Statistical Analysis Plan

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

Vortioxetine

Study No.: 12712A

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List of Abbreviations and Definitions of Terms

ANCOVA	analysis of covariance
APTS	all-patients-treated set
CI	confidence interval
DMC	Data Monitoring Committee
DSM	Diagnostic and Statistical Manual of Mental Disorders
eCRF	electronic case report form
FAS	full-analysis set
IMP	investigational medicinal product
LOCF	last observation carried forward
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
OC	observed case(s)
OLEXA	baseline extension A
PCS	potentially clinically significant
PYE	patient years of exposure
SAE	serious adverse event
SAS®	statistical software package from the SAS® Institute
SOC	system organ class
TEAE	treatment-emergent adverse event

1 Objectives

1.1 Primary Objective

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

1.2 Secondary Objectives

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

2 Study Design

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

The Baseline Visit, hereafter referred to as OLEXA, of this extension study, will be Visit 12 (Completion Visit) of lead-in Study 12709A or 12710A, see section 18.1.

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

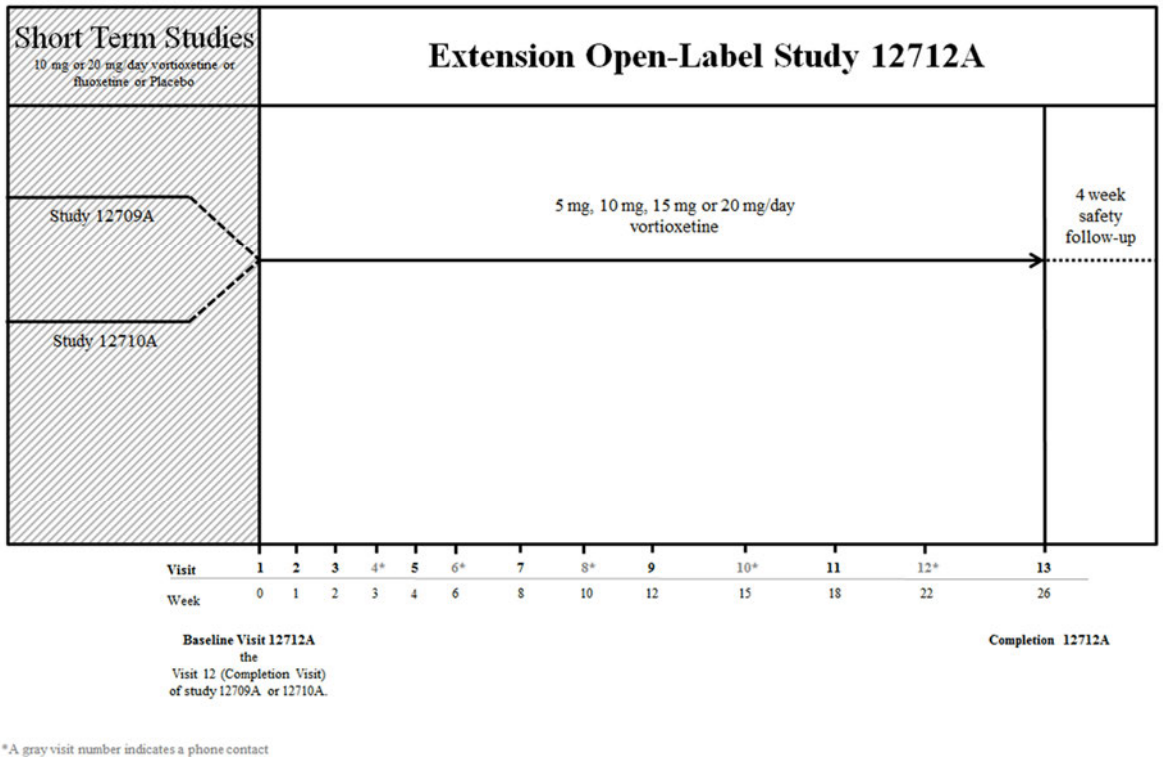
For subset of patients participating in the palatability assessment (patients enrolled in Bulgaria, Estonia, Germany, Latvia, Mexico, Poland, Russia, Serbia, Ukraine, and Colombia), palatability and acceptability of vortioxetine oral drops will be assessed after intake of a single dose (5-20 mg) corresponding to the patient’s current vortioxetine dose (instead of their vortioxetine tablet on that day). The assessment can be done at any visit to the clinic from Week 4 to Week 18 (i.e., at Visits 5, 7, 9, or 11).

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

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

The study design is presented in Panel 1.

Panel 1 Study Design



*A gray visit number indicates a phone contact

3 Endpoints

3.1 Primary Endpoint

Safety and tolerability:

- adverse events (AEs)
- PAERS assesment
- Tanner score
- absolute values and changes from OLEXA in clinical safety laboratory tests, vital signs, height, weight and ECG parameters
- length of menstrual cycle

- potentially clinically significant clinical safety laboratory test values, vital signs, weight, and ECG parameter values relative to OLEXA
- C-SSRS categorisation

3.2 Secondary Endpoints

Depressive symptoms:
- change from OLEXA to Week 26 in CDRS-R total score

Global Clinical Impression:
- change from OLEXA to Week 26 in CGI-S score
- CGI-I score at Week 26. The assessment of the CGI-I should be in reference to Baseline A in the lead-in studies. The Baseline A lies 12 weeks prior to OLEXA.

Cognitive function:

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

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

Functionality:
- change from OLEXA to Week 26 in CGAS score
- change from OLEXA to Week 26 in PedsQL VAS

Palatability and acceptability:
- absolute value of palatability and acceptability item scores

4 Analysis Sets

The following analysis sets will be used to analyse and present the data:
- all-patients-treated set (APTS) – all patients who took at least one dose of vortioxetine in 12712A.
- full-analysis set (FAS) –all patients in the APTS with valid OLEXA assessment and at least one valid post-OLEXA assessment of the CDRS-R total score.

The safety analyses will be based on the APTS. The efficacy analyses will be based on the FAS.

The patients and data will be classified into the analysis sets according to the definitions above after the study database has been released.

5 Descriptive Statistics

Unless otherwise specified, summary statistics (n, arithmetic mean, standard deviation [SD], 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.

Furthermore, and unless otherwise specified, the data will be summarised for all patients, and by lead-in study and by lead-in treatment, respectively.

Lastly, and unless otherwise specified, data listings will include site, lead-in study, patient number, sex, age, race, and weight at OLEXA.

6 Patient Disposition

6.1 Summary of Patient Disposition

Patient disposition will be summarized for all patients and by lead-in studies, and will include the number of patients in each analysis set defined in chapter 4, and the number of patients in the APTS who completed or withdrew from study.

6.2 Withdrawals

The number of patients who withdrew will be summarized for all patients, by lead-in studies and by lead-in treatment, respectively, and by primary reason for withdrawal and all reasons for withdrawal.

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

Kaplan-Meier plots of time to withdrawal will be presented for all patients, by lead-in studies and by lead-in treatment, respectively. The time will be calculated from the date of first dose of IMP in the current trial to the date of completion or withdrawal. Patients who completed study will be regarded as censored.

All tables, graphs, and listings will be based on the APTS.

7 Demographics and Baseline Characteristics

Demographics (sex, age, race); baseline (OLEXA) characteristics (height, weight, BMI and Tanner score); and baseline efficacy variables will be summarized for all patients and by lead-in study and by lead-in treatment when applicable.

Demographics and baseline characteristics will be summarized based on the APTS, and baseline efficacy variables will be summarized based on the FAS.

8 Recent and Concomitant Medication

Recent and concomitant medication will be coded using the *WHO Drug Dictionary* (WHO-DDE).

Medications will be classified according to the start and stop time and summarized by anatomical therapeutic chemical (ATC) code, generic drug name, for all patients and by lead-in study and by lead-in treatment, respectively:

- concomitant medication continued from lead-in studies
- concomitant medication started at or after Visit 1 of study 12712A

The tables will be based on the APTS.

9 Exposure and Compliance

Exposure (days) to IMP will be calculated as:

- Date of last dose of IMP – Date of first dose of IMP in study 12712A + 1

Exposure to IMP will be summarized for all patients and by lead-in study and by lead-in treatment using descriptive statistics, and, 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.

In addition, exposure to IMP will be categorized in intervals (1 – 14 days, 15 – 35 days, 36 – 70 days, 71 – 105 days, 106 – 140 days, 141 – 182 days and >182 – days) and summarized by lead-in study and by lead-in treatment. Missing values of exposure will not be imputed.

Non-compliant days are days on which no IMP has been taken, less than the full dose of IMP has been taken, or more than the full dose of IMP has been taken.

Compliance (%) with IMP will be calculated as:

- (date of Completion/Withdrawal Visit – date of Visit 1 – number of days of non-compliance)/ (date of Completion/Withdrawal Visit – date of Visit 1) × 100%

where the number of non-compliant days is defined as the sum of all non-compliant days in the treatment period.

Compliance with IMP will be categorized as "≤80% compliant" or ">80% compliant". The number and percentage of patients in each category will be summarized by lead-in study and lead-in treatment, respectively, by visit interval and for the entire study.

The mean and modal dose of IMP will be calculated for each patient and summarised (mean, median, and lower and upper quartiles for the mean and counts for the modal dose). IMP dose level at the completion or withdrawal of the study will be summarized. Number and percentage of patients who reached highest and lowest dose level will be summarised. In addition, number and percentage of patients with each dose level will be summarised by visit.

Number of patients who exposed to oral drops will be summarized.

Exposure and compliance will be summarized based on the APTS.

10 Efficacy

10.1 Overview of Planned Efficacy Analyses

An overview of all planned efficacy analyses is provided in Panel 2.

Panel 2 Overview of Planned Efficacy Analyses

	Endpoints	Description	Type
Depressive Symptoms	Change from OLEXA to week 26 in CDRS-R[1] total score		1
	Remission	Defined as CDRS-R ≤ 28	2
	Relapse	Defined as CDRS-R value ≥ 40	2
Global Clinical Impression	Change from OLEXA to week 26 in CGI-S score		1
	CGI-I score at week 26	In reference to Baseline A in the lead-in study	1
Cognitive Function	Change from OLEXA to week 26 in BRIEF (parent) using Global Executive Composite Score	For children (aged 7-11 years at OLEXA), 72 items are included in GEC	1
	Change from OLEXA to week 26 in BRIEF (parent) using Metacognition Index Score	For children (aged 7-11 years at OLEXA), 44 items are included in MI	1
	Change from OLEXA to week 26 in BRIEF-SR using Global Executive Composite Score	For adolescents (aged 12-18 years at OLEXA), 80 items are included in GEC	1
	Change from OLEXA to week 26 in BRIEF-SR using Metacognition Index Score	For adolescents (aged 12-18 years at OLEXA), 42 items are included in MI	1

Functionality	Change from OLEXA to week 26 in CGAS[2] score	1
	Change from OLEXA to week 26 in PedsQL[3] VAS score	1

1 = continuous; 2 = binary

10.2 General Efficacy Analysis Methodology

Unless otherwise specified, all the efficacy analyses will be based on the FAS.

All the tables and graphs will be presented for all patients and by lead-in studies and by lead-in treatments, respectively.

Analysis of the endpoints subjected to inferential statistical methods will be presented with 95% CIs.

10.3 Analysis Methodology for the Secondary Endpoints

10.3.1 Analysis of the Secondary Endpoints

Absolute values and change from OLEXA in the continuous efficacy variables, except CGI-I, will be summarized descriptively. Absolute values of CGI-I will be summarized.

CDRS-R remission and relapse during treatment period will be summarized descriptively by visit.

For the continuous efficacy variables CDRS-R and CGI-S, change from OLEXA will be analyzed using a restricted maximum likelihood (REML)-based Mixed Model Repeated Measurements (MMRM) approach, using all available observations until completion or withdrawal.

The model will include country, lead-in study interacting with week as factors, and baseline score interacting with week as covariate. An unstructured covariance structure will be used to model the within-patient errors and the Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

For the CDRS-R total score the primary analyses will be also presented by lead-in study by lead-in treatment.

In addition, ANCOVA models will be fitted for CDRS-R and CGI-S, including country and lead-in study as factors and baseline score as a covariate, the analysis will be conducted by visit, based on OC and LOCF.

11 Palatability and Acceptability

Palatability and acceptability assessments were performed in 10 countries only.

Each assessment contains 7 questions, 4 on palatability and 3 on acceptability. Palatability assessment includes taste, mouthfeel, aftertaste and smell, based on 5-points hedonic scales. Acceptability assessment includes acceptability of the taste, ease of use and willingness to take the drops every day, based on 3-points scales.

Palatability and acceptability item scores will be summarized using descriptive statistics.

The oral drops were considered acceptable if the mean hedonic scores were ≤3 for each aspect of palatability (taste, aftertaste, smell and mouthfeel), ***and*** <60% of participants responded "no" to each of the 3 questions regarding acceptability.

Panel 3 Palatability and acceptability

Endpoint	Description	Type
Palatability and acceptability	Absolute value of palatability	1
	Absolute value of acceptability item scores	1

1 = continuous; 2 = binary

12 Safety

12.1 Adverse Events

12.1.1 General Methodology for Adverse Events

Unless otherwise specified, tables, graphs, and listings will be based on the APTS.

All the tables will be presented for all patients and by lead-in study and by lead-in treatment, respectively, unless otherwise specified.

Tables by preferred term and tables by system organ class (SOC) and preferred term will be sorted in descending order by the overall percentage of patients.

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 events. For sex-specific preferred terms, the denominator in the % calculations will be the number of patients of that sex. Sex-specific preferred terms will be marked in the summaries.

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, lead-in study, lead-in treatment, patient number, and adverse event start date, and include preferred term, investigator term, adverse

event start date, days since first dose of IMP, duration of the adverse event, date of death, action taken, causality, intensity, seriousness, and outcome. For adverse events that change in intensity, each intensity will be included.

12.1.2 Handling of Adverse Events

12.1.2.1 Adverse Events Changing in Intensity or Seriousness

In ADaM data, changes in intensity are included as additional records (rows) to the originally reported adverse events.

If an adverse event changes from non-serious to serious, in addition to the originally reported adverse event start date, the start date for the seriousness is reported. In ADaM data, adverse events that change from non-serious to serious will be included as two records, one with seriousness non-serious and one with seriousness serious.

12.1.2.2 Coding of Adverse Events

Adverse events will be coded using MedDRA, Version 22 or later.

12.1.2.3 Classification of Adverse Events

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

- *Lead-in adverse event* – an adverse event starts before visit 1 in 12712A and ongoing from (= with start date in) lead-in study 12709A or 12710A
- *treatment-emergent adverse event* – an adverse event that starts or increases in intensity/or seriousness at or after visit 1 of study 12712A

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

12.1.2.4 Assigning Adverse Event Records to an Analysis Phase

All records for an adverse event will be assigned to an analysis phase. The analysis phase will determine how an adverse event record is reported, and an adverse event may be reported in more than one analysis phase insofar as it worsens.

For further details, see Data Handling Plan.

12.1.3 Summary of All Adverse Events

All adverse events will be listed, including a flag for TEAE.

An overview of the PYE, numbers, and percentages of patients with TEAE, serious adverse events (SAEs), or adverse events leading to withdraw, and of patients who died will be

provided for APTS. For TEAE, SAEs, and adverse events leading to withdrawal, the total number of events will be included.

12.1.4 Lead-in Adverse Events

Lead-in adverse events will be summarized by preferred term.

12.1.5 Summary of Treatment-emergent Adverse Events

The following summaries will be provided for the APTS:
- TEAE by SOC and preferred term
- TEAE by preferred term
- TEAE with an incidence > 2% and 5% by preferred term
- Causally related TEAE by SOC and preferred term
- TEAE by intensity (*mild*/*moderate*/*severe*), and preferred term
- Causally related TEAE by intensity and preferred term

12.1.6 Deaths

All the adverse events in patients who died will be listed.

12.1.7 Serious Adverse Events

All the SAEs will be listed.

Treatment-emergent SAEs for the APTS will be summarized by:
- SOC and preferred term
- Preferred term

12.1.8 Adverse Events Leading to Withdrawal

All the adverse events leading to withdrawal will be listed.

TEAE leading to withdrawal will be summarized by:
- SOC and preferred term
- preferred term

12.1.9 Adverse Events Related to Tolerability

Incidence and prevalence rates in every four-week interval will be presented for nausea based on the APTS for events with complete start and stop dates.

Incidence will be defined as the number of patients with a new event in the specified time interval. The denominator in each interval will be the number of patients without the event at

the start of the interval plus the number of patients with an ongoing event at the start of the interval for which the event stops before the end of the interval.

Prevalence will be defined as the number of patients with the event at the start of the interval or who have the event during the interval. The denominator will be the number of patients at the start of the interval.

12.1.10 Adverse Events of Special Interest

Treatment-emergent nausea (preferred term), vomiting (preferred term), insomnia (defined below), and sexual dysfunction (defined below) will be summarised. TEAE related to the musculoskeletal SOC will be summarized.

Insomnia related adverse events and sexual dysfunction related adverse events are defined in Panel 4 and Panel 5.

Panel 4 Insomnia related adverse events searches

Preferred term
Hyposomnia
Initial Insomnia
Insomnia
Middle Insomnia
Poor Quality Sleep
Sleep Disorder
Terminal Insomnia
Dyssomnia

Panel 5 Sexual dysfunction related adverse events searches

Preferred Term		
Anorgasmia	Genital hypoaesthesia	Kluver-Bucy syndrome
Ejaculation delayed	Persistent genital arousal disorder	Libido increased
Ejaculation failure	Adrenal androgen deficiency	Luteinising hormone deficiency
Female orgasmic disorder	Adrenal androgen excess	Masochism
Female sexual arousal disorder	Adrenogenital syndrome	Mauriac syndrome
Libido decreased	Albright's disease	Nocturnal emission
Loss of libido	Compulsive sexual behaviour	Painful ejaculation
Male orgasmic disorder	Delayed puberty	Painful erection
Orgasm abnormal	Erection increased	Paraphilia
Orgasmic sensation decreased	Excessive masturbation	Precocious puberty
Premature ejaculation	Excessive sexual fantasies	Priapism
Vulvovaginal dryness	Exhibitionism	Primary ciliary dyskinesia
Disturbance in sexual arousal	Fertility increased	Primary hypogonadism
Dyspareunia	Fetishism	Pseudoprecocious puberty
Ejaculation disorder	Follicle stimulating hormone deficiency	Psychosexual disorder
Erectile dysfunction	Frotteurism	Pubertal failure
Female sexual dysfunction	Gender dysphoria	Retrograde ejaculation
Genito-pelvic pain/penetration disorder	HAIR-AN syndrome	Sadism
Inadequate lubrication	Hyperandrogenism	Spontaneous ejaculation
Libido disorder	Hypergonadism	Spontaneous penile erection
Male sexual dysfunction	Hyperoestrogenism	Transvestism
Organic erectile dysfunction	Hyperprogesteronism	Voyeurism
Psychogenic erectile dysfunction	Hypersexuality	Paedophilia
Sexual aversion disorder	Hypogonadism	Post-sterilisation regret
Sexual dysfunction	Hypoprogesteronism	
Sexual inhibition	Incomplete precocious puberty	

The second and third column represent the preferred terms that has been added based on a post-marketing request by EMA.

12.2 General Methodology for Other Safety Data

Unless otherwise specified, tables, graphs, and listings will be based on the APTS, and the tables will be presented for all patients and by lead-in study and by lead-in treatment.

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 change from baselines (baseline at randomisation in lead-in study and OLEXA), will be presented by visit and for the last assessment. All available post-OLEXA assessments will be included in the identification of the last assessment.

The number and percentage of patients with at least one 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 definition will be provided by H. Lundbeck and are stated in Appendix IV.

12.3 Clinical Safety Laboratory Test Data

12.3.1 Data Presentation

The clinical safety laboratory test values will be presented in conventional and/or Système International (SI) units.

12.3.2 Urine analysis

For urine dipsticks, for which the results are categorical values (for example, negative, trace, 1+, 2+), the number and percentage of patients will be summarised for each test by visit.

The microscopy results will be listed for patients with findings by assessment time point.

12.3.3 Potential Drug-induced Liver Injury (DILI)

Signals of DILI will be assessed according to the FDA guideline[4] using the following criteria:

- alanine aminotransferase (ALT) or AST >2×-, >3×-, 5×-, 10×-, or 20×ULN
- total bilirubin (BILI) >2×ULN
- alkaline phosphatase (ALP) >1.5×ULN

- ALT or AST >3×ULN and BILI >1.5× or >2×ULN

In addition, assessment time points for patients for whom Hy's Law is potentially fulfilled will also be flagged in the listing (pHYL):

- ALT or AST >3×ULN AND
- BILI >2xULN AND
- ALP<2xULN

In the summaries, each patient should be counted only once using the maximum assessment, or the most severe for the combined criteria.

Patients fulfilling any of the individual criteria (ALT/AST, ALP, or BILI) will be listed, and the listing will include all available ALT, AST, BILI, and ALP, BILI, EOSLE, and GGT values (absolute and normalised), sorted by assessment date in ascending order.

Evaluation of potential Drug-Induced Serious Hepatotoxicity (eDISH) will also be done by plots. Scatter plots of maximum ALT/AST versus maximum BILI will be presented. The criteria for the individual tests will be considered separately (that this means that the maximum of ALT/AST and the maximum BILI may not occur at the same assessment timepoint). The values will be normalised by the ULN (unit xULN) and the X-and Y-axes will be on the log scale. The plot will include a reference line for ALT/AST values >3xULN, and a reference line for BILI values>2xULN. Four quadrants are defined by the reference lines, where the right upper quadrant being the most specific indicator for a drug's potential for causing serious liver injury (Hy's law quadrant).

Subject line plots with values-by-time for ALT, AST, ALP, BILI, GGT and EOSLE (overlaid in the same plot) will be generated for patients with ALT/AST > 3xULN. The test values will be normalised by the ULN (unit xULN) and the Y-axis will be on the log scale. All assessments will be included, and the time will be days since first IMP. Reference lines for the day of first-and last IMP will be included. If there is more than one assessment at the same time point for a test, the maximum value will be used.

For further details, see Data Handling Plan.

12.3.4 Changes in Fasting and non-fasting Lipid and Glucose Concentrations

Shift tables displaying the change in classification for fasting and non-fasting lipids and fasting and non-fasting glucose from OLEXA to any post-baseline visit will be provided for each test and include the numbers and percentages of patients.

12.4 Vital Signs and Weight

Descriptive statistics for the vital sign parameters will be presented by visit and the last assessment in the Period.

12.5 ECGs

Shift tables displaying shifts from normal to abnormal ECG findings from OLEXA to the Withdrawal/Completion Visit will be provided and include the numbers and percentages of patients.

12.6 Other Safety Endpoints

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

The C-SSRS was assessed after OLEXA using the *Since Last Visit Version*

The numbers and percentages of patients with suicide-related events based on the C-SSRS will be summarized for each category of suicidal ideation (items 1-5) and suicidal behaviour (items 6-10). The most severe score (Panel 6) 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 1 to 5 (related to suicidal ideation) and answered 'no' to items 6 to 10 (related to suicidal behavour)

Panel 6 C-SSRS Scores

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

In the C-SSRS, non-suicidal self-injurious behaviour is captured as a different behaviour; patients may have reported non-suicidal self-injurious behaviour in addition to suicidal ideation/behaviour. Positive responses to non-suicidal self-injurious behaviour will be summarised separately.

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

All assessments will be regarded as valid for C-SSRS.

Missing C-SSRS scores will not be imputed.

12.6.2 Paediatric Adverse Event Rating Scale (PAERS)

Note, all assessments will be regarded as valid for PAERS[5] (that is, the criteria that assessment date-date of last IMP must be ≤7 days will not be applied).

For each item, a severity score will be derived where the analysis value is defined as:

- If *Recently Present=No*, the analysis value will be *Absent*.
  Otherwise, the analysis value will be the reported Severity (*Mild*, *Moderate*, *Severe*, or *Extreme*)

The assessments for the PAERS will be prepared according to the description in the Data Handling Plan. For each item 1 to 43, the following parameters will be derived for each analysis phase following a baseline (all assessments within a phase will be included in the evaluation):

- *Worst severity score*:
  Worst severity score of the item (analysis value will be the worst severity)
- *Worsening of severity score compared to baseline*:
  Worsening of the item compared to OLEXA (analysis value will be 'Yes' or 'No')

If a patient had a worsening of an item, all original assessments at the OLEXA will be listed.

Also graphical presentations of the PAERS will be done.

Item 44 and 45 will only be listed, based on APES.

For further details, see Data Handling Plan.

12.6.3 Tanner Evaluation

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

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

Shift tables for the Tanner evaluation displaying shifts from OLEXA to withdrawal/ completion will be provided by sex, lead-in treatment and lead-in study, and include the numbers and percentages of patients.

12.6.4 Menstrual Cycle

Age of menarche, length of the menstrual cycle and menstrual cycle regularity will be summarized for girls by lead-in study and lead-in treatment.

12.6.5 Remote Visits

Patients with remote visits will be listed.

13 Pharmacokinetic/Pharmacodynamic Analyses

A separate analysis plan for pharmacokinetic/pharmacodynamic analyses will be prepared by Quantitative Pharmacology, H. Lundbeck A/S.

14 Interim Analyses

No interim analyses for efficacy are planned.

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

A CRO is contracted to perform the analyses for the DMC.

15 Sample Size Considerations

No sample size calculation has been performed for the present study, which just includes patients who have completed the studies 12709A or 12710A and are eligible for enrolment for this study.

It is expected that some 15-20% of the 1200 patients randomised to the lead-in studies will drop out these and that a maximum of 85% of these “lead-in completers” are expected to accept to continue into this extension study. This gives approximately 850 patients.

16 Statistical Software

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

17 Changes to Analyses Specified in the Protocol

The following changes have been made as compared to the latest version of the protocol:

- C-SSRS categorisation has been updated and will no longer include C-CASA.
- Treatment emergent adverse events (TEAE) in 12712A is defined as an adverse event that starts or increases in intensity or seriousness after visit 1 of study 12712A.
- The analyses regarding time to first relapse and time to first loss of remission have been removed
- The analysis of random slope and intercept has been removed

18 Details on Data Handling

18.1 Definition of Baseline and Period

OLEXA will be Visit 1 in 12712A for assessments *not* included in 12709A or 12710A. For assessments *included* study in 12709A or 12710A, Visit 12 in either 12709A or 12710A will otherwise serve as OLEXA.

No baseline in 12712A is defined for the C-SSRS.

18.2 Derived Variables

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

BRIEF[6] (parent) form was used for children aged 7-11 and contains 86 items, the BRIEF-SR (self-reported) form was used for adolescents aged 12-18 and contains 80 items. Items are rated on a 3-point scale, with 1 corresponding to Never, 2 corresponding to Sometimes, and 3 corresponding to Often. These items cover 8 non-overlapping clinical scales (Panel 7). For BRIEF (parent) form, only the first 72 items will be included in the clinical scales.

The clinical scales combine to form two Indexes, the Behavioural Regulation Index (BRI) and the Metacognition Index (MI), and one composite summary score, the Global Executive Composite (GEC), which is a summary score that incorporates all eight clinical scales.

For BRIEF (parent), the Metacognition Index (MI) is comprised of Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor scales. For BRIEF-SR, the Metacognition Index (MI) is comprised of Working Memory, Plan/Organize, Organization of Materials, and Task Completion.

For each clinical scale, the scale raw score is calculated as the sum of its item scores, and then converted to T-score based on the conversion table. The index (BRI and MI) scores are calculated as the sum of the corresponding scale T-scores, and, was converted to index T-

scores based on the conversion table. GEC score was then calculated as the sum of the index scores and converted to T scores based on the conversion Table.

If the total number of missing items that contribute to the calculation of total score (GEC) is greater than 14, then the total score will not be calculated. Similarly, if more than two items that contribute to the calculation of a scale score are missing, then the scale score should not be calculated for that scale. Otherwise, missing responses for one or two items that contribute to a scale score should be assigned a score of 1 when calculating the scale score.

If a patient used a wrong form at some visit, data from this visit would be excluded from the analysis. If a patient used a wrong form at the baseline visit, this patient will be excluded from the analysis of BRIEF scales.

Panel 7 Clinical Scales of BRIEF

BRIEF (Parent)		BRIEF-SR	
Clinical Scales	**Number of items**	**Clinical Scales**	**Number of items**
Inhibit	10	Inhibit	13
Shift	8	Shift	10
Emotional Control	10	Emotional Control	10
Initiate	8	Monitor	5
Working Memory	10	Working Memory	12
Plan/ Organize	12	Plan/ Organize	13
Organization of Materials	6	Organization of Materials	7
Monitor	8	Task Completion	10

18.3 Missing items on Rating Scales

The general rule when single-item scores are missing is that the total score will be calculated as the expected sum of items given non-missingness using SAS function CEIL: [(sum of non-missing items) × (total number of items) / (number of non-missing items)].

If more than 20% of the items for a rating scale or subscale are missing, the total score or subscore will be set to missing. Since most rating scales will be done as an Electronic clinical outcome assessment (eCOA) the number of missing items should be very limited.

The application of the above rules can be found in Panel 8.

Panel 8 Maximum Number of Missing Items on Rating Scales

Variable	Description	Maximum Number of Missing Items
CDRS-R TOT	CDRS-R total score	3
PEDSQL VAS TOT	PEDSQL VAS total score	1
BRIEF[a]	Global Executive Composite	14
BRIEF - SR	Global Executive Composite	14

a BRIEF SCALES: refer to section 18.2.1

18.4 Identifying rows for analysis

Assessments at Withdrawal Visits will be assigned to a target day according to Data Handling Plan. Unscheduled scale assessments will be windowed in the corresponding way as withdrawal assessments but after any assessments from Withdrawal Visits has been windowed.

Before protocol amendment (PA2), CDRS-R was only assessed at week 0, 12 and 26, however, the same visit window will be applied.

Analysis day will then be mapped based on target day. Analysis week will be analysis day/7.

18.5 Handling Missing or Incomplete Dates/Times

18.5.1 IMP Start and Stop Dates

In evaluation of valid efficacy and safety assessments (assessment is considered valid if assessment date-date of last IMP ≤7 days), a missing date of last IMP will be imputed by the latest attended Visit in the study before the safety follow-up.

Exposure with missing IMP start or stop date will not be calculated.

18.5.2 Withdrawal Date

For withdrawn patients with a missing Withdrawal Visit, the date of the last attended visit will be used in the calculation of time to withdrawal from study.

18.5.3 Medication Start and Stop Dates

In order to assign all medications to an analysis start-and stop phase, missing or incomplete start-or stop dates will be imputed. Ongoing medications at the end of a study will not be assigned a stop phase in that study.

No duration will be calculated for medications with imputed start-or stop date, or for ongoing medications.

For further details, see Data Handling Plan.

18.5.4 Adverse Event Start and Stop Dates

Incomplete adverse start dates will be imputed before handling of incomplete dates for change in intensity or seriousness.

For further details, see Data Handling Plan.

References

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3 Sherman SA, Eisen S, Burwinkle TM, Varni JW. The PedsQL™ present functioning visual analogue scales: preliminary reliability and validity. Health and Quality of Life Outcomes 2006; 4: 75.

4 United States Food and Drug Administration (US FDA). Guidance for Industry: Drug-induced liver injury: premarketing clinical evaluation. July 2009.

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6 Gioia GA, Isquith PK, Steven GC, Guy SC and Kenworthy L. Behavior Rating Inventory of Executive Function, Professional Manual; version 2000.

Appendix I
Statistical Analysis Plan
Authentication and Authorization

Statistical Analysis Plan
Authentication and Authorization

Study title:	Long-term, open-label, flexible-dose, extension study of vortioxetine in child and adolescent patients with Major Depressive Disorder (MDD) from 7 to 18 years of age
Study No.:	12712A
SAP date:	2 May 2022

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

Authentication

[redacted]

Authorization

[redacted]

Appendix II
Study Flow Chart

Study Flow Chart

Table 1 Study procedures and Assessments

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

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

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

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

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

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

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

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

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

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

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

j Females >10 years of age or female patients at lower age judged by the investigator to be of childbearing potential. Additional pregnancy tests during the study will be performed according to local requirements.

Females <11 years will be tested using a urine hCG test and females >11 years will be tested using a blood hCG test.

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

Appendix III
SAS® Code

SAS® Code

MMRM for analysing continuous endpoints

```
proc mixed noclprint data=xyz ic method=reml;
class usubjid country week lead-in _study;
model y=baseline country week lead-in_study*week baseline*week / s ddfm=kr;
repeated week/subject=usubjid type=un;
run;
```

Appendix IV
PCS Criteria

PCS Criteria

Table 2 Lundbeck PCS Criteria for Clinical Safety Laboratory Tests

Laboratory Test	CDISC Term	Unit	PCS LOW	PCS HIGH
Haematology / Coagulation				
B-haemoglobin	HGB	g/dL	≤ 9.5 (women); ≤ 11.5 (men)	≥ 16.5 (women); ≥ 18.5 (men)
B-erythrocytes (red cell count)	RBC	x 10E12/L	≤ 3.5 (women); ≤ 3.8 (men)	≥ 6.0 (women); ≥ 7.0 (men)
B-haematocrit (packed cell volume)	HCT	V/V	≤ 0.32 (women); ≤ 0.37 (men)	≥ 0.50 (women); ≥ 0.55 (men)
B-MCV (mean cell volume)	MCV	fL	≤ 0.8 x LLN	≥ 1.2 x ULN
B-total leucocyte (white cell count)	WBC	x 10E9/L	≤ 2.8	≥ 16
B-neutrophils/leucocytes	NEUTLE	%	≤ 20	≥ 85
B-eosinophils/leucocytes	EOSLE	%		≥ 10
B-basophils/leucocytes	BASOLE	%		≥ 10
B-lymphocytes/leucocytes	LYMLE	%	≤ 10	≥ 75
B-monocytes/leucocytes	MONOLE	%		≥ 15
B-thrombocytes (platelet count)	PLAT	x 10E9/L	≤ 75	≥ 600
P-INR (prothrombin ratio)	INR	Ratio		≥ 2.0
B-prothrombin time	PT	Sec		≥ 18
Liver				
S-aspartate aminotransferase	AST	IU/L		≥ 3 × ULN
S-alanine aminotransferase	ALT	IU/L		≥ 3 × ULN
S-bilirubin	BILI	µmol/L		≥ 34
S-bilirubin, direct	BILDIR	µmol/L		≥ 12
S-bilirubin, indirect	BILIND	µmol/L		≥ 22
S-alkaline phosphatase	ALP	IU/L		≥ 3 × ULN
S-gamma glutamyl transferase	GGT	IU/L		≥ 200
S-alpha-glutathione S-transferase (alpha-GST)	GSTAL	µg/L		≥ 20
Kidney				
S-creatinine	CREAT	µmol/L		≥ 1.5 x ULN
B-urea nitrogen (BUN)	BUN	mmol/L		≥ 11
S-uric acid (urate)	URATE	µmol/L		≥ 510 (women); ≥ 630 (men)
Electrolytes				
S-sodium (natrium)	SODIUM	mmol/L	≤ 125	≥ 155
S-potassium (kalium)	K	mmol/L	≤ 3.0	≥ 6.0
S-calcium	CA	mmol/L	≤ 1.8	≥ 3.0
S-chloride	CL MG	mmol/L	≤ 90	≥ 117
S-magnesium	PHOS	mmol/L	≤ 0.6	≥ 1.3
S-phosphate (phosphorus, (inorganic)	BICARB	mmol/L	≤ 0.65	≥ 1.95
S-bicarbonate		mmol/L	≤ 12	≥ 38

Endocrine / Metabolic				
B-glucose, non-fasting/unknown	GLUC	mmol/L	≤ 3.4	≥ 9.4
B-glucose, fasting	GLUC	mmol/L	≤ 3.0	≥ 6.0
S-glucose, non-fasting/unknown	GLUC	mmol/L	≤ 3.9	≥ 11.1
S-glucose, fasting	GLUC	mmol/L	≤ 3.5	≥ 7.0
B-glycosylated haemoglobin, fasting	HBA1C	%		≥ 6.5
S-prolactin	PROLCTN	mIU/L		≥ 1350
S-thyrotropin/TSH	TSH	mIU/L	≤ 0.3	≥ 5.5
S-protein (total)	PROT	g/L	≤ 45	≥ 95
S-albumin	ALB	g/L	≤ 27	
Lipids				
S-cholesterol total, non-fasting/unknown	CHOL	mmol/L		≥ 7.8
S-cholesterol total, fasting	CHOL	mmol/L		≥ 6.2
S-triglycerides, non-fasting/unknown	TRIG	mmol/L		≥ 5.65
S-triglycerides, fasting	TRIG	mmol/L		≥ 4.2
S-LDL cholesterol, non-fasting/unknown	LDL	mmol/L		≥ 5.3
S-LDL cholesterol, fasting	LDL	mmol/L		≥ 4.9
S-HDL cholesterol, non-fasting/unknown	HDL	mmol/L	≤ 0.8	
S-HDL cholesterol, fasting	HDL	mmol/L	≤ 0.9	
Cardiac / Skeletal/Muscle				
S-creatine kinase (total)	CK	IU/L		≥ 400 (women); ≥ 750 (men)
S-creatine kinase MB isoenzyme	CKMB	µg/L		≥ 8.5 or
	CKMBCK	%		≥ 3.5% of total CK
S-lactate dehydrogenase (total)	LDH	IU/L		≥ 750
S-troponin I	TROPONI	µg/L		≥ 1.5
S-troponin T	TROPONT	µg/L		≥ 0.4
Infection				
S-C-reactive protein	CRP	mg/L		≥ 25
S-globulin (total)	GLOBUL	g/L	≤ 15	≥ 55
Urine				
Urinary pH	PH		≤ 4	≥ 9

S=serum; B=whole blood; U=urine

Table 3 Lundbeck PCS Criteria for ECG Parameters

ECG Parameter	CDISC Term	Unit	PCS LOW	PCS HIGH
Absolute Time Interval				
PR interval	PRMEAN	Msec		≥ 260
QRS interval	QRSDUR	Msec		≥ 150
QT interval	QTMEAN	Msec		≥ 500
Derived Time Interval				
Heart rate	HRMEAN	beats/min	< 50 and decrease ≥ 15	≥ 120 and increase ≥ 15
QTcB interval	QTCB	Msec	< 300	> 500 or increase > 60
QTcF interval	QTCF	Msec	< 300	> 500 or increase > 60
RR interval	RR	Mses	<500	>1200

Increase/decrease is relative to the baseline value

Table 4 PCS Criteria for Vital Signs, Weight/BMI, and Waist Circumference

Parameter	CDISC Term	Unit	PCS LOW	PCS HIGH
Waist circumference	WSTCIR	Cm	decrease ≥ 7%	increase ≥ 7%
Weight	WEIGHT	Kg	decrease ≥ 7%	increase ≥ 7%
Body Mass Index	BMI	kg/m2	decrease ≥ 7%	increase ≥ 7%
Pulse rate, supine/sitting/unknown	PULSE	beats/min	< 50 and decrease ≥ 15	≥ 120 and increase ≥ 15
Diastolic blood pressure, supine/sitting/unknown	DIABP	mmHg	≤ 50 and decrease ≥ 15	≥ 105 and increase ≥ 15
Systolic blood pressure, supine/sitting/unknown	SYSBP	mmHg	≤ 90 and decrease ≥ 20	≥ 180 and increase ≥ 20
Orthostatic systolic blood pressure[a]	OBP	mmHg	≤ -30	
Orthostatic pulse rate[a]	OPR	beats/min		≥ 20
Temperature[b]	TEMP	°C	decrease ≥ 2	≥ 38.3 and increase ≥ 2

Increase/decrease is relative to the baseline value

[a] For definition of orthostatic blood pressure and pulse rate, see text after Table 3

[b] Note, the diurnal variation may affect the temperature. Morning temperature is lower

Table 5 PCS Criteria for Vital Signs (Continued)

	Normal Range (mm Hg)	PCS High (mm Hg)	PCS Low (mm Hg)
Systolic blood pressure, supine	7-9 years: 80-115 10-12 years: 85-120 13-17 years: 90-130 ≥ 18 years: 110-140	≥ 140 and increase ≥ 20 ≥ 140 and increase ≥ 20 ≥ 140 and increase ≥ 20 ≥ 180 and increase ≥ 20	≤ 90 and decrease ≥ 20
Diastolic blood pressure, supine	7-9 years: 40-75 10-12 years: 40-80 13-17 years: 40-80 ≥ 18 years: 51-85	≥ 90 and increase ≥ 15 ≥ 90 and increase ≥ 15 ≥ 90 and increase ≥ 15 ≥ 105 and increase ≥ 15	≤ 50 and decrease ≥ 15