NEW RESEARCH

Q7Q8 Vortioxetine for Major Depressive Disorder in Adolescents: 12-Week Randomized, Placebo-Controlled, Fluoxetine-Referenced, Q1Q2 Fixed-Dose Study

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Objective: To evaluate the efficacy and safety of vortioxetine in adolescents with major depressive disorder (MDD).

Method: After 4 weeks of single-blind lead-in treatment with a Brief Psychosocial Intervention (BPI) plus placebo, patients (aged 12−17 years) with MDD (*DSM-5*) who did not meet response criteria (Children's Depression Rating Scale–Revised [CDRS-R]; total score ≥40 plus <40% reduction and a Parent Global Assessment score >2) were randomized 1:1:1:1 to 8 weeks of BPI plus double-blind treatment with vortioxetine 10 mg, vortioxetine 20 mg, fluoxetine 20 mg, or placebo. The primary endpoint was change from randomization in CDRS-R total score at week 8; the primary comparison was the average effect of 2 vortioxetine doses vs placebo.

Results: Of 784 patients enrolled in the lead-in, 616 were randomized. At week 8, the mean change in CDRS-R total score averaged for vortioxetine doses was –18.01 (SE = 0.98) and the mean difference vs placebo was 0.21 (P = .878; not significant). For fluoxetine, the mean change in CDRS-R total score was –21.95 and the mean difference vs placebo was –3.73 (P = .015). Treatment-emergent adverse events occurring in ≥5% of patients in either vortioxetine arm and at least twice more frequently than placebo were nausea, headache, vomiting, and dizziness.

Conclusion: Patients in all groups showed reduction in CDRS-R scores by the end of the study, with no difference between combined doses of vortioxetine and placebo. The primary endpoint was not met, thereby rendering the study negative. The overall favorable safety profile of vortioxetine in an adolescent patient population was consistent with that seen in adults.

Clinical trial registration information: Active Reference (Fluoxetine) Fixed-Dose Study of Vortioxetine in Paediatric Patients Aged 12 to 17 Years With Major Depressive Disorder (MDD); http://clinicaltrials.gov; NCT02709746.

Key words: antidepressants, major depressive disorder, adolescents, clinical trial, treatment outcome

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Although major depressive disorder (MDD) is relatively common in adolescence, with an estimated lifetime prevalence at the end of adolescence of 11% to 12%,[1,2] currently only 2 antidepressant pharmacotherapies have regulatory approval for adolescent patient populations: fluoxetine (ages 8−17 years) and escitalopram (ages 12−17 years; approved in the United States only).[3] Pediatric studies evaluating the efficacy of antidepressants have generally been faced with the challenge of high placebo response rates, with several studies failing to demonstrate separation from placebo.[3-9] Considering the burden of this disease, which includes suicide risk, there is a high unmet need for safe and efficacious treatments for this patient population.[10]

Vortioxetine is an antidepressant with multimodal activity and effects across a range of neurotransmitter systems: it is a serotonin $(5\text{-HT})_3$, 5-HT_7, and 5-HT_{1D} receptor antagonist, a 5-HT_{1B} partial agonist, a 5-HT_{1A} agonist, and an inhibitor of the serotonin transporter.[11,12] Vortioxetine has demonstrated efficacy on a par with most other antidepressants in adults,[13,14] has established benefits for cognitive symptoms in depression,[15] and is generally well tolerated.[11]

The objective of this study was to evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of vortioxetine in the acute treatment of adolescents with MDD. Pharmacokinetic analysis in this study supplemented the

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previous study in pediatric patients[16] and provided an objective measure of medication adherence (in addition to pill count),[16,17] which is important for accurate evaluation of treatment effects.[18] The study design integrated features aimed at mitigating limitations in previous pediatric MDD studies, primarily high placebo response rates. Unlike prior studies, the present study permitted randomization only of patients who did not respond to three 30-minute sessions of Brief Psychosocial Intervention (BPI; plus placebo added for blinding purposes) and who were thus considered appropriate for pharmacotherapy. This design feature is in alignment with treatment and regulatory guidelines in Europe, which recommend pharmacotherapy only for patients with insufficient response to psychotherapy.[19,20]

Therefore, a 4-week, single-blind lead-in period with a 3-session version of a standardized BPI plus placebo served the multiple purposes of (1) selecting a population of MDD patients eligible for pharmacotherapy per treatment guidelines as described above; (2) attenuating placebo response in the double-blind treatment period by excluding patients who responded to a combination of BPI and placebo; and (3) reducing expectation bias in the randomized period by blinding patients and their families to the time of randomization. The 3-session version of BPI was consistent with the only prior and similarly designed study, which reported a 23% response of enrolled participants to the pretrial BPI, excluding responders from randomization to the full trial.[21]

Fluoxetine was included as an active reference to provide evidence of assay sensitivity, because it has demonstrated efficacy in several pediatric MDD studies and is the only antidepressant approved for MDD in both children and adolescents.[22,23]

METHOD

Study Design

This 12-week placebo-controlled, active-reference (fluoxetine) study consisted of a screening period of 5 to 15 days; a 4-week, single-blind lead-in period; and an 8-week, double-blind, randomized treatment period. Placebo capsules were added to BPI during the single-blind lead-in phase to ensure the blinding of the patients and their families to the time point of randomization, with the aims of avoiding a high placebo response rate and lowering expectation bias. All study sites (see below) received training in BPI methodology and practice through face-to-face or video-link teaching, and BPI manuals and workbooks were distributed to all sites. This training method has been reported to have a high level of protocol fidelity in a previous study (the IMPACT study).[24] However, evaluating fidelity to BPI was not undertaken in the current study.

Only patients who met the randomization criteria for incomplete improvement in depressive symptoms in the single-blind lead-in period (defined below) were subsequently randomized with a ratio of 1:1:1:1 to 8 weeks of continued BPI combined with double-blind treatment with vortioxetine 10 mg, vortioxetine 20 mg, fluoxetine 20 mg, or placebo. Randomization was stratified by site. Blinding of patients, investigators, and study site personnel was implemented and maintained by Interactive Voice/Web Response System, assigning randomization numbers according to specifications from the Department of Biostatistics, H. Lundbeck A/S. Site personnel were not blinded to the study design, but they were reminded about the importance of keeping patients and parents blinded to phases and the randomization time point. The scales rating data for a site or rater-specific effect, where patients became immediately unrealistically better as soon as they were randomized, were internally monitored. When such findings were observed, site personnel were contacted and remediation was discussed. However, no specific tests of the fidelity of the blinding were conducted at week 8.

Incomplete improvement at the end of the 4-week, single-blind lead-in period was defined as a <40% reduction in Children's Depression Rating Scale–Revised (CDRS-R) total score (subtracted by 17 to avoid a flooring effect), CDRS-R total score ≥40, and a Parent-rated Global Assessment (PGA)–Global Improvement score >2. Patients who did not meet the randomization criteria in the single-blind lead-in period were withdrawn from the study. A safety follow-up was conducted up to 30 days after the end of the treatment and included patients who were not randomized after the lead-in single-blind period.

The study was conducted from June 2016 to July 2019 at 118 study sites in 19 countries: Bulgaria, Canada, Colombia, Estonia, France, Germany, Hungary, Italy, Republic of Korea, Latvia, Mexico, Poland, Russia, Serbia, South Africa, Spain, Ukraine, United Kingdom, and United States. Study protocols and amendments were approved by the independent ethics committee of each study site. Written informed assent from the patients as well as written informed consent from their parents/legal representatives were obtained before any study procedure was performed. Patients and families were reimbursed for their time associated with study participation, in accordance with local ethics committee guidelines.

The study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and with the ethical principles of the Declaration of Helsinki. The study is registered at ClinicalTrials.gov (NCT02709746; https://clinicaltrials.gov/ct2/show/NCT02709746).

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Study Participants

The study enrolled male and female outpatients aged 12 to 17 years with a primary diagnosis of MDD (according to the *DSM-5,* and confirmed using the Kiddie Schedule for Affective Disorders and Schizophrenia), a CDRS-R total score ≥45, and a Clinical Global Impression Scale–Severity (CGI-S) score ≥4, indicating moderate severity or worse. Main exclusion criteria included psychiatric comorbidities (except comorbid anxiety disorders other than post-traumatic stress disorder and obsessive-compulsive disorder); current diagnosis or history of substance dependence (excluding nicotine and caffeine) or alcohol dependence <6 months before the screening visit; current use of or a positive test for drugs of abuse (opiates, methadone, cocaine, amphetamines [including ecstasy], barbiturates, benzodiazepines, and cannabinoids); intellectual disability (IQ <70 or based on clinical evidence); having a first-degree relative with a history of bipolar disorder; stimulant treatment for attention-deficit/hyperactivity disorder (ADHD) that could not be maintained on a stable dose for at least 4 weeks before entering the study; planned augmentation/intensity increase of ongoing psychotherapy; and interpersonal psychotherapy or cognitive−behavioral therapy. Patients who had attempted suicide within the past 12 months or were at significant risk for suicide (in the opinion of the investigator or answered "yes" to the Columbia–Suicide Severity Rating Scale [C-SSRS] suicidal ideation questions 4 or 5 or "yes" to suicidal behavior within the past 12 months) were excluded.

Nonstimulant ADHD medications (eg, atomoxetine, guanfacine, and clonidine) were disallowed later than 2 weeks before the beginning of the study; stimulant ADHD medications (eg, methylphenidate or amphetamine) were allowed if the patient had been on a stable dose for at least 4 weeks before study treatment. Other disallowed medications included psychotropic agents such as antipsychotics, mood stabilizers, anxiolytics, and hypnotics.

Treatments

The patients received a total of 5 BPI sessions lasting up to 30 minutes: 3 sessions in the lead-in, continuing with 2 sessions in the double-blind treatment period (for study design, see Figure S1, available online). BPI for depression is a manualized, comprehensive package of specialist care for children and adolescents with depression.[24] It originates from a Specialist Clinical Care program and includes assessment, formulation, case management, achieving engagement with the young people and their parents, and planning and delivery of treatment. The clinicians were directed to use their clinical discretion to decide in which session to apply which element of BPI practice, which, in addition to a behavioral activation strategy, includes psychoeducation explaining depression and effects of mental illness, dealing with acute family or friendship stressors, social prescribing, empathic support, and reinforcing adaptive behaviors. The 3 practice principles of BPI are therefore pedagogic, social prescribing, and habilitation, meaning supporting adaptive behaviors gained or regained through the intervention.

The selected doses of vortioxetine 10 and 20 mg/d in the double-blind treatment period were based on an open-label pediatric PK study showing PK (as assessed by C_{max} and AUC_{0-24}) and safety/tolerability profiles of vortioxetine comparable to those seen in adults; hence, supporting the dose range of 5 to 20 mg/d.[16,25] Patients randomized to vortioxetine 10 mg received 5 mg/d for 2 days, and those randomized to vortioxetine 20 mg received 5 mg/d for 2 days followed by 10 mg/d and 15 mg/d for the next 2 days each before receiving the end dose. Patients in the fluoxetine arm received 10 mg/d for 6 days before the end dose of 20 mg/d. The fluoxetine dose of 20 mg was chosen per fluoxetine label recommendation, which is based on pediatric MDD clinical trial data.[26] The doses could be reduced once for tolerability by 5 mg for vortioxetine and 10 mg for fluoxetine at week 4 in the double-blind treatment period. After week 4, doses remained fixed.

Efficacy Assessments

The primary efficacy measure was the CDRS-R total score,[27] a clinician-rated assessment of depressive symptoms based on patient and parent interviews. The scale is composed of 17 items: 14 recording verbal reporting (5-point scales) and 3 recording observed nonverbal behavior (7-point scale). The CDRS-R total score is derived as the sum of single items, ranging from 17 (not depressed) to 113 (severe depression). The CDRS-R was assessed during screening, at enrollment, at weeks 2 and 3 of the single-blind lead-in period, at randomization, and at weeks 6, 8, 10, and 12 of the double-blind treatment period.

Secondary efficacy measures included the CGI, PGA, and General Behavior Inventory 10-item Depression Scale (GBI-D10). Using the CGI scales, clinicians recorded patients' overall clinical status and improvement/worsening at all visits throughout the study[28]: severity of illness (CGI-S, ranging from 1 [normal – not at all ill] to 7 [among the most extremely ill patients]) and Improvement (CGI-I, ranging from 1 [very much improved] to 7 [very much worse]). In addition, a parent-rated version of the CGI-I, the PGA,[29] was used to evaluate the severity of the

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child's symptoms, ranging from 1 (very much improved) to 7 (very much worse), and the GBI-D10, a parent- and patient-rated scale[30] (with scores ranging from 0 to 30, and higher scores indicating worse symptom severity) was also completed.[31] Figure S1, available online, shows the assessments schedule.

Pharmacokinetic Assessments

PK sampling was completed at weeks 4 and 8 of the double-blind treatment (or at study withdrawal, if relevant). Population pharmacokinetic (popPK) analysis for vortioxetine was performed by using nonlinear mixed effect methods based on a popPK model in healthy adults.[28] The PK parameters, maximum (peak) concentration (C_{max}), and area under the concentration−time curve ($AUC_{0\text{-}24}$) at steady-state for 10 mg were estimated. A 2-compartment model for vortioxetine PK data with first-order absorption and elimination was evaluated based on the general goodness-of-fit, normalized prediction distribution error plots, and visual predictive check plot. The popPK/pharmacodynamic relation between CDRS-R and Children's Global Assessment Scale (CGAS) scores and plasma exposure to vortioxetine was assessed at week 8 and post hoc at week 4. Patients who received placebo during double-blind treatment were included in the analysis with a concentration at steady state (C_{av}) of zero, whereas patients receiving fluoxetine were excluded, as were patients considered nonadherent based on drug plasma concentration.

Nonadherence to treatment was evaluated based on plasma concentration data and the popPK analysis. Patients were regarded as noncompliant if they had plasma drug concentrations of fluoxetine or vortioxetine below the lower limits of quantification at any visit or an estimated oral clearance >120 L/h for vortioxetine. Oral clearance values >120 L/h for vortioxetine were regarded as unrealistic based on previous popPK analysis,[32] as well as on data from healthy adult participants treated under well-controlled conditions.[33]

Safety Assessments

Safety assessments, conducted at all visits, included adverse events (AEs) recorded by investigators' open questioning and observation, and by patients' spontaneous reporting and vital signs. Patients were asked open-ended questions to allow them to give spontaneous answers to how they were feeling and whether they had any AEs. After these open-ended questions were asked and answered, the Pediatric Adverse Event Rating Scale, a clinician-rated scale designed and validated to assess AEs occurring in pediatric patients treated with psychotropic medication in clinical studies, was completed. Systematic querying of side effects using self-rated checklists or scales was not used in this study. Clinical safety laboratory tests and electrocardiograms were collected at screening and randomization, and at weeks 4 and 8 in the double-blind period. Standardized safety assessment tools were the clinician-rated C-SSRS (the "baseline screening" version at screening and the "since last visit" version at all other assessments), a semi-structured interview assessing suicidal ideation, intensity, and suicidal behavior, and the parent- and patient-rated General Behavior Inventory 10-item Mania Scale (GBI-M10).[31] A GBI-M10 score ≥18 was considered indicative of a potential risk of mania.

Study Personnel/Rater Training

Study personnel who interacted with study participants and performed the clinical ratings were health care professionals experienced with pediatric patients with MDD and with rating scales. The CDRS-R and CGI scales were administered only by qualified raters who underwent training on the use of the instrument and met predetermined interrater reliability criteria, which were evaluated during rater training sessions. The rater was either a psychiatrist or doctor of osteopathic medicine specializing in child and adolescent psychiatry, or a clinical pediatric (neuro-) psychologist involved in clinical practice. All raters were requalified (recalibrated) every 6 months.

Patients had CDRS-R and CGI scales completed by their treating physicians throughout the study, unless unforeseen circumstances required that a certified backup rater be used. Thus, ratings were completed by the same personnel who were inquiring about side effects and concerns.

Study Monitoring

To control for variability, an outlier flagging system on scales on the individual patient, site, and country level was implemented, and outliers were continuously monitored and discussed with site personnel when deemed necessary. In extreme cases in which remediation was unsuccessful, sites were closed for further screening. Two sites were closed because of data quality concerns.

Statistical Methods

Safety analyses included all patients randomized to the 8-week treatment period who received at least 1 tablet of vortioxetine, fluoxetine, or placebo (treated patients); treatment-emergent AEs (TEAEs) were summarized using descriptive statistics. Efficacy analyses included all treated patients with a valid CDRS-R total score assessment at randomization and at least 1 valid CDRS-R total score post-randomization assessment (the full analysis set [FAS]).

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CDRS-R response was calculated as the percent change in CDRS-R total score (subtracted by 17 to avoid flooring effect) compared with score at enrollment. The primary efficacy endpoint assessing the changes from randomization in CDRS-R total score to week 8 averaged for the 2 vortioxetine doses of 10 mg and 20 mg was analyzed by using a mixed model for repeated measurements (MMRM) with freely varying mean and covariance structures, and included the fixed categorical effects of treatment, country, and week, and the continuous covariates of CDRS-R total score at randomization, treatment-by-week interaction, and CDRS-R at randomization-by-week interaction. To evaluate the average treatment difference for vortioxetine 10 mg and 20 mg vs placebo, a contrast test with weights of 0.5 and 0.5, respectively, for the 2 vortioxetine doses, 0 for the fluoxetine, and –1 for placebo was used based on least squares means for the treatment-by-visit interaction evaluated at a 2-sided significance level of 5%. Each dose of vortioxetine was tested separately vs placebo using a 2-sided 5% significance level, and to adjust for multiplicity, statistical significance for the individual doses could be claimed only if the test for the vortioxetine 10 mg and 20 mg average reached statistical significance. If not, testing according to this strategy was stopped, and subsequent *P* values were considered nominal. Other endpoints were analyzed by using MMRM models similar to the one specified for the primary endpoint. In exploratory analyses, the primary analysis was conducted for subgroups stratified by randomization CDRS-R total score (≤55; ≥56 and ≤65; ≥66), age (<15 years; ≥15 years), and sex (male; female).

All statistical tests were 2-sided. Data were analyzed by using SAS, version 9.4 statistical software.

Sample Size Determination. Assuming a standardized effect size of 0.36 (based on the standardized effect size found on the Montgomery–Åsberg Depression Rating Scale in vortioxetine studies in adults) on the comparison of the averaged effect of the 2 vortioxetine doses vs placebo (primary endpoint), and a withdrawal rate of 15% to 20%, randomizing 120 patients per treatment arm would yield a power of at least 85% for claiming statistical significance at an α level of 5% if both vortioxetine doses had an effect of 4 points at week 8 in the double-blind treatment period. The number of patients to be enrolled (ie, to the lead-in) to achieve the number of patients to be randomized was determined based on an expected total withdrawal rate in the single-blind lead-in (including fulfillment of response criteria) of 20%. After a prespecified blinded sample size reassessment conducted at 75% study completion, the number of patients to be randomized was adjusted to 150 per treatment arm.

RESULTS

Patient Disposition

A total of 118 study sites were involved in the study, with 6 to 7 patients enrolled on average at each site. Figure 1 provides the Consolidated Standards of Reporting Trials (CONSORT) flow chart for both phases of the study. Of 1,035 patients screened, 784 entered the single-blind lead-in period, and 777 were treated (Figure 1). Of the enrolled patients, 616 were randomized to the 8-week, double-blind treatment period. A majority (103 of 161) of the patients treated who discontinued during the single-blind lead-in period did so because they responded to placebo + BPI and thus did not meet randomization criteria.

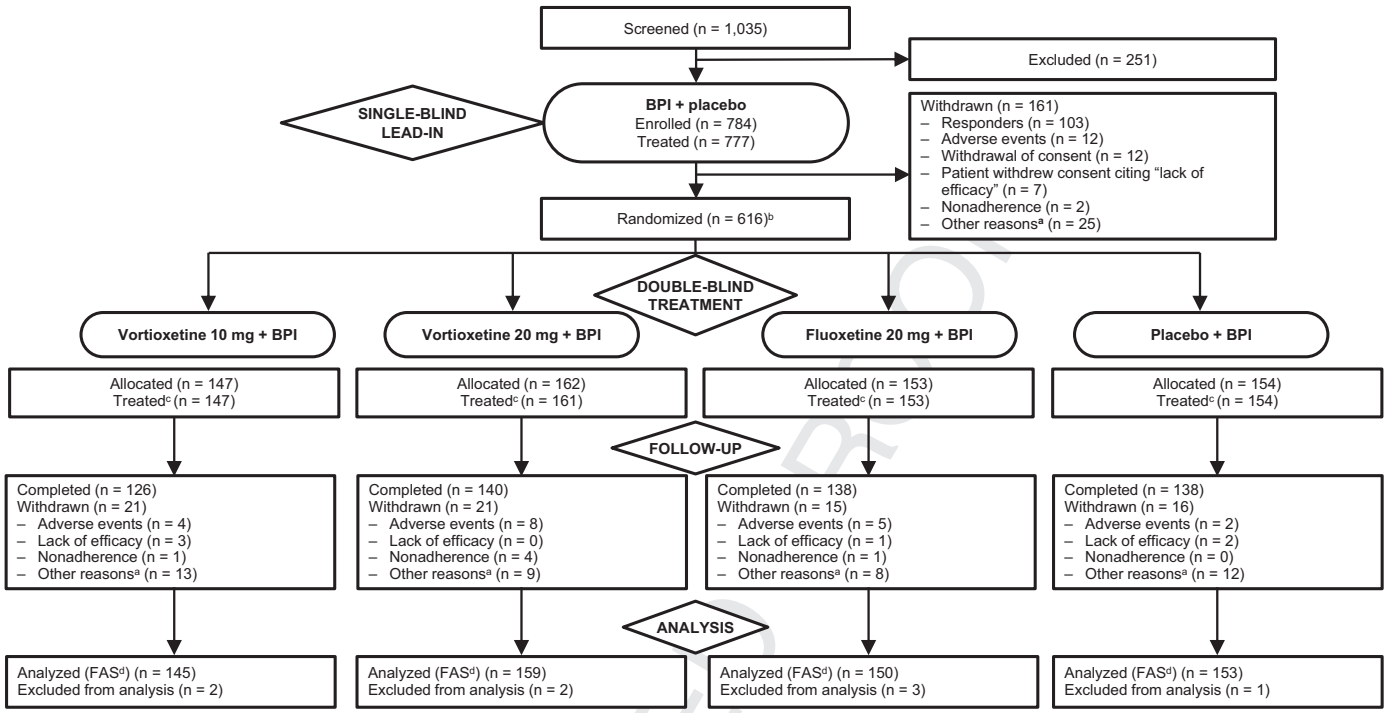
For the most part, patients who responded to the combination of BPI and placebo in the single-blind lead-in period and did not meet the criteria for randomization were comparable in demographics, height, weight, and body mass index (BMI), as well as in baseline disease characteristics, with those who did not respond and were randomized (see Table S1, available online). However, compared with responders, the nonresponders had a numerically higher mean CDRS-R total score at enrollment (64.6 vs 59.6) and a longer duration of the current depressive episode (40.9 vs 31.6 weeks), whereas relatively more responders had at least 1 previous episode (47.6% vs 37.7%) and comorbid ADHD (16.5% vs 9.7%).

Overall, patients in the 4 double-blind treatment groups were comparable in demographic and baseline clinical characteristics (Table 1). Of all randomized patients, 22% had at least 1 comorbid psychiatric condition; however, there were numerically more patients with comorbid ADHD among patients in the 10-mg vortioxetine group than in the fluoxetine group (12.2% vs 6.5%) (Table 2). Completion rates in the treatment arms were comparable, ranging from 126 of 147 (85.7%, vortioxetine 10 mg) to 138 of 153 (90.2%, fluoxetine). Only small proportions of patients had their dose reduced because of poor tolerability, with the largest proportion in the placebo arm (5.2%, vortioxetine 10 mg; 6.5%, vortioxetine 20 mg; 6.9%, fluoxetine; 9.0%, placebo).

Efficacy Outcomes

From the beginning of the 4-week, single-blind lead-in to randomization, patients (n = 777 week 0; n = 658 week 4) improved by 3.4 points, from 63.9 (SD = 9.5) to 60.5 (SD = 10.5) in CDRS-R total score. From randomization to week 8 in the double-blind period, all treatment groups showed substantial and continuous improvements, with mean (SE) changes from randomization in CDRS-R total score of −17.1 (1.3), −18.9 (1.2), −22.0 (1.2), and −18.2

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) Flowchart



Note: *BPI = Brief Psychosocial Intervention; CDRS-R = Children's Depression Rating Scale–Revised; FAS = full analysis set; PGA = Parent-rated Global Assessment.* [a]*Other reasons also include protocol violation, lost to follow-up, and not specified.* [b]*Nonresponders to single-blind BPI + placebo at weeks 3 and 4 of the lead-in period, defined as (1) <40% reduction in CDRS-R total score from enrollment, (2) CDRS-R total score ≥40, and 3) PGA – Global Improvement score >2.* [c]*All patients who received at least 1 dose of drug or placebo.* [d]*The FAS included all treated patients with a valid baseline assessment at randomization and at least 1 valid post-randomization primary endpoint assessment (CDRS-R).*

(1.2) for vortioxetine 10 mg and 20 mg, fluoxetine, and placebo, respectively (Figure 2A). At week 8, the mean change from randomization in CDRS-R total score averaged for the 2 doses of vortioxetine was −18.01 (SE = 0.98), with a mean difference from placebo of 0.2 points (p = .878). The primary endpoint was therefore not met, and subsequent p values were considered nominal. Likewise, neither of the single doses of vortioxetine separated from placebo. For fluoxetine, however, the mean difference from placebo was −3.7 CDRS-R points (p = .015), corresponding to a standardized effect size (d) of 0.3.

Comparable results were seen for other outcomes (CGI-S, PGA, and GBI-D10) (Table 3), except for CGI-S score, for which a nominally significant difference vs placebo for the 20-mg vortioxetine dose was seen at earlier time points (mean difference at week 6 = −1.3; P = .048) but not at week 8 (Figure 2B).

For both doses of vortioxetine, results from exploratory subgroup analyses of baseline depression severity (CDRS-R) categories, age, and sex (results not shown) were consistent with results seen in the total population. For fluoxetine, separation from placebo was seen only in the group with high baseline depression severity (CDRS-R score ≥66), with a mean difference from placebo of −7.0 (SE = 3.2; p = .029), whereas the mean differences from placebo were −2.4 (SE = 2.1; p = .254) and −0.4 (SE = 2.3; p = .870) for the groups with CDRS-R baseline scores ≤55 and 56 to 65, respectively.

As expected with the large sample size, both site- and country-specific effects were highly significant when included as factors in the primary analysis model. However, the impact on estimated treatment differences was very low, and no evidence was found for differential treatment effects for either site- or country-specific differences in the statistical analyses.

Pharmacokinetics. The estimated mean (SD) for vortioxetine exposure at steady-state was C_{max} = 13 (9.2) ng/mL and AUC_{0-24} = 301 (221) ng*h/mL. The 2-compartment model with first-order absorption and elimination described the PK data for vortioxetine well. Although there was no apparent relationship between the efficacy variables and plasma exposure to vortioxetine at week 8, post hoc analyses showed significant linear relationships (p < .05) for improvements in CDRS-R and CGAS scores at week 4.

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TABLE 1 Demographic and Baseline Clinical Characteristics (Double-Blind Treatment Period) Q6

	Vortioxetine 10 mg	Vortioxetine 20 mg	Fluoxetine 20 mg	Placebo
Demographic and clinical characteristics				
N[a]	147	161	153	154
Female patients, n (%)	93 (63.3)	96 (59.6)	103 (67.3)	105 (68.2)
Age, mean (SD), y	14.8 (1.7)	14.5 (1.6)	14.8 (1.6)	14.6 (1.6)
Ethnicity, n (%)				
White	108 (73.5)	109 (67.7)	112 (73.2)	106 (68.8)
African American or African	19 (12.9)	19 (11.8)	20 (13.1)	22 (14.3)
Asian	0	4 (2.5)	2 (1.3)	4 (2.6)
Other	17 (11.6)	25 (15.5)	17 (11.1)	21 (13.6)
BMI mean (SD) (kg/m^2)[b]	22.9 (5.9)	23.0 (6.5)	23.2 (6.0)	22.9 (5.4)
Mean duration of current episode, mean (SD), wk	43.1 (55.9)	43.2 (57.6)	42.8 (66.8)	34.6 (37.0)
Range	2.7-463.9	1.7-473.6	3.3-626.4	2.4-222.9
N	145	159	150	153
At least 1 previous episode, n (%)	56 (38.6)	66 (41.5)	53 (35.3)	55 (35.9)
Clinical assessments, mean (SD)				
N (FAS)[c]	145	159	150	153
CDRS-R total score	61.2 (9.4)	62.5 (9.8)	61.8 (8.9)	60.6 (9.1)
CGI-S score	4.8 (0.8)	4.8 (0.8)	4.8 (0.7)	4.8 (0.7)
PGA score	3.8 (0.7)[d]	3.9 (0.8)	4 (0.9)	3.9 (0.8)
GBI-D10 total score	15.3 (6.4)	15.2 (6.3)	15.3 (6.1)	15.8 (6.2)

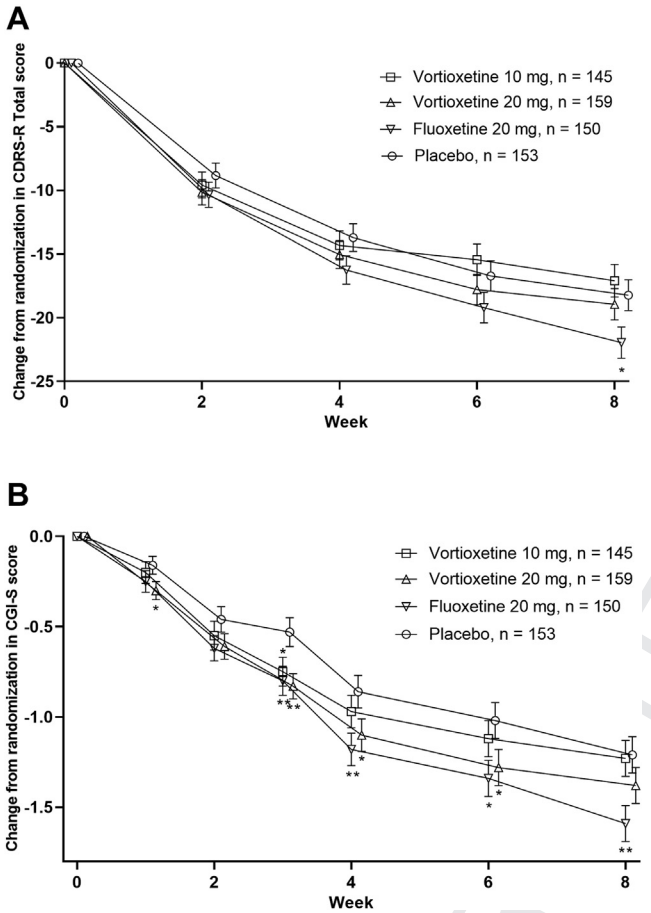
Note: BMI = body mass index; CDRS-R = Children's Depression Rating Scale–Revised; CGI-S = Clinical Global Impression–Severity of Illness; FAS = full analysis set; GBI-D10 = General Behavior Inventory 10-item Depression Scale; PGA = Parent-rated Global Assessment; wk = week.
[a]*Patients treated in the double-blind period.*
[b]*Vortioxetine 10 mg, n = 146; vortioxetine 20 mg, n = 160; fluoxetine 20 mg, n =152.*
[c]*At randomization, full analysis set.*
[d]*n = 144.*

TABLE 2 Concurrent Psychiatric Disorders

	Vortioxetine 10 mg	Vortioxetine 20 mg	Fluoxetine 20 mg	Placebo	Total
N[a]	147	162	153	154	616
Number of patients with concurrent psychiatric disorders, n (%)	36 (24.5)	36 (22.2)	30 (19.6)	33 (21.4)	135 (21.9)
Most common comorbidities,[b] n (%)					
ADHD	18 (12.2)	14 (8.6)	10 (6.5)	18 (11.7)	60 (9.7)
Insomnia	10 (6.8)	7 (4.3)	13 (8.5)	7 (4.5)	37 (6.0)
Anxiety disorder	5 (3.4)	7 (4.3)	4 (2.6)	2 (1.3)	18 (2.9)
GAD	2 (1.4)	4 (2.5)	5 (3.3)	5 (3.2)	16 (2.6)
Social anxiety disorder	4 (2.7)	6 (3.7)	3 (2.0)	2 (1.3)	15 (2.4)
Insomnia related to another mental condition	3 (2.0)	3 (1.9)	4 (2.6)	4 (2.6)	14 (2.3)

Note: ADHD = attention-deficit hyperactivity disorder; GAD = generalized anxiety disorder.
[a]*Randomized patients.*
[b]*Prevalence ≥2% in any treatment group.*

FIGURE 2 Change From Randomization Across Study Period in (A) Children's Depression Rating Scale–Revised (CDRS-R) Total Score and (B) Clinical Global Impression–Severity of Illness (CGI-S Score [FAS, MMRM])



*Note: Treatment differences are based on the least squares mean; error bars represent standard errors. CDRS-R = Children's Depression Rating Scale–Revised; CGI-S = Clinical Global Impression–Severity of Illness; FAS = full analysis set; MMRM = mixed model for repeated measurements. *p < .05; **p < .01.*

Rates of nonadherence based on drug plasma concentrations were 11% in the vortioxetine 10-mg group, 20% in the vortioxetine 20-mg group, and 14% in the fluoxetine group.

Safety Outcomes

In the 4-week, single-blind lead-in period, 252 of 777 (32.4%) patients reported AEs; except for headache (occurring in 8.4% of patients), the incidences of all AEs were lower than 5%. Serious AEs (SAEs) were reported by 13 patients (1.7%) in the lead-in period, and 14 patients (1.8%) discontinued because of an AE. Suicide-related AEs were reported by 13 patients (1.7%), of which 8 reported 1 or more suicide-related SAE.

Treatment-Emergent Adverse Events. TEAEs across treatment arms in the double-blind treatment period with incidences ranging from 59% (vortioxetine 20 mg) to 40.9% (placebo) are summarized in Table 4. TEAEs with an incidence of 5% or more in either vortioxetine arm were nausea, headache, vomiting, nasopharyngitis, diarrhea, and dizziness. Discontinuation rates due to an AE ranged from 5.6% (vortioxetine 20 mg) to 1.3% (placebo). TEAEs leading to discontinuation for more than 1 patient in any treatment arm were suicidal ideation, nausea, and vomiting. The incidence of SAEs ranged from 4.3% (vortioxetine 20 mg) to 0.6% (placebo).

In the double-blind treatment period, a total of 14 patients reported suicide-related TEAEs, the incidence ranging from 1.4% (vortioxetine 10 mg) to 3.9% (fluoxetine), and none in the placebo group. For 6 of those patients, at least 1 of the suicide-related TEAEs was reported as an SAE (suicidal ideation, 6 patients; suicide attempt, 1 patient), all of which occurred after more than 14 days of treatment. The C-SSRS assessment of suicidality showed comparable proportions of patients with any suicidal ideation or behavior across all 4 treatment arms, ranging from 8% to 10% in the double-blind period.

With 6% of patients having a GBI-M10 score of 18 or above in the placebo group, and rates below 5% in any other treatment group, there was no indication of elevated risk for mania postrandomization, nor were any TEAEs of mania reported. No clinically relevant changes from randomization in laboratory tests, vital signs, BMI, height, and electrocardiogram parameters were seen in any of the patients in any of the treatment arms, nor were there any significant proportions of patients with postrandomization potentially clinically significant values for these variables.

No treatment-related deaths occurred during the study. One patient died by suicide during the screening period, and 1 patient allocated to placebo during the study died by suicide approximately 1 year after the study.

DISCUSSION

In this study, patients in all treatment groups improved substantially from randomization to week 8 in CDRS-R total score, with no statistically significant differences between those treated with vortioxetine vs placebo; thus, the study did not meet its primary endpoint, rendering it a negative trial. An early nominally significant difference from placebo in global clinical status (CGI-S) for vortioxetine 20 mg seen until week 6 was not present at week 8; a difference from placebo was seen for fluoxetine only.

In a previous PK study, slightly lower exposure in adolescents than in adults (possibly related to nonadherence) was observed.[16] This study confirmed that vortioxetine

TABLE 3 Efficacy Endpoints at Week 8 (Full Analysis Set [FAS], Mixed Model for Repeated Measurements [MMRM])

	Vortioxetine 10 mg	Vortioxetine 20 mg	Fluoxetine 20 mg	Placebo
N	126	139	137	137
CDRS-R total score				
Mean (SE) change from randomization	−17.1 (1.3)	−18.9 (1.2)	−22.0 (1.2)	−18.2 (1.2)
Mean (SE) difference vs placebo	1.1 (1.6)	−0.7 (1.5)	−3.7 (1.5)	—
p Value	.470	.637	.015	—
CGI-S score				
Mean (SE) change from randomization	−1.2 (0.1)	−1.4 (0.1)	−1.6 (0.1)	−1.2 (0.1)
Mean (SE) difference vs placebo	−0.0 (0.1)	−0.2 (0.1)	−0.4 (0.1)	—
p Value	.861	.189	.005	—
CGI-I score[a,b]				
Absolute score at week 8	2.8 (0.1)	2.7 (0.1)	2.5 (0.1)	2.7 (0.1)
Mean (SE) difference vs placebo	0.1 (0.1)	−0.0 (0.1)	−0.2 (0.1)	—
p Value	.536	.739	.063	—
PGA score[b]				
Absolute score at week 8	2.8 (0.1)	2.7 (0.1)	2.5 (0.1)	2.7 (0.1)
Mean (SE) difference vs placebo	0.1 (0.1)	0.0 (0.1)	−0.2 (0.1)	—
p Value	.541	.931	.047	—
GBI-D10 score[c]				
Mean (SE) change from randomization	−5.5 (0.6)	−5.6 (0.6)	−6.3 (0.6)	−6.0 (0.6)
Mean (SE) difference vs placebo	0.6 (0.8)	0.5 (0.7)	−0.3 (0.7)	—
p Value	.462	.507	.712	—

***Note**: Treatment differences are based on the least squares mean. CDRS-R = Children's Depression Rating Scale–Revised; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity of Illness; GBI-D10 = General Behavior Inventory 10-item Depression Scale; PGA = Parent-rated Global Assessment.*
[a]For CGI-I, improvement or worsening assessed vs enrollment.
[b]n = 125 for vortioxetine 10 mg.
[c]Assessed by the child.

steady-state exposure with both doses was comparable to that observed in adult populations.[16,32]

This study supported the acceptable safety profile of vortioxetine previously seen in an adolescent MDD population,[16,25] with nausea as the most common AE, as seen in adult patient populations.[11] Variability in the incidence of specific AEs compared with adult populations, most specifically, suicide-related events, might be expected based on the elevated risk of suicide-related behavior vs placebo observed in pediatric MDD trials.[34]

The response rate of 13% (103 of 777 patients) to the 3-session BPI and placebo in the single-blind treatment period is somewhat low compared with that in the prior study (23%) using this design and a similar level of BPI prior to randomization.[21] Furthermore, although response during the single-blind lead-in was modest, patients allocated to BPI and placebo improved substantially after randomization by the end of the study (5 BPI sessions). This might reflect a lag in the effect of the BPI during the lead-in so that the benefits of BPI came into effect after the subsequent randomization period. A longer term effect has been reported for both cognitive–behavioral therapy and BPI where positive effects have continued for at least 12 months posttreatment.[35]

Expectation bias on the part of clinicians, who were not blinded to timing of randomization, as well as allowing the treating clinician to also perform the clinical ratings, may have contributed to the study findings. However, although expectation bias may have been an issue prior to

TABLE 4 Treatment-Emergent Adverse Events (TEAEs) With an Incidence of ≥5% in Any Treatment Arm and TEAEs Leading to Discontinuation in the 8-Week Double-Blind Treatment Period

	Vortioxetine 10 mg	Vortioxetine 20 mg	Fluoxetine 20 mg	Placebo
Patients treated	147	161	153	154
Patients with TEAEs, n (%)	69 (46.9)	95 (59.0)	75 (49.0)	63 (40.9)
Patients with serious adverse events, n (%)	4 (2.7)	7 (4.3)	3 (2.0)	1 (0.6)
TEAEs with an incidence ≥5%, n (%)				
Nausea	21 (14.3)	31 (19.3)	10 (6.5)	7 (4.5)
Headache	23 (15.6)	20 (12.4)	10 (6.5)	12 (7.8)
Vomiting	7 (4.8)	15 (9.3)	8 (5.2)	1 (0.6)
Nasopharyngitis	6 (4.1)	10 (6.2)	10 (6.5)	5 (3.2)
Diarrhea	5 (3.4)	9 (5.6)	7 (4.6)	5 (3.2)
Dizziness	11 (7.5)	7 (4.3)	6 (3.9)	5 (3.2)
Patients with TEAEs leading to discontinuation,[a] n (%)	4 (2.7)	9 (5.6)	5 (3.3)	2 (1.3)
Suicidal ideation	1 (0.7)	3 (1.9)	2 (1.3)	0
Nausea	1 (0.7)	2 (1.2)	0	0
Vomiting	0	2 (1.2)	0	0
Alanine aminotransferase increased	0	1 (0.6)	0	0
Depression	0	1 (0.6)	1 (0.7)	0
Headache	1 (0.7)	1 (0.6)	0	0
Meningitis	0	1 (0.6)	0	0
Anxiety	0	0	1 (0.7)	0
Dry mouth	0	0	0	1 (0.6)
Gastroenteritis	0	0	0	1 (0.6)
Hyperesthesia	0	0	0	1 (0.6)
Insomnia	0	0	0	1 (0.6)
Pregnancy	1 (0.7)	0	0	0
White blood cell count decreased	0	0	1 (0.7)	0

Note: No deaths occurred during the study.
[a]*Patients in all treatment groups had more than 1 TEAE that led to discontinuation.*

randomization, previous research has shown that this is not the case after randomization. In the original pediatric fluoxetine trial,[36] the ability of treating clinicians who served as primary raters to predict participants' treatment conditions was no better than chance, but in the current study treatment predictions were not assessed.

In addition, although the methodology for the 3-session version of BPI was consistent with the only prior and similarly designed study (IMPACT),[24] fidelity was not separately assessed in the current study. However, results similar to those of CDRS-R were seen for the parent- and patient-reported assessments (PGA and GBI-D10 scores), potentially indicating a mechanism whereby clinicians' expectations are unintentionally transmitted to patients and their families.

Similar to MDD trials in adults, pediatric trials have been challenged by substantial placebo response, hampering assay sensitivity to detect a treatment signal.[37,38] This study included a single-blind lead-in period designed to reduce expectation bias, and thereby the placebo response, by blinding patients and their families to the time of randomization, as well as identifying and selecting patients who did not respond to placebo combined with BPI. Patients allocated to placebo improved on average by −18 CDRS-R points from randomization to week 8, with a corresponding response rate (≥50% change from randomization in CDRS-R total score) of 36%, whereas the response rates ranged from 42% to 43% for the vortioxetine 10 mg and 20 mg groups, respectively, and 50% for fluoxetine (see Table S2, available online). This is in the

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lower range of studies of comparable duration that have also implemented a lead-in period,[37] and is lower than in previous MDD trials in adolescents that have included an active comparator.[3,7-9] With fluoxetine separating from placebo at a clinically relevant effect size (0.3), these study design features may have had some impact in reducing the placebo response.

Although marked improvements from randomization scores were observed in all treatment groups, it remains unclear why vortioxetine did not separate from placebo. It should be noted that the effect of fluoxetine vs placebo was driven by effects in the most severely ill patients. This finding highlights the heterogeneity of the disease as well as the antidepressant response, as baseline illness severity is commonly observed to be a predictor of treatment response.[37] Such heterogeneity (within pediatric MDD and relative to MDD in adults) could hypothetically have contributed to the differential results seen for vortioxetine and fluoxetine in this population. Furthermore, nonadherence, which was more prevalent in the vortioxetine 20-mg group (20%) compared with the fluoxetine group (14%), might also have had an impact on the results, although this would not explain the lack of separation from placebo. Whereas the elimination half-life of vortioxetine is 66 hours, or approximately 3 days,[32] the half-life of fluoxetine ranges from 2 to 6 days and 7 to 15 days for its active metabolite norfluoxetine, potentially rendering the therapeutic effect of fluoxetine less sensitive to 1 or more omitted doses.[39]

It cannot be excluded that the single-blind lead-in period may have been too short to achieve a response in all potential BPI responders, particularly as BPI and other psychological treatments show a piecewise improvement trajectory with rapid gains noted for the first 18 weeks, slowing subsequently thereafter.[35] In addition, the single-blinding of patients and their families to the lead-in period and time of randomization may not have sufficiently eliminated expectation bias, considering the small placebo response during the lead-in period relative to the substantial response observed immediately after randomization, although this would not explain the lack of separation from placebo. It is not, however, possible in this study to separate the effects of placebo from those of BPI, because the study did not include a placebo-only arm. The inclusion of 3 active arms in the study design, and thus the high probability (75%) of receiving an active treatment, may have further increased expectation bias. Also, difficulties recruiting patients because of issues such as patient or parent refusal, presence of exclusionary psychiatric diagnoses, or use of disallowed concomitant medications resulted in a large number of study sites, which has been associated with a greater placebo response.[37] Finally, it should be noted that the results of this study cannot be generalized to MDD populations beyond the age and clinical profile of this study population.

The inclusion and exclusion criteria to enroll patients without several comorbid psychiatric conditions, other unstable medical illnesses, or at risk for suicide may also affect its generalizability. Of note, although several antidepressant studies in MDD[7-9,40] have reported comorbidity profiles similar to those in our study, the anxiety disorder profile in our study was considerably lower than those observed in previous studies,[21,41,42] and thus may have had an impact on study findings.

In this study, patients in all treatment groups improved, with no difference at week 8 in CDRS-R total score for vortioxetine vs placebo, and therefore the study did not meet its primary endpoint, rendering it a negative trial. The study confirmed the favorable safety profile of vortioxetine in an adolescent patient population, consistent with that seen in adults.

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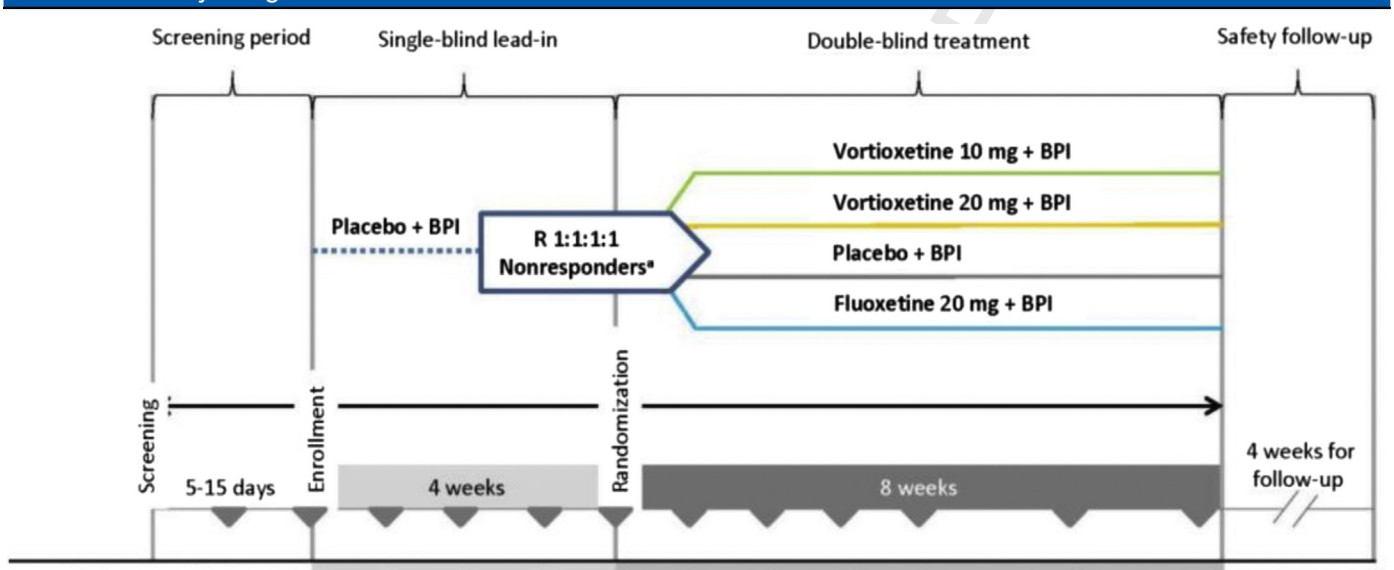
SUPPLEMENTAL MATERIAL

FIGURE S1 Study Design and Assessments



Week	Day -5 to -15	0	1	2	3	4	5	6	7	8	10	12	16
BPI			✓	✓	✓		✓			✓			
Efficacy													
CDRS-R	✓	✓		✓	✓	✓		✓		✓	✓	✓	
CGI-S	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CGI-I			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
PGA				✓	✓	✓		✓		✓	✓	✓	
GBI-D10	✓	✓		✓		✓		✓		✓	✓	✓	
Safety													
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
C-SSRS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
GBI-M10	✓	✓		✓		✓		✓		✓	✓	✓	
PK sampling										✓		✓	

Note: BPI = Brief Psychological Intervention; CDRS-R = Children's Depression Rating Scale–Revised; CGI-S/I = Clinical Global Impression–Severity of Illness/Improvement; C-SSRS = Columbia–Suicide Severity Rating Scale; GBI-D10 = General Behavior Inventory Depression 10-item Depression Scale; GBI-M10 = General Behavior Inventory 10-item Mania Scale; PGA = Parent-rated Global Assessment; PK = pharmacokinetics; R = randomization. [a]Patients meeting all of the following criteria at weeks 3 and 4 of the single-blind lead-in period: (1) <40% reduction in CDRS-R total score from enrollment, (2) CDRS-R total score ≥40, and 3) Parent Global Assessment–Global Improvement score >2.

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TABLE S1 Demographic and Clinical Characteristics[a] for Patients Not Randomized (Responders in the Single-Blind Lead-in Period[b]) Versus Randomized

	Responders, not randomized[c]	Nonresponders, randomized	Withdrawn from single-blind lead-in for other reasons[d]
N	103	616	58
Female participants, n (%)	71 (68.9)	398 (64.6)	35 (60.3)
Age, mean (SD), y	14.6 (1.6)	14.7 (1.6)	14.9 (1.7)
BMI, mean (SD), kg/m^2	24.4 (6.4)	22.9 (5.9)	23.5 (7.0)
Duration of current episode, mean (SD), wk	31.6 (36.0)	40.9 (55.4)	41.3 (43.7)
Range	2.4-265.6	1.7-626.4	5.1-259.1
At least 1 previous episode, n (%)	49 (47.6)	232 (37.7)	27 (46.6)
Most common comorbidities, n (%)			
ADHD	17 (16.5)	60 (9.7)	5 (8.6)
Insomnia	6 (5.8)	37 (6.0)	5 (8.6)
CDRS-R total score at enrollment, mean (SD)	59.6 (8.9)	64.6 (9.2)	64 (11.3)
CDRS-R total score at end/last assessment in single-blind lead-in, mean (SD)	39.0 (11.1)	61.6 (9.3)	58.9 (14.1)[e]

Note: ADHD = attention deficit hyperactivity disorder; BMI = body mass index; CDRS-R = Children's Depression Rating Scale–Revised.
[a]*At enrollment.*
[b]*Randomization criteria for incomplete improvement:*
[c]*Patients meeting all of the following criteria at weeks 3 and 4 of the single-blind lead-in period: (1) <40% reduction in CDRS-R total score from enrollment, (2) CDRS-R total score ≥40, and (3) Parent Global Assessment–Global Improvement score >2.*
[d]*Primary reasons for withdrawal: adverse events, n = 12; withdrawal of consent, n = 12; lack of efficacy, n = 7; nonadherence, n = 2; protocol violations, n = 4; loss to follow-up, n = 7; other reasons, n = 14).*
[e]*Eighteen patients with no follow-up assessment in the single-blind lead-in period had a mean (SD) CDRS-R total score of 61.1 (9.7) at the beginning of the lead-in period; for the patients who had a follow-up assessment in the single-blind lead-in period (n = 40), the mean CDRS-R total score was 57.9 (15.6) at the end/last assessment of the lead-in period.*

TABLE S2 Responders and Remitters at Week 8

	Vortioxetine 10 mg	Vortioxetine 20 mg	Fluoxetine 20 mg	Placebo
N	126	139	137	137
CDRS-R response,[a] n (%)	53 (42.1)	60 (43.2)	68 (49.6)[b]	49 (35.8)
CDRS-R remission,[c] n (%)	21 (16.7)	24 (17.3)	32 (23.4)[b]	20 (14.6)

Note: CDRS-R = Children's Depression Rating Scale–Revised.
[a]*Defined as a ≥50% decrease in CDRS-R total score, calculated as (change from baseline randomization])/(baseline value – 17).*
[b]*Nominal p < .05 vs placebo.*
[c]*Defined as a CDRS-R total score ≤28.*