1 Multidimensional Anxiety Scale for Children short version (MASC-10)

The MASC-10[48] is designed to screen for anxiety in children, and is based on the 39-item MASC. The MASC-10 consists of 10 items assessing physiological symptoms, social anxiety, harm avoidance, and separation/panic. The anxiety symptoms are rated on a 4-point scale from 0 (never true about me) to 3 (often true about me). Total score ranges from 0 to 30, with higher scores indicating higher levels of anxiety. The MASC-10 takes approximately 5 minutes to administer and score.

10.6 Exploratory Biomarker Assessments

10.6.1 General Considerations

Although the possible future exploratory biomarker analyses will help to increase our understanding of the aetiology of MDD and the molecular basis of the drug response, the efforts described in this protocol are strictly research based. Therefore, as the complex interactions between genes and disease are currently not characterised to a level that translates to a meaningful clinical advantage, individual results from the exploratory biomarker analyses

will not be given to the patients. For the same reasons, individual results will not be added to the patients' medical records.

The patients will have no direct benefit from the exploratory biomarker analyses.

As blood sampling for the exploratory genomics, proteomics, and metabolomics is an integral part of the study, the main *Patient Information Sheet* covers these analyses. Conversely, blood sampling for the possible future genetic biomarker analysis is optional and a separate *Patient Information Sheet* covers this analysis.

The blood samples for possible future exploratory biomarker analysis, or the data derived from these blood samples, may be shared with academic and public institutions and other companies. However, Lundbeck will retain full control of the samples and their use in accordance with the information in the *Patient Information Sheet* and a *Material Transfer Agreement*. Furthermore, the results based on the analysis of the samples may be pooled across studies to increase the statistical power of the analyses.

A patient and/or his or her legal representative (if applicable) may, at any time and without stating a reason, specifically request the destruction of the patient's exploratory biomarker sample, irrespective of his or her continued participation in the study. The investigator must send a written request on behalf of the patient to the international study manager. The investigator will receive written confirmation from Lundbeck when the sample has been destroyed.

The blood samples for genomics, proteomics, and metabolomics will be single-coded using the patient's screening number. The blood samples for genetic biomarker analysis will be double-coded as described in EMA's position paper on pharmacogenetic terminology[49] to ensure patient privacy protection.

10.6.2 Blood Sampling for Gene Expression Profiling

Blood samples for gene expression profiling will be collected in 2.5 mL PaxGene RNA tubes.

The maximum volume of blood to be collected during the study for this purpose will be 7.5 mL.

The samples for gene expression profiling will be shipped to a Central Laboratory for sample storage. Sample preparation and analysis may be performed by a Contract Research Organisation (CRO) or by a bona fide research collaborator.

10.6.3 Blood Sampling for Metabolomic/Proteomic Biomarkers

Blood samples for metabolomic/proteomic biomarkers will be collected in 2 mL K2 EDTA tubes.

The maximum volume of blood to be collected during the study for this purpose will be 6 mL.

The samples for metabolomic/proteomic biomarkers will be shipped to a Central Laboratory in the United States for sample storage. The analysis may be performed by a Contract Research Organisation (CRO) or by a bona fide research collaborator.

10.6.4 Blood Sampling for Pharmacogenetics

It is optional for the patient to donate a blood sample for exploratory pharmacogenetic analysis.

A blood sample (2 mL) will be collected in K3 EDTA tube for subsequent DNA extraction.

Blood tubes will be shipped on dry ice to the central laboratory, where DNA will be extracted and retained. DNA aliquots will be shipped to a Central Laboratory for storage.

The genetic variants to be analysed may include single nucleotide polymorphisms (SNPs) and copy number variations (CNVs). The analytical methods may be polymerase chain reaction (PCR), qPCR (quantitative PCR), sequencing, or whole genome scans on microarrays. The analysis may be performed by a Contract Research Organisation (CRO) or by a bona fide research collaborator.

10.7 Order of Assessments

The scales should preferably be administered in the following order:

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

At visits other than the Screening Visit:
- CDRS-R
- PGA
- CGAS
- PedsQL VAS, PQ-LES-Q, MASC-10
- GBI
- PAERS
- C-SSRS
- CGI-S, CGI-I

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

10.8 Total Volume of Blood Drawn and Destruction of Biological Material

The total volume of blood drawn from each patient will be approximately 47.5 mL during the study.

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

All biological samples will be retained at the bioanalytical facility until the results have been reported. The samples will subsequently be destroyed by the responsible analytical laboratory. The bioanalytical lab will retain the samples until the bioanalytical report is final and no longer than 1 year from LPLV. The ISM/CRS will be notified that the samples are to be destroyed, and the documentation for sample destruction will be kept in the bioanalytical study file.

The blood samples and any derived material for possible future exploratory pharmacogenetic analyses will be destroyed ≤15 years after the end of the study (see definition in section 8.7) by a Central Laboratory.

The blood samples and any derived material for possible future exploratory gene expression profiling and metabolic or proteomic biomarker assessments will be destroyed ≤10 years after the end of the study (see definition in section 8.7) by a Central Laboratory.

10.9 Treatment Compliance

It is the responsibility of the investigator to account for all IMP (ref 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 and fluoxetine will indicate whether patient has been overall compliant throughout the study.

11 Adverse Events

11.1 Definitions

11.1.1 Adverse Event Definitions[50]

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

An adverse event can therefore be any unfavourable and unintended sign (including clinically significant out-of-range values from relevant tests, such as clinical safety laboratory tests,

vital signs, ECGs), symptom, or disease temporally associated with the use of a medicinal product, regardless of whether it is considered related to the medicinal product.

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 *Informed Assent 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 hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent any of the SAEs defined above)

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

Planned hospitalisations or surgical interventions for a condition that existed before the patient signed the *Informed Assent Form* and that did not change in intensity are not SAEs. Emergency room visits that do not result in admission to the hospital are not necessarily SAEs; however, they must be evaluated to determine whether they meet any of the SAE definitions (for example, life-threatening or other serious [medically important] event).

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

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

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

Suspected unexpected serious adverse reaction (SUSAR) – is any adverse event that is assessed as serious, unexpected (its nature or intensity is not consistent with the current version of the *Investigator's Brochure* for vortioxetine[12] or the *Summary of Product Characteristics (SmPC)/Prescribing Information* for Fluoxetine), and related to an investigational product by either the investigator or the sponsor.

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

11.1.2 Adverse Event Assessment Definitions

Assessment of Intensity

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

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

Assessment of Causality

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

- *Probable* – the adverse event has a strong temporal relationship to the IMP or recurs on rechallenge, and another aetiology is unlikely or significantly less likely.
- *Possible* – the adverse event has a suggestive temporal relationship to the IMP, and an alternative aetiology is equally or less likely.
- *Not related* – the adverse event has no temporal relationship to the IMP or is due to underlying/concurrent illness or effect of another drug (that is, there is no causal relationship between the IMP and the adverse event).

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

For pre-treatment adverse events, a causality assessment is not relevant.

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*

11.2 Pregnancy

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

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

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

11.3 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 IMP; action taken; and outcome. If the adverse event is an overdose, the nature of the overdose must be stated (for example, medication error, accidental overdose, or intentional overdose). If the intensity changes during the course of the adverse event, this must be recorded on the *AE Intensity Log*.

If the adverse event is *serious*, this must be indicated on the *Adverse Event Form*. Furthermore, the investigator must fill out a *Serious Adverse Event Form* and report the SAE to Lundbeck immediately (within 24 hours) after becoming aware of it (section 11.4).

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

11.4 Reporting Serious Adverse Events

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

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

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

Global Pharmacovigilance (GPV)
Fax: [redacted]
e-mail: [redacted]

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

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

Lundbeck will assume responsibility for reporting SUSARs to the authorities in accordance with local regulations. In those Member States of the European Union that have implemented the *European Union Clinical Trials Directive*[51] and in Norway, Liechtenstein, and Iceland, that is, in the countries where unblinded expedited safety reporting is required, Lundbeck will also assume responsibility for reporting SUSARs to the ethics committees.

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

11.5 Treatment and Follow-up of Adverse Events

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

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

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

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

Patients with clinically significant out-of-range clinical safety laboratory test values at the Completion or Withdrawal Visit must be followed in accordance with usual clinical practice and be scheduled for a Safety Follow-up Visit to allow for a medical examination and/or blood sampling (see section 8.6).

Patients who withdraw due to elevated AST or ALT values (see section 5.4) must be followed until the values normalise or stabilise or a diagnosis or a reasonable explanation has been established. Additional medical examinations (for example, ultrasound scanning and/or sampling for serology, conjugated bilirubin, INR) should be considered. A gastroenterology or hepatology consultation should also be considered.

Data Monitoring Committee

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

The same DMC will cover all the clinical studies in the paediatric vortioxetine program.

12 Data Handling and Record Keeping

12.1 Data Collection

12.1.1 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 12.1.3.

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 ICON. All entries, corrections, and changes must be made by the investigator or a delegate.

12.1.2 Patient Binders

12.1.2.1 Use of Patient Binders

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

12.1.2.2 Rating Scales and Patient-reported Outcomes (PROs)

The patient binder contains paper version of the rating scale, K-SADS-PL and PRO, PedsQL-VAS. These will be completed by the rater(s) and the patient, respectively. The data will be transcribed to the *Scoring Sheets* in the eCRF by the investigator or a delegate.

The rater(s) must verify that all the entries in the *Scale Section* are accurate and correct by signing and dating the relevant pages.

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

12.1.2.3 Serious Adverse Event Fallback Forms

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

12.1.3 External Data

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

The clinical safety and/or efficacy laboratory test results will be transferred by the central laboratory. The data will be loaded into the eCRF

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

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

12.2 Retention of Study Documents at the Site

12.2.1 eCRF Data

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

12.2.2 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.

13 Monitoring Procedures

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

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

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

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

14 Audits and Inspections

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

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

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

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

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

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

15 Protocol Compliance

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

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

16 Study Termination

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

- safety concerns
- proven lack of efficacy of the IMP in other studies
- result of interim analysis (either efficacy or futility)

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

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

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

17 Endpoints

This section refers to the 8 week double-blind phase (Phase B) measuring changes from Baseline B (Week 4) after/during 8 weeks of treatment (Week 12 visit). Baseline refers to Baseline B.

17.1 Primary Endpoints

- depressive symptoms:
  - change from Baseline B in the CDRS-R total score after 8 weeks of treatment

17.2 Secondary Endpoints

- depressive symptoms:
  - change from Baseline B in the CDRS-R total score during the 8 weeks of treatment
  - CDRS-R response (defined as >50% reduction in the CDRS-R total score (subtracted 17 points) from Baseline B) during the 8 weeks treatment period.
  - remission over the 8 week treatment period (defined as CDRS-R ≤28), at each visit assessed
  - change from Baseline B in the General Behaviour Inventory (GBI), using the 10-item depression subscale, during the 8 weeks of treatment
    score in the PGA during the 8 weeks treatment period

- Global Clinical Impression:
  - change from Baseline B in the CGI-S score during the 8 weeks treatment period
  - score in the CGI-I during the 8 weeks treatment period
  - remission in the CGI-S score (defined as a CGI-S score of 1or 2) during the 8 week treatment period, at each visit assessed
  - response in the CGI-I score (defined as a CGI-I score of 1or 2) during the 8 week treatment period

- functionality:
  - change from Baseline B in the CGAS score during the 8 weeks treatment period
  - change from Baseline B in the PedsQL VAS score during the 8 weeks treatment period

- health-related quality of life:
  - change from Baseline B in the PQ-LES-Q scores during the 8 weeks treatment period
- pharmacokinetics:
  - pharmacokinetic parameters for vortioxetine and fluoxetine

17.3 Exploratory Endpoints

- co-morbid symptoms:
  - change from Baseline B in the MASC-10 score during the 8 weeks treatment period

17.4 Safety Endpoints

- adverse events (AEs)
- tolerability will be assessed using the (PAERS)
- absolute values and changes from baseline in clinical safety laboratory tests, vital signs, weight, height and ECG parameters
- potentially clinically significant clinical safety laboratory test values, vital signs, weight, and ECG parameter values
- C-SSRS categorisation based on C-CASA definitions (1, 2, 3, 4, and 7)
- GBI using the 10-item mania subscales (patient and parental versions)

18 Statistical Methodology

18.1 Responsibilities

The Department of Biostatistics, H. Lundbeck A/S will perform the statistical analyses described below. An independent biostatistician will perform the interim analysis.

18.2 Analysis Sets

- The following analysis sets will be used to analyse and present the data:
  - *all-patients-enrolled* (APES) – all patients enrolled to the 4-week Single-blind period (Phase A) who received at least one dose of IMP
  - *all-patients-randomised Phase B* (APRS) – all patients randomised to the double-blind, 8-week treatment period (Phase B)
  - *all-patients-treated set Phase B* (APTS) – all patients randomised to the double-blind, 8-week treatment period (Phase B) who took at least one dose of double-blind IMP
    full-analysis set Phase B (FAS) – all patients in the APTS who had a valid Baseline B assessment and at least one valid post-Baseline B assessment of the CDRS-R total score.
- The patients and data will be classified according to these definitions at a *Classification Meeting* held after all the data have been entered in the study database and before the blind

has been broken. There will be two *Classification Meetings*. The first meeting will classify the patients for the interim analysis, and this classification will be kept at the second classification (after the end of the study).
- The efficacy analysis will be based on the FAS.

18.3 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 and counts and, if relevant, percentages will be presented for categorical variables.

18.4 Patient Disposition

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

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

Patient disposition and demographics will be summarised using descriptive statistics.

18.5 Demographics and Other Baseline Characteristics

Demographics (sex, age, race), other baseline characteristics (height, weight and BMI), and baseline efficacy variables will be summarised by treatment group.

18.6 Recent and Concomitant Medication

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

18.7 Exposure and Compliance

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

18.8 Efficacy Analyses

18.8.1 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.

18.8.2 Primary Analysis of the Primary Endpoint

For the primary endpoint (change from Baseline B in the CDRS-R total score to Week 8 in phase B (Week 12)), comparisons of the pooled doses of vortioxetine 10 and 20 mg/day *versus* placebo will be made using Mixed Model Repeated Measurements (MMRM) with freely varying mean and covariance structure and with country as a fixed factor and Baseline B CDRS-R score as a covariate interacting with visit. Treatment (vortioxetine 10 mg/day, vortioxetine 20 mg/day, fluoxetine, and placebo) is included as a fixed factor interacting with visit. For the primary endpoint a contrast test with weights 0.5, 0.5, 0, and -1, respectively, to estimate the average effect of the pooled doses of vortioxetine against placebo, based on the LSMeans for the treatment by visit interaction at Week 8 in phase B (Week 12) will be used. This will be evaluated at a one-sided 2.5% significance level.

18.8.3 Sensitivity Analyses of the Primary Endpoint

The primary endpoint will also be analysed using an analysis of covariance (ANCOVA; OC and last observation carried forward [LOCF]) as sensitivity analysis. The Missing at Random assumption behind the MMRM model will be investigated. This sensitivity analysis will be performed with a) the same covariates and factors as the primary analysis and b) with age, weight and height as covariates as well.

A sensitivity analysis investigating the impact of the study methodological changes will be performed if the study is not stopped at interim analysis. This will be done by adding a factor to the primary analysis indicating, whether the individual patient was enrolled prior to the change in study design or after.

18.8.4 Key Secondary Analyses

Using the same model as in the primary analysis an evaluation of the separate comparisons of vortioxetine 10 mg/day and vortioxetine 20 mg/day versus placebo will be made. These will be estimated based on LSMeans for the treatment by visit interaction at Week 8 in phase B (Week 12). Both of the comparisons will be evaluated at a one-sided 2.5% significance level.

18.8.5 Testing Strategy for multiplicity controlled analyses

Statistical significance can be claimed on the individual doses only if significance is claimed for the pooled vortioxetine doses. The multiplicity control for the primary and key secondary analyses is kept due to the closed testing principle.

To further account for the sequential approach, including one interim analysis with stopping rules for efficacy and futility, an error-spending approach based on Kim & DeMets method will be applied on the outcome from the MMRM model.[52] The precise procedure will be described in the Statistical Analysis Plan.

18.8.6 Analysis of the Secondary Endpoints

For continuous endpoints, the same methodology as the primary analysis described for the primary endpoint will be used. In addition ANCOVA will be performed (OC and LOCF).

For dichotomous endpoints, such as response and remission, logistic regression with treatment as a factor and the baseline score as a covariate will be used. This will be done based on OC, LOCF and NRI.

18.8.7 Analysis of the Exploratory Endpoints

For continuous endpoints, the same methodology as the primary analysis described for the primary endpoint will be used. In addition ANCOVA will be performed (OC and LOCF).

18.9 Pharmacokinetic Analyses

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

18.10 Safety Analyses

18.10.1 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 summarised by treatment group.

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

Adverse events will be summarised using descriptive statistics. Adverse events from Phase A will be reported separately as will adverse events and other safety endpoints from Phase B.

Allocation of TEAEs to Treatment Periods

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

18.10.2 Analysis of Other Safety Endpoints

The clinical safety laboratory test values, vital signs, and ECG parameters will be summarised by treatment group. Potentially clinically significant (PCS) values will be flagged and summarised.

- Adverse events, PAERS scores, clinical safety laboratory tests, vital signs, weight/BMI, ECG parameters, physical examinations, GBI scores (using the 10-item mania subscale), and C-SSRS scores will be summarised using descriptive statistics. Adverse events and other safety endpoints will be reported separately for Phase A and Phase B

18.11 Interim Analyses

A DMC will monitor safety data in a blinded manner at regular intervals as specified in the *DMC Charter*.

In addition, an interim analysis for efficacy and futility is planned to be performed. The interim analysis will take place when at least 240 patients (approximately 60 patients per treatment arm) have been randomised and have completed or been withdrawn from the study, and when the last patient has been randomised in study 12710A (the study in adolescents), whichever occurs latest. The details of interim analysis will be described in an Interim Analysis Plan.

A sequential one-sided (also called asymmetric two-sided) testing strategy will be applied at a one-sided significance level of 2.5% and a power of 85%. Kim & deMets error spending function will be used for both the lower and upper boundaries. The model described in section 18.8.2 will be used for the interim comparison of the pooled doses of vortioxetine *versus* placebo.

The interim analysis will be performed by an independent statistical group. The Sponsor will only be informed about the decision to terminate or continue the study, as described in the *Statistical Charter.* If the decision is to terminate the study early, all patients ongoing in the study Phase B should complete the study according to the protocol.

If the study continues after the interim analysis, the fluoxetine arm will be dropped.

To ensure that the study is sufficiently powered an estimate of the variability of the primary endpoint and the withdrawal rate will be obtained. The analysis will be performed prior to the interim analysis and will be based on blinded and pooled data from all groups. Based on these estimates the power calculation will be updated and adequate actions will be taken if the study has lost power.

18.12 Sample Size and Power

To obtain a power of 85%, with a one-sided significance level of 2.5% and an expected effect size of 4 for each vortioxetine dose, and a standard deviation of 11 for the change from baseline for each dose, 102 patients need to be included in a non-sequential trial.

To maintain the power at 85%, the sample size needs to be increased for the loss of power due to the sequential approach.

As a result, then taking a drop-out rate of 15% in Phase B into account, 126 randomized patients per arm will be required.

In total, 378 randomised patients are required in the final analysis if the study continues after the interim analysis, and in addition approximately 60 patients will be randomised to the fluoxetine group (Study part 1), which means a total of 438 randomised patients.

More details are provided in the statistical analysis plan.

18.13 Statistical Analysis Plan

An *Interim Statistical Analysis Plan* as well as a *Statistical Analysis Plan* describing the handling of data issues and the planned statistical analyses in more detail will be prepared by the Department of Biostatistics, H. Lundbeck A/S, before the interim analysis.

19 Clinical Study Report and Publications

19.1 Clinical Study Report

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

19.2 Data Ownership

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

19.3 Publications

The results of this study will be submitted for publication.

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

Authors of the primary publication must fulfil the criteria defined by the International Committee of Medical Journal Editors (ICMJE).[53]

20 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*.

21 Finance

21.1 Site Agreement

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

21.2 Financial Disclosure

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

21.3 Equipment

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

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Appendix I

Clinical Study Protocol Authentication and Authorisation

Clinical Study Protocol
Authentication and Authorisation

Study title:	Interventional, randomised, double-blind, placebo-controlled, active reference (fluoxetine), fixed-dose study of vortioxetine in paediatric patients aged 7 to 11 years, with Major Depressive Disorder (MDD)
Study No.:	12709A
Edition No.:	4.0
Date of edition:	21 August 2018

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

Authentication

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

International study manager: [redacted]

Clinical research scientist: [redacted]

Head, Biostatistics: [redacted]

Head of Med.Safety Psychiatry: [redacted]

Authorisation

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

Clinical Research - Paediatrics: [redacted]

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

Disallowed Recent and Concomitant Medication

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

Drug Class		Disallowed prior to Baseline A Visit	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 A Visit	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 kava, valerian, ginkgo biloba)	2 weeks	X	X	
Hormones		X	X	Only thyroid hormone replacement, contraceptives and progesterone replacement therapy are allowed.
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 12.