Statistical Analysis Plan

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

Vortioxetine

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Table of Contents

Appendices

List of Panels

List of Abbreviations and Definitions of Terms

ANCOVA	Analysis Of Covariance
APES	All-Patients-Enrolled Set
APRS	All-Patients-Randomized Set
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CDRS-R	Children Depression Rating Scale Revised Version
CGI-I	Clinical Global Impression – Global Improvement
CGI-S	Clinical Global Impression – Severity Of Illness
CI	Confidence Interval
COVID	Coronavirus Disease
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5™	Diagnostic And Statistical Manual Of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full- Fda Analysis Set
FSH	Follicle-Stimulating Hormone
GBI	General Behaviour Inventory
IMP	Investigational Medicinal Product
K-SADS-PL	The Kiddie-Schedule For Affective Disorders And Schizophrenia For School-Aged Children, Present And Lifetime Version
LH	Luteinising Hormone
LOCF	Last Observation Carried Forward
MDD	Major Depressive Disorder
MMRM	Mixed Model For Repeated Measurements
OCD	Obsessive Compulsive Disorder
PCS	Potentially Clinically Significant
PK	Pharmacokinetic(s)
PK	Pharmacokinetics
PQ-LES-Q	Pediatric Quality Of Life Enjoyment And Satisfaction Questionnaire
SAE	Serious Adverse Event
SAS®	Statistical Software Package From The SAS® Institute
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for study protocol 13546A "A double blind, randomized, placebo-controlled, multicentre, relapse-prevention study of vortioxetine in paediatric patients aged 7 to 11 years with Major Depressive Disorder". The table of contents and templates for the TFLs will be produced in a separate document.
The analysis plan may change due to unforeseen circumstances. Any deviations from this SAP will be described and justified in an amendment or the Clinical Study Report (CSR).

2 Objectives and Endpoints

The study objectives and endpoints are summarized in Panel 1.

Panel 1 Objectives and Endpoints

Objectives	Endpoints
Primary Objective • to evaluate the efficacy of vortioxetine in the prevention of relapse of major depressive episodes in paediatric patients with MDD	**Depressive Symptoms** • Primary endpoint: – time to relapse in the Double-Blind Treatment Period • Secondary endpoint: – relapse in the Double-Blind Treatment Period
Secondary Objectives • to evaluate efficacy of vortioxetine during continuation treatment of paediatric patients with MDD • to evaluate the efficacy of vortioxetine on: – clinical global impression – quality of life • to assess adherence to investigational medicinal product (IMP) through pharmacokinetic analysis	**Depressive Symptoms** • Secondary endpoint: – change from baseline to Week 26 in the Children Depression Rating Scale Revised Version (CDRS-R) total score **Global Clinical Impression** • Secondary endpoints: – change from baseline to Week 26 in the Clinical Global Impression – Severity of Illness (CGI-S) score – Clinical Global Impression – Global Improvement (CGI-I) score at Week 26 **Quality of life** • Secondary endpoint: – Change from baseline to Week 26 in Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) – total score of item 1-14 during the 26 weeks treatment period. – Change from baseline to Week 26 in Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q) – overall evaluation score (item 15) during the 26 weeks treatment period. **Pharmacokinetics** • Secondary endpoints: – plasma exposure to vortioxetine – population pharmacokinetic parameter values

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

3 Study Design

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

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

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

De novo patients

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

Rollover patients from Study 12709A (enrolled to the Open Label Period)

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

De novo patients and rollover patients from study 12709A can be randomized to the Double-Blind Treatment Period, if eligible.

Rollover patients (remitters) from Study 12712A (randomized to the Double-Blind Treatment Period)

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

- Eligible patients will be randomized directly to the 26-week, Double Blind treatment period.

An overview of the study is presented in the Schedule of Study Design (including the study periods) and the scheduled study procedures and assessments per study period are summarized in Appendix II.

3.1 Open Label Period

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

- The duration of the open-label, flexible-dose treatment period will be 12 weeks.

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

    - The target dose is 10 mg/day, however, the investigator has the possibility to increase the dose to a maximum of 20 mg/day in case of unsatisfactory response or decrease the dose to 5 mg/day in case of dose-limiting AEs. The dose can be up- or down-titrated with 5 mg/day. The patient should receive the same dose for 2 days before being up- or down-titrated to a new dose. Changes in dosing may occur at any visit during the first 8 weeks at the investigator's discretion. In addition, between Week 2 and Week 8, the patient and/or parent(s)/legal representative(s) can request an unscheduled visit to discuss their current dose. The minimum dose is 5 mg/day.

- From Week 8 and onwards the dose has to remain fixed.

- Patients in remission (CDRS-R total score ≤28) at both Weeks 10 and 12 or with an adequate clinical response (defined as ≥50% reduction in the CDRS-R total score compared to the baseline score in this study [subtracted 17 as 17 is the minimum CDRS-R Total Score] and a CDRS-R total score ≤35) at both Weeks 10 and 12 will be randomized in the Double Blind, placebo-controlled, fixed-dose period.

- Patients who do not fulfil randomization criteria for remission or adequate response at Week 10 and/or Week 12 will be withdrawn from the study and will complete an early Withdrawal Visit. Non-remitters/non-responders who leave the study will be treated at the investigator's discretion.

  A Safety Follow-up Visit will be performed approximately 4 weeks after withdrawal from the Open Label Period.

3.2 Double-Blind Treatment Period

Double-Blind Treatment Period (for all randomized patients)

- Patients who fulfil the randomization criteria and do not meet any of the withdrawal criteria during the Open Label Period or at the time of randomization will be randomly assigned via a centralized randomization system to receive vortioxetine or placebo in a 1:1 ratio. Randomization will be stratified by patient inclusion sources (*de novo* patients, rollover patients from 12709A, or from 12712A).

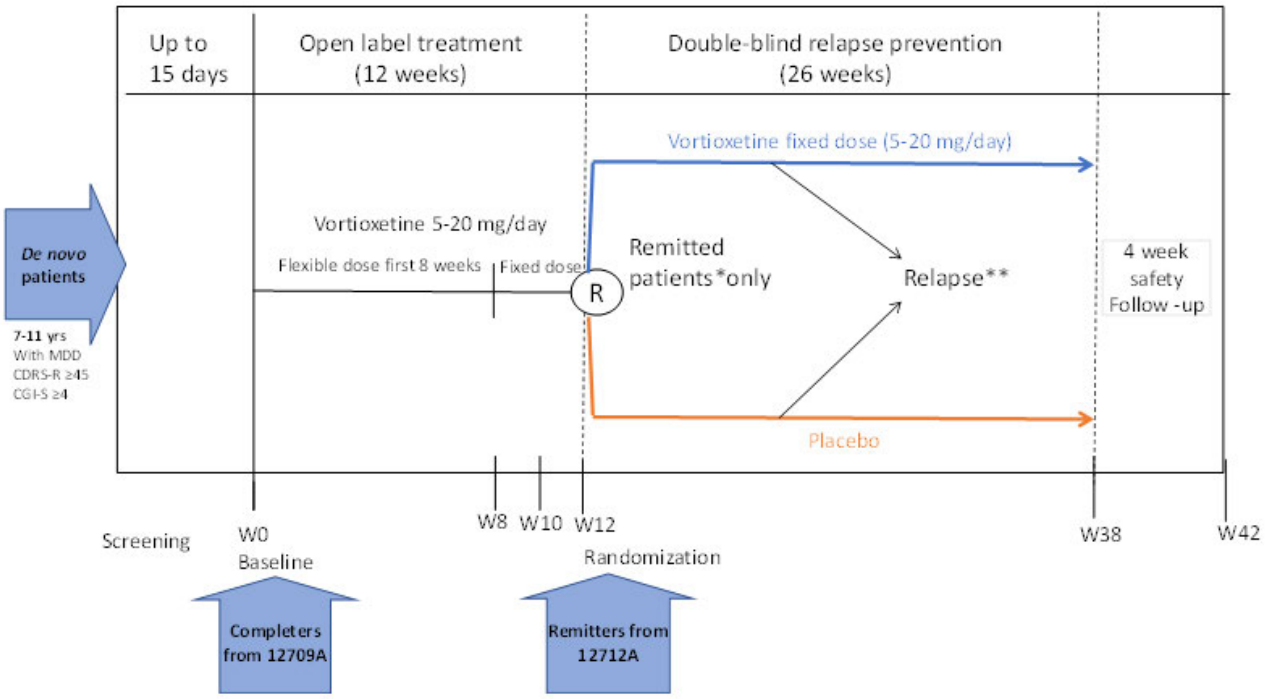
- Patients randomized to vortioxetine will continue on their final dose from the Open Label Period or the dose they had on their last visit in Study 12712A, as applicable.

- The maximum duration of the Double-Blind Treatment Period will be 26 weeks.

- Patients who relapse during the Double-Blind Treatment Period must be withdrawn from the study. The criterion for a relapse is a CDRS-R total score of ≥40 with a history of 2 weeks of clinical deterioration, or a clinical deterioration that in the investigator's opinion warrants alteration of treatment to prevent full relapse.

A Safety Follow-up Visit will be performed 4 weeks after withdrawal or completion of the Double-Blind Treatment Period.

Panel 2 Schedule of Study Design



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

4 Definitions

4.1 Definition of Baseline

The primary analysis of the study focuses on the results of the Double-Blind Treatment Period. Therefore, baseline for the primary analysis will be defined as the randomization visit, i.e. the start of the Double-Blind treatment period. This baseline will be referred to as Randomization (Visit).

For the analysis of safety, baseline is defined as the start of the Open Label Period for *de novo* and 12709A rollover patients. This baseline will be referred to as Baseline (Visit). For 12712A rollover patients baseline will be defined as the start of the Double-Blind Treatment Period, i.e. the randomization visit.

4.2 Definition of Periods

The following periods can be identified:

Screening period
A Screening Visit will be performed only for de novo patients. Patients rolling over from Study 12709A will proceed directly to the Baseline Visit. Therefore, the screening period is not applicable for these patients. In addition, this period is not applicable for patients rolling over from Study 12712A, as these patients will enrol the study at the randomization visit. The screening period begins when the first screening assessment is done after written Informed Assent/Consent has been obtained, and ends at the Baseline Visit for the Open Label Period (visit 2).

Open Label Period
De novo patients who continue to meet all inclusion criteria and none of the exclusion criteria (see section 5.3 of the study protocol) will be enrolled into a 12-week Open Label Period. For patients rolling over from Study 12709A, the Baseline Visit of the Open Label Period will be performed the same day as the Week 12 (Completion) Visit of Study 12709A.

Patients eligible for entering the Open Label Period will start IMP (vortioxetine) at the Baseline Visit of the Open Label Period.

The duration of the Open Label Period is 12 weeks or until the patient is withdrawn from the study, whichever comes first. If a patient withdraws from the study, the Open Label Period ends at the withdrawal visit.

Double-Blind Treatment Period
The Double-Blind Treatment Period starts at the randomization visit (visit 8) and ends after 26 weeks of treatment (visit 17), or until the patient will be withdrawn from the study, whichever comes first. If a patient withdraws from the study the Double-Blind Treatment Period ends at the withdrawal visit.

Patients rolling over from Study 12712A will have their first visit in this study at visit 8 (the Randomization Visit). For 12712A-patients the last available values from assessments and procedures (efficacy/safety, and use of concomitant medication) performed at either Visit 7 (Week 8) and/or Visit 8 (Week 10), or Visit 9 (Week 12) in Study 12712A will be the Randomization Visit values for this study.

Safety Follow-up Period
The Safety Follow-up Period has a duration of 4 weeks after the last IMP intake. This period starts at the date of last IMP intake.

A Safety Follow-up Period is planned at the end of the study (i.e. after completion of visit 17) and after withdrawal of a patient in either the Open Label Period or the Double-Blind Treatment Period. The end of the Safety Follow-up Period will be at visit 18 (SFU visit).

4.3 Definition of Withdrawal

The patients who withdraw from the Open Label Period or the Double-Blind Treatment period will be described as *withdrawn from the study*. The remaining patients will be described as *completed the study*.

5 Analysis Sets

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

all-patients-enrolled (APES) – all-patients-enrolled to the 12-week Open Label Treatment Period who took at least one dose of IMP

all-patients-randomized set (APRS) – all patients randomized to the 26-week Double-Blind Treatment Period

full-analysis set (FAS) – all patients randomized to the 26-week Double-Blind Treatment Period who took at least one dose of Double Blind IMP

The efficacy analyses will be based on the FAS and the safety analyses will be based on the APES (for *de novo* and 12709A rollover patients) and the APRS (for 12712A rollover patients).

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

6 Descriptive Statistics

In general, summary statistics (n, arithmetic mean, standard deviation, median, minimum and maximum values) will be presented for continuous variables. Counts and, if relevant, percentages will be presented for categorical variables. The denominator for the percentage calculation will be noted.

Unless otherwise specified, data listings will include enrolment source, site, treatment group, patient screening number, sex, age, race, and baseline weight.

7 Patient Disposition

7.1 Summary of Patient Disposition

The disposition data will be summarized for the Open Label Period (split out by *de novo* patients, rollover patients from Study 12709A and total), and the Double-Blind Treatment Period (split out by treatment groups and total) separately. The number of patients in APES and APRS who completed or withdrew from the study, as well as the number of patients in each analysis set (APES, APRS and FAS) will be presented.

7.2 Withdrawals

The number of patients who withdrew from the Open Label Period will be summarized by *de novo* patients, rollover patients from Study 12709A and total. The number of patients who withdrew from the Double-Blind Treatment Period will be summarized by treatment group and total. The primary reason for withdrawal as well as all reasons for withdrawal will be presented per period.

Patients who withdrew from the study will be listed and the listing will include the number of days in the study until withdrawal from the study, the number of days on IMP, the primary reason for withdrawal, and all reasons for withdrawal.

8 Demographics and Baseline Characteristics

Summary tables on demographic and baseline characteristics will be presented for both the Open Label Period and the Double-Blind Treatment Period separately. The baseline characteristics for the Open Label Period will be based on the APES and will be presented for *de novo* patients, rollover patients (from Study 12709A) and overall.

For the Double-Blind Treatment Period the summary tables on demographics will be based on the FAS and results will be presented per treatment group (vortioxetine and placebo) and in total.

Demographics (sex, age, ethnicity and race), baseline characteristics (height, weight and BMI), disease characteristics and baseline efficacy variables will be summarized.

The following baseline (randomization) efficacy variables will be summarized:
- CDRS-R total score
- CGI-S score
- PQ-LES-Q scores (total score and overall score (item 15))

Disease characteristics will include MDE history (MDD history, including number of MDEs, duration of current episode, treatment type (physchotherapy / pharmacotherapy) for MDD. In addition, MDD treatment will be summarized.

Medical history from the Medical History eCRF page will be coded with medical dictionary for regulatory activities (MedDRA) version 19.0 or above. All medical histories, data on major depressive disorder history and treatment, the family psychiatric history and the history of stimulant medication will be listed.

9 Recent and Concomitant Medication

Recent and concomitant medication will be coded using the WHO Drug Dictionary (WHO Global B3 Mar 2020).

Medications will be classified according to the start and stop time and summarized by anatomical therapeutic chemical (ATC) code, generic drug name:

- medication discontinued prior to first dose of IMP in Open Label Period
- concomitant medication continued after first dose of IMP in Open Label Period
- concomitant medication started at or after first dose of IMP in Open Label Period

- concomitant medication continued after first dose of IMP in Double-Blind Treatment Period
- concomitant medication started at or after first dose of IMP in Double-Blind Treatment Period
- concomitant medication started after last dose of IMP in Double-Blind Treatment Period

Concomitant medications started after withdrawal from treatment will be listed separately.

Two sets of tables will be produced; for the Open Label Period tables will be based on the APES and will present the *de novo* patients and 12709A rollover patients separately as well as in total.
For the Double-Blind Treatment Period, tables will be based on the APRS and presented per treatment group as well as overall.

10 Exposure

Exposure and compliance will be calculated per patient and summarized for Open Label Period and Double-Blind Treatment Period separately. For the Open Label Period results will be summarized for *de novo* and 12709A rollover patients separately as well as in total, whereas for the Double-Blind Treatment Period results will be presented per treatment group and overall.

Exposure (days) to IMP, irrespective of missing doses, in each period, will be calculated as:
Date of last IMP intake – Date of first IMP intake in the respective period+ 1
Exposure in weeks will be calculated as: Exposure in days/7

The calculation will include the patient years of exposure (PYE). PYE will be calculated as the sum of the number of days of exposure to IMP for each patient, divided by 365.25 days.

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

Compliance in each treatment period will be calculated as:
(the number of days of dose taken / the number of days a dose was planned)*100

Exposure and compliance will be summarized using standard summary statistics. In addition, exposure to IMP will be categorized in the following intervals:
< 1 week
1-2 weeks
3-4 weeks
5-8 weeks
9-10 weeks
11-12 weeks
>12 weeks
for the Open Label Period,
and:
< 1 week
1-2 weeks
3-4 weeks
5-6 weeks
7-10 weeks
11-14 weeks
15-18 weeks
19-22 weeks
23-26 weeks
>26 weeks relative to randomisation for the Double-Blind Treatment Period.

For the Open Label Period an overview of the dosing pattern per patient will be presented.

For both the Double-Blind Treatment Period and the Open Label Period, summary statistics on the mean daily dose will be presented. The results for the Open Label Period will be presented for *de novo* and rollover patients separately, as well as in total. For the Double-Blind Treatment Period this will only be presented for the vortioxetine treated patients.

The mean daily dose will be defined as:

Total dose received during the Double-Blind Treatment Period / number of exposure days in the Double-Blind Treatment Period.

For the Double-Blind Treatment Period a frequency count on the dosage received, including the number of patients withdrawn per dose, will be presented.

Exposure will be summarized based on the APES for Open Label Period and on the APRS for Double-Blind Treatment Period.

11 Efficacy

11.1 Overview of Planned Efficacy Analysis

An overview of all planned effectiveness analyses in provided in Panel 3.

Panel 3 Overview of Planned Efficacy Analyses

Variable (Analysis Set): Endpoint	Type	Descriptive Statistics[a]		Logistic Regression		Cox Regression	ANCOVA	MMRM
		OC	LOCF	OC	LOCF			
Time to relapse (FAS)	4					X		
Relapse (FAS)	3	X		X	X			
CDRS-R (FAS) -Total score	1	X	X				X	X
PQ-LES-Q (FAS) -Total score (sum of item 1-14) -Overall score (item 15)	1 1	X X	X X				X X	X X
CGI-S (FAS)	1/2	X	X				X	X
CGI-I (FAS) score	1/2	X	X				X	X

1 = continuous; 2 = categorical; 3 = binary; 4 = time to event
a Including summaries of absolute values and changes from randomization for endpoints based on changes

In addition to the planned efficacy analysis on the FAS, descriptive statistics and the change from randomization in the CDRS-R total score, per inclusion source, will be presented for the Open Label Period.
Also the number of relapses will be summarized descriptively according to relapse criteria: CDRS-R total score ≥40 with 2 weeks of clinical deterioration, investigator's judgement, or both.

11.2 General Efficacy Analysis Methodology

All the statistical tests of the efficacy endpoints will be one-sided tests performed at the 5% significance level and all confidence intervals (CIs) will be 95% CIs, unless otherwise specified.
For all proposed analyses the applicable assumptions will be checked before the respective analysis is carried out.

The efficacy analyses will be based on the FAS for the Double-Blind Treatment Period.
The SAS code for the statistical analyses is provided in Appendix III.

11.3 Analysis Methodology for the Primary Endpoint

11.3.1 Primary Analysis of the Primary Endpoint

The primary efficacy analysis will compare the time to relapse in the Double-Blind Treatment Period between vortioxetine and placebo treated patients. Relapse will be defined as either a

total score ≥40 on the CDRS-R with a history of 2 weeks of clinical deterioration, or clinical deterioration as judged by the clinician and documented in the eCRF.

The time to relapse is defined as the number of days from the start of the Double-Blind Treatment Period (Randomization visit) to the date of relapse. This will be calculated as follows:

(Date of relapse – Date of start of Double-Blind Treatment Period)

Patients who do not relapse before the end of the Double-Blind Treatment Period (26 weeks) will be censored at week 26. Patients who withdraw from the study for other reason(s) than relapse will be censored at the time of withdrawal.

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

Cox Regression Model

The time to relapse will be analysed using a Cox regression model that includes treatment as a fixed factor, and the randomization CDRS-R total score as covariate, and stratifying by inclusion source to allow for different baseline hazards for each inclusion group.

The hazard ratio for vortioxetine compared to placebo will be estimated from the model and presented with p-values and 95% CIs.
In case of non-convergence of the Cox regression model the strata will be grouped in a new stratum variable, and this variable will be defined at the classification meeting based on blinded treatment and relapses from the different enrolment sources.

A one-sided 5% alpha level of confidence will be used.

11.3.2 Sensitivity Analyses of the Primary Endpoint

The following sensitivity analyses will be performed:

1. The primary analysis will be repeated ignoring relapses occurring during the first week, two weeks and four weeks of the Double-Blind Treatment Period, respectively.

   For the purpose of this sensitivity analysis 3 subsets of data will be defined:
   i) A subset excluding all patients with a relapse within the first 7 days after the start of the Double-Blind Treatment Period.
   ii) A subset excluding all patients with a relapse within the first 14 days after the start of the Double-Blind Treatment Period.
   iii) A subset excluding all patients with a relapse within the first 28 days after the start of the Double-Blind Treatment Period.

The primary analysis of the study, as described, will be repeated in each of the 3 subsets above and for each subset the hazard ratio for vortioxetine compared to placebo will be estimated from the model and presented with p-values and 95% CIs.

2. The primary analysis will be repeated for the *de novo* patients and for the (pooled) 12709A patients and 12712A patients additionally.

The hazard ratio's for vortioxetine compared to placebo will be estimated from the model and presented with p-values and 95% CIs for *de novo* and rollover patients (pooled 12709A and 12712A) separately.

On an exploratory basis, if feasible, the impact of the use of psychotherapy, severity of illness, gender and age may be investigated. Therefore, these may be added as fixed factors or covariates to the Cox regression model, or subgroups may be created.

11.4 Analysis Methodology for the Secondary Endpoints

11.4.1 Analysis of the Secondary Endpoint(s)

Relapse
The number of relapses will be summarized per visit, per treatment group and overall. The relapse criteria as defined in in section 11.3 will be used.

The relapse over the 26 weeks Double-Blind Treatment Period will be analysed using logistic regression, with treatment and inclusion source as fixed factors and CDRS-R Total Score at randomization as covariate. In addition, the analysis will be repeated using the LOCF (Last Observation Carried Forward) approach for missing data.

The odds ratio estimates with 95% confidence intervals will be presented. The odds ratio and the confidence limits will be based on the profile likelihood.

Secondary efficacy variables (CDRS-R total score, PQ-LES-Q scores (total score and overall score), CGI-S and CGI-I) will be analysed on an exploratory basis over the 26-week Double-Blind Treatment Period by Mixed Model Repeated Measurements (MMRM) and analysis of covariance (ANCOVA).

For the purpose of the analysis the change from randomization in CDRS-R total score, PQ-LES-Q scores, and in CGI-S score will be computed.

For both the MMRM and the ANCOVA, the dependent variable will be the change from randomization in CDRS-R total score, change from randomization in PQ-LES-Q scores, change from Randomization in CGI-S score and the absolute CGI-I score, respectively.

The MMRM will have treatment, week and inclusion source as fixed factors and the randomization score will be added as a covariate. For CGI-I, the score at randomization for the CGI-S will be used as covariate.

In addition, the interaction between treatment and week and between randomization score and week will be included and an unstructured covariance matrix will be applied. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

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

Only the observed cases (OC) approach will be used.

Paediatric Quality of Life Enjoyment and Satisfaction Questionnaire

The PQ-LES-Q consist of 15 items, item 1 to 14 assess the degree of satisfaction experienced by patients in various areas of daily functioning and item 15 allows patients to summarize their experience in a global rating.

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

The same analysis as for item 1-14 will be applied on the global rating (item 15).

Summary statistics on total score (items 1 -14) and the overall score (item 15) will be presented for each visit, per treatment group and overall.

Children depression rating scale revised version (CDRS-R)

The CDRS-R is a clinician-rated scale to measure the severity of depression of children and adolescents. The CDRS-R is rated by a clinician following interviews with the child and parent(s) and consists of 17 items: 14 items rate verbal observations, and 3 items rate non-verbal observations (tempo of language, hypoactivity, and nonverbal expression of depressed affect). Items are rated for severity on a 7-point scale (1 to 7) for 14 items, and on a 5-point scale (1 to 5) for 3 items (sleep disturbance, appetite disturbance, and listless speech). The total score ranges from 17 (normal) to 113 (severe depression).

Summary statistics on total score and all items scores will be presented for each visit, per treatment group and overall.

Clinical Global Impression

The CGI is a clinician rated scale that consist of two subscales: severity of illness (CGI-S) and global improvement (CGI-I).

CGI-S

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).

CGI-I
The CGI-I provides the clinician's impression of the patient's improvement (or worsening). The clinician assesses the patient's condition relative to randomization on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

For both the CGI-S as the CGI-I descriptive statistics as well as frequency counts and percentages will be given for each time point per treatment group and overall.

11.5 Analysis of the Exploratory Endpoints

No formal exploratory endpoints have been defined.

On an exploratory basis, severity of illness, gender and age may be assessed as covariates or to generate subgroups for the Cox regression model as described in section 11.3.1.1. In addition, descriptive statistics will be used to compare patient populations and treatment outcome between the geographical regions.

Also on an exploratory basis, the primary analysis of the study will be repeated for each of the two definitions of relapse below and the hazard ratio for vortioxetine compared to placebo will be estimated from the model and presented with p-values and 95% CIs:

i) Relapse based on investigator judgement.
ii) Relapse defined as CDRS-R total score ≥40 with 2 weeks of clinical deterioration

11.6 Pharmacokinetic Analyses

The pharmacokinetic analyses will be described in a separate population PK analysis plan.

12 Safety

The safety analyses will be performed for each period, based on the APES and the APRS. Unless otherwise specified the tables and listings of the Open Label Period are based on APES. The tables and listings of the Double-Blind Treatment Period are based on the APRS.

All safety endpoints will be reported for the 12-week Open Label Period and the 26-week Double-Blind Treatment Period separately. The results of the safety analysis of the Open Label Period will be presented by patient group (*de novo* patients and rollover patients from Study 12709A) and overall.

The results of the safety analyses of the Double-Blind Treatment Period will be displayed by treatment group and overall.

12.1 Adverse Events

12.1.1 General Methodology for Adverse Events

Tables by preferred term and tables by system organ class (SOC) and preferred term will be sorted in descending order based on the percentages of patients in the total column.

Unless otherwise specified, the summaries of adverse events will include the total number and percentage of patients with an adverse event and the total number of AEs.
In summaries of adverse events presented by intensity, the maximum intensity of the adverse event will be used for patients who have more than one intensity of that event. Adverse events for which information on intensity is missing will be classified as *severe*.

Listings of adverse events will be sorted by site, patient screening number, and adverse event start date, and include period, preferred term, investigator term, adverse event start date, days since first dose of IMP, dose at onset of AE, duration of the adverse event, action taken, causality, intensity, seriousness, and outcome. For adverse events that change in intensity, each intensity will be included.

12.1.2 Coding of Adverse Events

Adverse events will be coded using MedDRA, Version 23.0 or later.

12.1.3 Classification 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. As such, this definition will only be used for *de novo* patients.
- *treatment-emergent adverse event (TEAE) – an adverse event that starts or increases in intensity and/or seriousness on or after the date of first dose of IMP*

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

An adverse event is considered causally related to the use of the IMP when the causality assessment by the investigator is *probable* or *possible*. For pre-treatment adverse events, a causality assessment is not relevant.

12.1.4 Allocation of TEAEs to Treatment Periods

TEAEs will be allocated to treatment periods according to the time of onset of the adverse event:

Pre-treatment AEs – 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 in Open Label Period. This definition will only be used for *de novo* patients.

TEAE in the Open Label Period – an AE that starts on or after the date of the first IMP intake in the Open Label Period and before the date of the end of Open Label Period. In addition, for *de novo* patients only, this also includes AEs that start before the date of the start of Open Label Period and worsens before the date of the end of the Open Label Period.

TEAE in the Double-Blind Treatment Period – a TEAE that starts on or after the date of the first IMP intake in the Double-Blind Treatment Period and before the date of the end of Double-Blind Treatment Period, **OR** starts before the date of the start of Double-Blind Treatment Period and worsens on or after the date of the first IMP intake in the DB treatment period and before the date of the end of the Double-Blind Treatment Period

TEAE in the Safety Follow-up Period – an AE that starts on or after the date of the end of Double-Blind Treatment Period or on or after the date of withdrawal (in either the Open Label Period or the Double-Blind Treatment Period).

Adverse events that are ongoing in either parent study at the time of entry into the current study will be included in the present study. All data will be transcribed and the rules as described above will apply.

12.1.5 Presentation of Adverse Events

All adverse events will be listed for the APES and APRS for the Open Label Period and the Double-Blind Treatment Period, including a flag for TEAEs. The period in which the AE started will be displayed.

For each period, an overview of the number and percentage of patients with TEAEs, serious adverse events (SAEs), or adverse events leading to withdrawal and patients who died during the study will be provided.
This overview will be based on the APES for the Open Label Period and APRS for the Double-Blind Treatment Period. For TEAEs, SAEs, and adverse events leading to withdrawal, the total number of events will be included.

12.1.6 Presentation of Pre-treatment Adverse Events

Pre-treatment adverse events will be summarized by preferred term based on APES.

12.1.7 Presentation of Treatment-emergent Adverse Events

The following summaries will be provided for the Open Label Period (based on the APES) and for the Double-Blind Treatment Period (based on the APRS) separately:

- TEAEs by SOC and preferred term
- TEAEs by preferred term
- TEAEs with an incidence ≥5% by preferred term

- Causally related TEAEs by SOC and preferred term
- TEAEs by intensity (*mild*/*moderate*/*severe*), SOC, and preferred term
- Causally related TEAEs by intensity, SOC, and preferred term

12.1.8 Presentation of Deaths

All the adverse events in patients who died during the study will be listed for the APES in the Open Label Period and for the APRS in the Double-Blind Treatment Period.

12.1.9 Presentation of Serious Adverse Events

All the SAEs will be listed for the APES in the Open Label Period and for the APRS in the Double-Blind Treatment Period.

Treatment-emergent SAEs will be summarized for each treatment period by:

- SOC and preferred term
- Preferred term

A listing presenting all SAEs will be prepared.

12.1.10 Presentation of Adverse Events Leading to Withdrawal

All the adverse events leading to withdrawal will be listed. TEAEs leading to withdrawal will be summarized per treatment period by:

- SOC and preferred term
- Preferred term

12.2 General Methodology for Other Safety Data

Unless otherwise specified, tables, graphs and listings will be based on the APES (Open Label Period) and the APRS (Double-Blind Treatment Period).

All tables and graphs will be presented by inclusion source (Open Label Period) and treatment group (Double-Blind Treatment Period).

All safety endpoints will be reported for the 12-week Open Label Period and the 26-week Double-Blind Treatment Period separately.

The denominators for the summaries of a given variable will be based on the number of patients with non-missing values at a given visit or during the assessment period.

Descriptive statistics for the safety variables, both absolute values and changes from baseline, will be presented by visit and for the last assessment. All available post-baseline assessments (including data collected at unscheduled visits) will be included in the identification of the last assessment. With respect to baseline, the definition as presented in section 4.1 will be used.

The number and percentage of patients with at least one potentially clinically significant (PCS) value at any post-baseline assessment time point will be summarized by variable. All available assessments will be included in the evaluation of PCS values.

The number and percentage of patients with values out-of-reference range and/or PCS range will be summarized by variable, visit, and last post-baseline assessment.

For patients with post-baseline PCS values, listings will be provided including all the values for those patients for the variable, with flagging of PCS values and out-of-reference-range values.

The PCS values relating to the paediatric population in this study will be applied.

Lundbeck standard criteria for identifying PCS values will be used.

12.3 Clinical Safety Laboratory Test Data

The clinical safety laboratory tests that are evaluated at baseline and post-baseline are included in the panel below.

Panel 4 Clinical Safety Laboratory Tests

Haematology	**Clinical Chemistry**	**Urine**
haemoglobin erythrocyte count total leucocyte count neutrophils[a] eosinophils[a] basophils[a] lymphocytes[a] monocytes[a] thrombocyte count	total bilirubin conjugated bilirubin alkaline phosphatase alanine aminotransferase aspartate aminotransferase gamma-glutamyl transferase creatinine urea nitrogen sodium potassium calcium (total) albumin estradiol [girls only] luteinising hormone [LH] follicle-stimulating hormone [FSH]) prolactin [PROLCTN] glucose low density lipoprotein high density lipoprotein triglycerides cholesterol (total)	protein (dipstick) glucose (dipstick) blood (dipstick)

Absolute and change from baseline in clinical safety laboratory tests will be summarized per treatment period. For the Open Label Period results will be presented per inclusion source and

overall, whereas for the Double-Blind Treatment Period the results will be summarized per treatment group and in total.

Urine results (dipstick) will be listed only. The microscopy results will be listed for patients with findings by assessment time point.
In case of any pregnancies these will be listed.

PCS values on laboratory tests will be flagged and summarized for the Open Label Period and Double-Blind Treatment Period as described in section 12.2.

12.4 ECG, Vital Signs and Weight

Results on blood pressure, pulse rate, height and weight will be presented as described in section 12.2.

The results from the central ECG readings will include the RR, PR, QRS, QT, QTc, and QTcF intervals. All of the ECG parameters will be summarized as described in section 12.2.

12.5 Other Safety Endpoints

Tanner staging is a scale for assessing physical development and sexual maturity during onset and progress of puberty. The scale includes 5 stages of pubertal changes (called Tanner stages) separate for males and for females.

Data on Tanner staging and menstrual cycle (age of menarche, length of the menstrual cycle and menstrual cycle regularity) will be listed only.

12.5.1 Columbia-Suicide Severity Rating Scale (C-SSRS) Scores

The C-SSRS was administered:

At screening using *the Baseline Screening version* to capture the baseline result (de novo patients only) and at every scheduled visit thereafter using the *Since last Visit version* to capture the C-SSRS assessments after baseline.

A summary capturing the patients with suicidal ideation, suicidal behaviour

The numbers and percentages of patients with baseline, or post-baseline suicide-related events based on the C-SSRS will be summarized. For the post-baseline assessments, the most severe score (Panel 5) per patient related to suicidal ideation and/or behaviour will be summarized.

The number and percentage of patients with no suicidal ideation or behaviour will be summarized. Patients in this category are those who:

answered ‘no’ to all ideation and behaviour questions; that is, answered ‘no’ to items in Panel 8 related to suicidal ideation and answered ‘no’ to items related to suicidal behaviour.

Panel 5 C-SSRS Scores

C-SSRS Score	Related to:
Wish to be dead	Suicidal ideation
Non-specific active suicidal thoughts	
Active suicidal ideation with any methods (not plan) without intent to act	
Active suicidal ideation with some intent to act, without specific plan	
Active suicidal ideation with specific plan and intent	
Preparatory acts or behaviour	Suicidal behaviour
Aborted attempt	
Interrupted attempt	
Non-fatal suicide attempt	
Completed suicide (only applicable for the post-baseline assessments)	

The C-SSRS scores will be summarized per study period and by visit based on the APES (Open Label Period) or APRS (Double- blind Period) for patients with at least one post-baseline C-SSRS assessment in the respective period, regardless of whether they had a baseline C-SSRS assessment.

Missing C-SSRS scores will not be imputed.

Positive responses to *non-suicidal self-injurious behaviour* will be summarized separately.

For patients with any post-baseline suicidal behaviour (C-SSRS scores of 6 to 10), listings will be provided including all C-SSRS scores for those patients; C-SSRS scores related to suicidal behaviour will be flagged.

In addition, a listing with (highest) suicidal behaviour in the study or a period based on C-SSRS scores for those patients, and all SAEs related to suicidality, will be prepared.

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

The GBI 10-item mania scale is a parent- and patient-rated scale designed to screen for manic symptoms in children and adolescents. The ten items are rated on a 4-point scale from 0 (never or hardly ever) to 3 (very often or almost constantly). The total score ranges from 0 to 30, with higher scores indicating greater pathology. Only the parent-rated scale will be used in this study.

Summary statistics on the total score, absolute scores as well as changes from baseline for each visit as well as the latest assessment will be presented per study period and inclusion source (Open Label Period) and treatment group (Double-Blind Treatment Period).

13 Interim Analyses

No interim analyses will be performed.

14 Sample Size Considerations

The calculation of power is based on a log-rank test for the time to relapse at a one-sided 5% level of significance using SAS Proc Power. A sample size of 80 randomized patients (40 patients per treatment group) will provide at least 80% power to find a difference between vortioxetine and placebo as statistically significant, when expecting cumulative relapse rates at 0.42 and 0.69 over 26 weeks, respectively corresponding to a hazard-ratio of 2.15. The assumption of relapse rates (42% and 69% over 6 months for vortioxetine and placebo, respectively) is based on observed rates from a similarly designed relapse-prevention study of fluoxetine in pediatric patients with MDD who had an adequate response after 12 weeks of acute treatment[1].

It is anticipated that approximately 60% of *de novo* patients enrolled into the Open Label Period will qualify for the Double-Blind Treatment Period. To achieve 80 randomized patients, 150 patients are estimated to be enrolled into the study (depending on number and randomization rate of *de novo* and rollover patients).

15 Statistical Software

The statistical software used will be SAS®, Version 9.4 or later.

16 Details on Data Handling

An LOCF approach will be used for the Double-Blind Treatment Period of the following scales:

CDRS-R, PQ-LES-Q, CGI-I and CGI-S.

The LOCF approach will only be used for the total scores (if applicable). The last usable assessment in the Double-Blind Treatment Period (excluding the randomization assessment) will be used to impute missing values for the LOCF. See also section Section 16.1.3 for the handling of missing data related to COVID-19.

16.1 Assigning Data to Visits

16.1.1 Visit Window

The assessments at the scheduled visits will be used for the analyses. The assessment at the Withdrawal Visit for patients withdrawn from study will be assigned to a nominal visit in the Treatment Period, according to the visit windowing specified in Panel 6. If the assessment at the Withdrawal Visit is assigned to the same visit as an assessment at a scheduled visit, the assessment from the Withdrawal Visit, which by definition always will be the latest, will be used.

Panel 6 Visit Windows

Nominal Visit Number	Nominal Visit Week	Nominal Visit Week (relative to randomization)	Nominal Visit Day	Time Window (days)	Mapping Window (days)
Open Label Period					
V1(screen)			-15	-5 to -15	
V2(baseline)	0	NA	0	-	
V3	1	NA	7	4 to 10	1 to 10
V4	2	NA	14	11 to 17	11 to 21
V5	4	NA	28	25 to 31	22 to 42
V6	8	NA	56	53 to 59	43 to 63
V7	10	NA	70	67 to 73	64 to 77
V8(end of Open Label Period)	12	NA	84	81 to 87	78 to 86
Safety follow-up (end of Open Label, for patients not entering Double-Blind Treatment Period)	16	NA	112	110 to 114	>86
Double-Blind Treatment Period					
V8(baseline of Double-Blind Treatment Period)	12	0	84	81 to 87	78 to 86
V9	13	1	91	88 to 93	87 to 95
V10	14	2	98	95 to 101	96 to 105
V11	16	4	112	107 to 117	106 to 119
V11, CGI-I only*	16	4	112	107 to 117	101 to 133
V12	18	6	126	121 to 131	120 to 140
V13	22	10	154	149 to 159	141 to 168
V13, CGI-I and PQ-LES-Q only*	22	10	154	149 to 159	134 to 182
V14	26	14	182	177 to 187	169 to 196
V15	30	18	210	205 to 215	197 to 224
V15, CGI-I and PQ-LES-Q only*	30	18	210	205 to 215	183 to 238
V16	34	22	238	233 to 243	225 to 252
V17	38	26	266	261 to 271	253 to 280
V18 - Safety follow-up (end of Double-Blind Treatment Period, for patients who completed the Double-Blind Treatment Period)	42	30	294	289 to 299	>281

*Different mapping for these variables only, due to a different schedule of assessments

16.1.2 Safety Variables

For laboratory test values (including estradiol [girls only], and luteinizing hormone [LH], follicle-stimulating hormone [FSH]), vital signs, height, weight, Tanner staging, electrocardiogram (ECG) parameter values, GBI scores (using the 10-item mania subscale), and C-SSRS scores, missing values will be not be imputed.

16.1.3 Covid-19 impact

This study has been carried out during the pandemic of COVID-19. As a result, impact on assessments and the timing of assessments is expected. Data will be collected to evaluate the impact of COVID-19 on the conduct of the study. These data will be presented in listings and summarized if needed.

Missing visits:

Depending on the impact of COVID-19 on data collection, it will be decided whether data from missing visits due to COVID-19 will be imputed using the LOCF approach as well.

Remote visits:

Scheduled and unscheduled visits are allowed to take place remotely via voice call or voice and video call. All the data from scheduled visits recorded remotely will be included in the analysis at the designated visit. Visit windowing as explained in Panel 6 above will be applied to remote visits.

A listing will be presented on the details of remote visits including which visit was conducted remotely, date of remote visit, and whether or not patient reported outcomes and clinician reported outcomes were assessed during the remote visit.

16.2 Handling Missing or Incomplete Dates/Times

16.2.1 IMP Start and Stop Dates

A missing IMP start date will be imputed with the date of baseline of Open Label Period for *De novo* patients, Rollover patients from Study 12709A;
A missing IMP start date will be imputed with the date of baseline of Double-Blind Treatment Period for Rollover patients (remitters) from Study 12712A;
A missing IMP stop date will be imputed using last attended visit date.

16.2.2 Withdrawal Date

Missing withdrawal dates will not be imputed.

16.2.3 Medication Start and Stop Dates

Following rules will be followed to classify recent and concomitant medications for each of the two periods:

Panel 7 Classification of Concomitant Medication

Medication Start Date in period	Medication Stop Date	Classification
Unknown	< Date of first dose of IMP in period	Discontinued prior to first dose of IMP in period
Unknown	≥ date of first dose of IMP in period	Started at or after first dose of IMP in period
< Date of first dose of IMP in period	Unknown	Continued after first dose of IMP in period
≥ date of first dose of IMP in period	Unknown	Started at or after first dose of IMP in period
Unknown	Unknown	Started at or after first dose of IMP in period

16.2.4 Adverse Event Start and Stop Dates

With regard to classification of adverse events with incomplete dates, the following rule will be used:

If the start date is missing for an adverse event and the stop date is prior to the first dose of IMP, the adverse event will be classified as a pre-treatment adverse event. In all other cases of an adverse event with a missing start or stop date, the adverse event will be classified as a TEAE.

For the calculation of duration, missing or incomplete start and/or stop dates will imputed as follows:

If only day is missing in the end date of an AE, the last day of the month will be used, whereas for missing start days the first day of the month will be used.

For ongoing adverse events, the date of the last study contact will be used as the stop date for the adverse event in the calculation of duration. For other adverse events with a missing start or stop date, the duration will not be calculated.

16.3 Data with Multiple Records

16.3.1 Dose Changes in Medication

Dose changes in medications are recorded on multiple rows in the dataset, with different start and stop dates. When classifying medications into periods (prior to IMP, started or continued in treatment period), each dose is considered a separate medication, and the same medication can be assigned to several periods for the same patient. Within a period, multiple entries contribute as a single count.

16.3.2 Changes in Intensity or Seriousness of Adverse Events

Changes in adverse event intensity or seriousness are recorded on multiple rows in the dataset. When classifying adverse events into periods, an event will be assigned to more than one period only if the intensity increases or if a non-serious event becomes serious. An adverse event that changes in intensity or seriousness in a period will contribute to the count of events as a single event.

In summaries of adverse events presented by intensity, the maximum intensity of the adverse event will be used. The maximum intensity is searched for in events with changes, as well as over repeated events based on the preferred term. Adverse events for which information on intensity is missing will be classified as *severe*.

Adverse events for which information on seriousness is missing will be classified as *serious*.

References

1 Emslie GJ, Ventura D, Korotzer A, Tourkodimitris S: Escitalopram in the treatment of adolescent depression: A randomized placebocontrolled multisite trial. J Am Acad Child Adolesc Psychiatry. 2009; 48: 721–729.

Appendix I: Statistical Analysis Plan Authentication and Authorization

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

Study No.: 13546A

SAP date: Final Version 1.0: 09 April 2021

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

Authentication

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Authorization

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Appendix II: Overview of Study Procedures

A) Study Procedures and Assessments – Open Label Period for *de novo* Patients and Rollover Patients from Study 12709A

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

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

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

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

b Applicable only for *De novo* patients.

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

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

e Applicable for patients withdrawn prior or at Visit 8: Safety follow-up should be scheduled approximately 30 days after the last dose of IMP. It can be a telephone contact, unless an SAE has occurred since the last visit or unless there was a clinically significant abnormal safety laboratory test value at the last visit. In such cases, safety follow-up(s) must be scheduled to allow for a medical examination and/or blood sampling. Further safety follow-up visits beyond 30 days may be needed as judged by the investigator (if further safety follow-up visits are performed, these must be recorded in the patient's medical record, and not in the eCRF).

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

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

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

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

j Only for AEs ongoing at Withdrawal and new SAEs.

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

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

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

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

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

B) Study Procedures and Assessments – Double-Blind Treatment Period

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

Recent and concomitant medication	√[e]	√	√	√	√	√	√	√	√	√	
Pregnancy test[g]	√					√				√	
Drug and alcohol screen[h]											

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

a Patients from Study 12712A who are in remission after 8 to 12 weeks of open-label treatment in study 12712A will enter directly into the Randomization Visit of this study.

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

c If the date of a patient visit does not conform to the study plan, subsequent visits should be planned to maintain the visit schedule relative to the Randomization Visit (Visit 8). Consider that the number of days between 2 visits must not exceed the number of days for which the patient has been dispensed IMP.

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

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

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

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

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

i Only for 12712A-patients who rollover into Double Blind phase.

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

Appendix III: SAS Codes

Primary endpoint	Cox regression Model	proc phreg data=xyz; class treatment; strata inclusion; model time_to_relapse*censor(0)=treatment randomization_total_cdrs-r / rl=both ties=exact; run;

Secondary Endpoint(s) – Relapse	Logistic Regression	proc logistic data=xyz;
		class treatment(ref='Placebo') inclusion;
		model relapse=treatment inclusion cdrs_baseline / clodds=pl clparm=pl;
		run;

CDRS-R total score
PQ-LES-Q
CGI-S
CGI-I
	MMRM	proc mixed data=xyz ic method=reml;
		class usubjid treatment(ref='Placebo') week inclusion;
		model Change=treatment week inclusion baseline treatment*week baseline*week / s ddfm=kr;
		repeated week / patient usubjid type=un;
		lsmeans treatment*week / cl alpha=0.05;

CDRS-R total score
PQ-LES-Q
CGI-S
CGI-I
	ANCOVA	proc mixed data=xyz ic method=reml;
		class treatment inclusion;
		model Change=treatment inclusion baseline;
		lsmeans treatment / cl alpha=0.05;