Supplementary Data

Supplementary Data S1

Exclusion Criteria

Patients were excluded from the study if they were not in a generally healthy medical condition as determined by the investigator, had any major acute illness within 90 days before the screening visit, had a history of seizure disorder other than a single childhood febrile seizure, had a history or current evidence of gastrointestinal disease or surgery known to interfere with absorption or excretion of drugs, or had a severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased patient risk or interfered with the interpretation of study results. Patients with a history or presence of major depressive disorder (MDD) with psychotic features or any psychotic disorder, bipolar disorder (or first-degree relative with bipolar disorder) or manic episodes; current psychoactive substance or alcohol abuse or dependence, posttraumatic stress disorder, obsessive-compulsive disorder; current generalized anxiety disorder, panic disorder, social anxiety disorder, or attention-deficit/hyperactivity disorder considered a primary diagnosis; history or presence of borderline personality disorder, clinically important personality disorder, or history of recurrent, intentional self-injurious behavior; or depression associated with the presence of a mental disorder due to a general medical condition were excluded, as were patients with a history or presence of anorexia or bulimia.

Patients were also excluded if they had a history or current evidence of suicidal behavior or suicidal ideation associated with actual intent and/or plan at any time in their lifetime based on clinical judgment or Columbia-Suicide Severity Rating Scale responses at the screening or baseline visit, or first-degree relative who had committed suicide. Patients were not enrolled if they had clinically important abnormalities on physical examination, electrocardiography, laboratory tests, or urine drug screen; total bilirubin 2.0 mg/dL (34.2 μmol/L) or greater (unless there was documented history of Gilbert's syndrome); alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase three or more times upper limit of normal; prolactin level 40 ng/mL (40 μg/L) or greater; or prerandomization blood pressure elevation in the 95th percentile or greater for gender, age, and height. Patients with a known allergy or hypersensitivity or previous adverse event related to venlafaxine, desvenlafaxine, or fluoxetine, or history of failure to respond to an adequate course of treatment for MDD with fluoxetine, venlafaxine, or desvenlafaxine were excluded, as were patients with a history of electroconvulsive therapy.

Patients who were pregnant, breastfeeding, or had a positive serum beta human chorionic gonadotropin pregnancy test result were excluded from the study. Immediate family members of investigational site staff or Pfizer Inc employees directly involved in the conduct of the trial were not permitted, nor were patients who had a parent or legal guardian who was responsible for another individual enrolled in the study.

Prohibited Treatments

Prohibited treatments included venlafaxine (immediate release or extended release), desvenlafaxine, stimulants, or atomoxetine within 60 days of first dose of study medication; formal psychotherapy for MDD, fluoxetine, antipsychotic medications, investigational medications or devices within 30 days of first dose of study medication; antidepressants other than fluoxetine, venlafaxine, or desvenlafaxine, monoamine oxidase inhibitors (MAOIs), anxiolytics, benzodiazepines and nonbenzodiazepines, sumatriptan, naratriptan, zolmitriptan (or other medications indicated for the treatment of migraine with a similar mechanism of action), or tryptophan supplements within 14 days of first dose of study medication; and herbal products intended to treat anxiety, insomnia or depression, sedative-hypnotic medications, other psychotropic medications or substances, or nonpsychopharmacologic medications or herbal preparations with psychotropic effects (unless the patient has maintained a stable dose for at least 90 days) within 7 days of first dose of study medication. Pimozide, thioridazine, and MAOIs were also prohibited for up to 5 weeks after last dose of study medication. Common cold preparations and over-the-counter preparations to aid sleep were permitted on an as-needed basis; patients were instructed not to take these medications 24 hours before any visit, whenever possible.

Supplementary Data S2

Statistical Analyses

Interim analysis

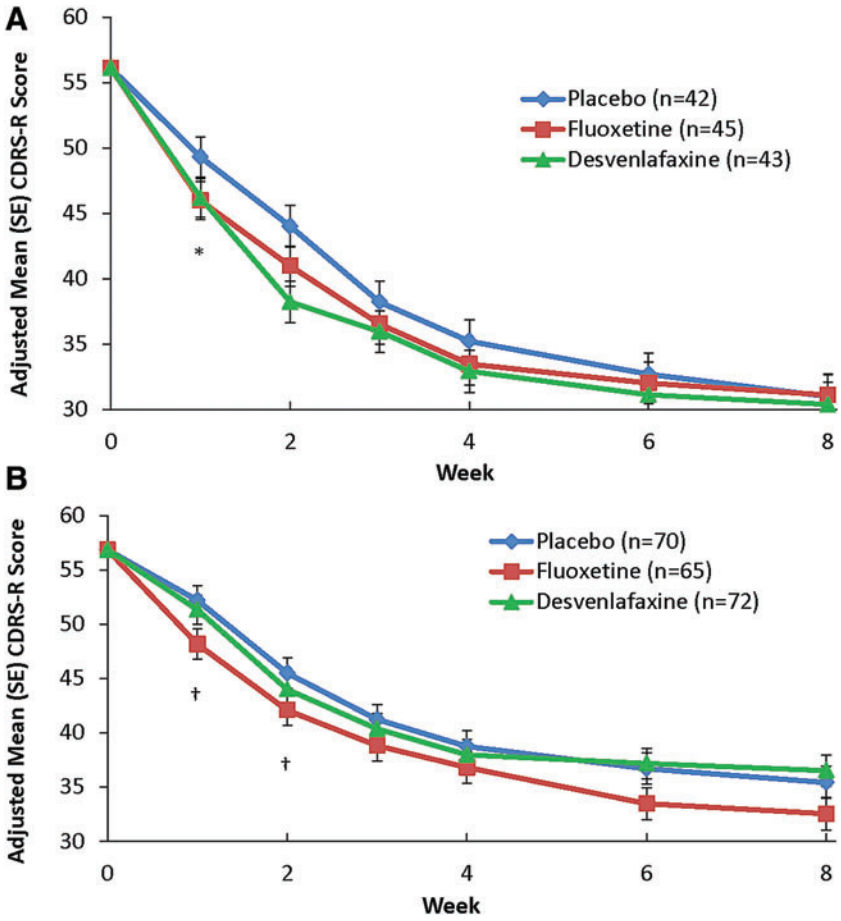
A partially unblinded interim analysis was conducted by a third party and reviewed by the Data Monitoring Committee after 75% of patients had completed the 8-week double-blind phase, to determine if a sample size increase was required. Group membership, but not treatment assignment, was unblinded. The standard deviation of the change from baseline of Children's Depression Rating Scale–Revised (CDRS-R) total score was estimated for each treatment arm and pooled as the interim estimate for potential sample size increase. Results of the interim analysis indicated that no sample size increase was required.

Sensitivity analyses

Sensitivity analyses using observed cases and last observation carried forward approaches were performed on change from baseline in CDRS-R total score at each postbaseline visit. The sensitivity analyses used an analysis of covariance model with terms for treatment, age group, country, and gender as fixed effects and baseline CDRS-R total score as a covariate. The primary analysis using a mixed-effects model for repeated measures was also repeated in the per protocol population, defined as patients from the intent-to-treat population who did not have major protocol violations, determined before data unblinding.

The effect of patient completion of the study on analysis results was evaluated with a pattern-mixture analysis using a repeated measures model with an unstructured covariance structure, with the following terms: treatment, week, week squared, interaction of treatment and week, interaction of treatment and week squared, pattern, interaction of pattern and week, interaction of pattern and week squared, interaction of pattern and treatment, interaction of pattern, treatment and week, interaction of pattern, treatment and week squared, age group, country, gender, and baseline score. Pattern was a variable that distinguishes patients according to their missing data pattern; completers were defined as patients who provided CDRS-R data at week 8, and noncompleters were patients who did not have week 8 CDRS-R data. Week and week squared were used in a quadratic model as a continuous representation of time. Adjusted means from the pattern-mixture model were obtained through a weighted average over patterns, where the weight was based on the proportion of completers, following the approach by Hedeker and Gibbons (2006).

All sensitivity analysis results were consistent with the results of the primary analyses.



SUPPLEMENTARY FIG. S1. Adjusted mean (SE) change from baseline in CDRS-R total score; exploratory MMRM analysis, ITT population: **(A)** children (7–11 years), **(B)** adolescents (12–17 years). *$p < 0.01$, desvenlafaxine versus placebo. †$p < 0.05$, fluoxetine versus placebo. CDRS-R, Children's Depression Rating Scale–Revised; ITT, intent-to-treat; MMRM, mixed-effects model for repeated measures; SE, standard error.

Supplementary Table S1. Titration, Taper, and Transition Period Dosing

	Desvenlafaxine			*Fluoxetine*
Baseline body weight, kg	20 to <35	35 to <70	≥70	—
Assigned dose, mg/d	25	35	50	20
Titration, (mg/d)				
Days 1–7	10	10	20	10
Taper (mg/d)				
Taper days 1–7	10	10	20	Placebo
Transition (mg/d)				
Transition days 1–7	25	25	25	Placebo

Supplementary Table S2. Number (%) of Patients Reporting Prespecified Treatment-Emergent Adverse Events of Clinical Importance (Tier-1 Treatment-Emergent Adverse Events), Safety Population

	Placebo (n = *112*)	*Fluoxetine* (n = *112*)	*Desvenlafaxine* (n = *115*)
Aggression	0	0	2 (1.7)
Akathisia	0	1 (0.9)	0
Anger	1 (0.9)	0	0
Blood pressure increased	0	0	1 (0.9)
Blood pressure, systolic increased	0	2 (1.8)	0
Contusion	0	1 (0.9)	0
Epistaxis	1 (0.9)	3 (2.7)	1 (0.9)
Homicidal ideation	1 (0.9)	0	0
Intentional self-injury	1 (0.9)	0	0
Laceration	1 (0.9)	1 (0.9)	0
Orthostatic hypotension	0	0	1 (0.9)
Self-injurious behavior	1 (0.9)	1 (0.9)	0
Suicide attempt	0	1 (0.9)	0
Suicidal ideation	0	2 (1.8)	1 (0.9)

Supplementary Table S3. Summary of Suicidal Ideation and Behavior Reported on the Columbia-Suicide Severity Rating Scale at Baseline, at Any Postbaseline Assessment, and at Any Postbaseline Assessment but Not at Baseline, Safety Population

	Placebo (n = *112*)	*Fluoxetine* (n = *112*)	*Desvenlafaxine* (n = *115*)
Baseline			
No. assessed	112	112	115
Suicidal behavior and/or ideation, *n* (%)	8 (7.1)	13 (11.6)	13 (11.3)
Suicidal behavior	0	0	0
Suicidal ideation	8 (7.1)	13 (11.6)	13 (11.3)
Wish to be dead	7 (6.3)	13 (11.6)	13 (11.3)
Nonspecific active suicidal thoughts	2 (1.8)	5 (4.5)	5 (4.3)
Active suicidal ideation with any methods (no plan) without intent to act	1 (0.9)	2 (1.8)	2 (1.7)
Active suicidal ideation with some intent to act, without specific plan	0	0	0
Active suicidal ideation with specific plan and intent	0	0	0
Self-injurious behavior, no suicidal intent	1 (0.9)	0	3 (2.6)
Any postbaseline assessment			
No. assessed	112	110	115
Suicidal behavior and/or ideation, *n* (%)	9 (8.0)	17 (15.5)	15 (13.0)
Suicidal behavior	0	1 (0.9)	0
Completed suicide	0	0	0
Suicide attempt[a]	0	0	0
Preparatory acts toward imminent suicidal behavior	0	1 (0.9)	0
Aborted attempt	0	0	0
Interrupted attempt	0	1 (0.9)	0
Preparatory acts or behavior	0	1 (0.9)	0
Suicidal ideation	9 (8.0)	17 (15.5)	15 (13.0)
Wish to be dead	9 (8.0)	17 (15.5)	13 (11.3)
Nonspecific active suicidal thoughts	3 (2.7)	9 (8.2)	8 (7.0)
Active suicidal ideation with any methods (no plan) without intent to act	1 (0.9)	7 (6.4)	7 (6.1)
Active suicidal ideation with some intent to act, without specific plan	0	1 (0.9)	0
Active suicidal ideation with specific plan and intent	0	1 (0.9)	0
Self-injurious behavior, no suicidal intent	2 (1.8)	3 (2.7)	1 (0.9)
No at baseline, yes at any postbaseline assessment, *n* (%)			
No. assessed	112	110	115
Suicide attempt	0	0	0
Suicidal ideation	7 (6.3)	10 (9.1)	8 (7.0)
Any suicidal behavior and/or ideation	7 (6.3)	10 (9.1)	8 (7.0)
Self-injurious behavior, no suicidal intent	0	2 (1.8)	1 (0.9)

[a]The suicide attempt reported as a serious adverse event was not captured on the C-SSRS; C-SSRS was not performed following that event.
C-SSRS, Columbia-Suicide Severity Rating Scale.

SUPPLEMENTARY TABLE S4. PATIENTS WITH POTENTIALLY CLINICALLY IMPORTANT VITAL SIGN VALUES DURING THE ON-THERAPY PERIOD, SAFETY POPULATION

	Placebo (n = *112*)	*Fluoxetine* (n = *112*[a])	*Desvenlafaxine* (n = *115*)
Total	66 (58.9)	63 (57.3)	71 (61.7)
Systolic[b] BP (mm Hg), supine Elevation at three consecutive visits[c]	0	0	1 (0.9)
Systolic BP (mm Hg), orthostatic Decrease of ≥20 mm Hg from last supine to first standing	1 (0.9)	3 (2.7)	9 (7.8)
Diastolic BP (mm Hg), orthostatic Decrease of ≥15 mm Hg from last supine to first standing	6 (5.4)	3 (2.7)	3 (2.6)
Pulse (beats/min), supine Less than PCI lower limit or greater than PCI higher limit	24 (21.4)	26 (23.6)	16 (13.9)
Pulse (beats/min), orthostatic Increase of ≥20 bpm from last supine to first standing	42 (37.5)	38 (34.5)	47 (40.9)
Weight (kg) Increase from baseline ≥7% or decrease from baseline ≥3.5%	12/112 (10.7)	25/110 (22.7)	17/115 (14.8)

[a]One hundred and ten fluoxetine-treated patients had vital sign data in the on-therapy period.
[b]No occurrences of elevation of diastolic BP at three or more consecutive visits were observed.
[c]Individual occurrences of increased BP at less than three consecutive visits are reported as prespecified events of clinical importance.
BP, blood pressure; PCI, potentially clinically important.

Supplementary Table S5. Physical and Vital Sign Results, Mean Change from Baseline at Final On-Therapy Evaluation, Safety Population

	Children			*Adolescents*		
	Placebo (n = 42)	*Fluoxetine (n = 45)*	*Desvenlafaxine (n = 43)*	*Placebo (n = 70)*	*Fluoxetine (n = 67)*	*Desvenlafaxine (n = 72)*
Systolic BP, supine (mm Hg)	1.6	0.9	0.2	–0.4	–1.1	–0.8
Diastolic BP, supine (mm Hg)	3.1[a]	–0.5[b]	0.0[b]	1.5	–0.7	0.2
Pulse, supine (beats/min)	1.4	–3.7[c]	–0.7	2.8[d]	0.2	0.4
Systolic BP, orthostatic (mm Hg)	–1.2	–0.7	2.4	0.2	–0.1	–1.0
Diastolic BP, orthostatic (mm Hg)	–2.8[c]	0.4	0.4	–1.1	0.2	0.5
Pulse, orthostatic (beats/min)	–0.9	–2.8	0.3	–1.7	0.1	2.3
Weight (kg)	1.2[a]	0.3[e]	0.1[e]	0.3	0.0	0.3
Height (cm)	0.7[a]	0.6[a]	0.8[a]	0.3[c]	0.5[c]	0.3[d]
BMI (kg/m^2)	0.4[a]	–0.1	–0.2	0.0	–0.2[d]	0.0

[a] $p < 0.001$ versus baseline.
[b] $p < 0.05$ versus placebo.
[c] $p < 0.01$ versus baseline.
[d] $p < 0.05$ versus baseline.
[e] $p \leq 0.001$ versus placebo.
BMI, body mass index; BP, blood pressure; SE, standard error.

Supplementary Table S6. Number of Patients with Potentially Clinically Important Laboratory Findings During the On-Therapy Period, Safety Population, *n* (%)

	Placebo (n = *112*)	*Fluoxetine* (n = *112*)	*Desvenlafaxine* (n = *115*)
Total	69/109 (63.3)	75/107 (70.1)	74/108 (68.5)
Alanine aminotransferase			
≥3 × ULN	0/105	1/105 (1.0)	0/102
Aspartate aminotransferase			
≥3 × ULN	0/105	1/105 (1.0)	0/102
Bicarbonate			
Increase or decrease from baseline of ≥4 mmol/L and ONR	1/99 (1.0)	1/95 (1.1)	2/94 (2.1)
Bilirubin			
≥1.5 × ULN	2/105 (1.9)	2/105 (1.9)	1/102 (1.0)
Cholesterol			
Increase >1.29 mmol/L and value ≥6.21 mmol/L	1/105 (1.0)	0/105	1/102 (1.0)
HDL cholesterol			
Decrease >0.21 mmol/L and value ≤1.16 mmol/L	9/105 (8.6)	9/105 (8.6)	13/102 (12.7)
LDL cholesterol			
Increase ≥0.78 mmol/L and value ≥4.14 mmol/L	1/104 (1.0)	0/105	0/102
Triglycerides			
≥2.258 mmol/L	8/105 (7.6)	9/105 (8.6)	14/102 (13.7)
Increase ≥1.13 mmol/L and value ≥3.39 mmol/L	1/105 (1.0)	1/105 (1.0)	3/102 (2.9)
Prolactin			
≥40 μg/L	0/99	1/98 (1.0)	0/98
Hematocrit			
<0.32 or >0.50 (Females)	0/54	1/47 (2.1)	1/53 (1.9)
<0.37 or >0.55 (Males)	7/45 (15.6)	7/50 (14.0)	6/43 (14.0)
Hemoglobin			
<115 or >185 g/L (Males)	3/45 (6.7)	2/50 (4.0)	1/44 (2.3)
<95 or >165 g/L (Females)	0/55	0/47	1/53 (1.9)
Leukocytes			
$<2.8 \times 10^9$/L or $>16 \times 10^9$/L	0/100	0/97	1/97 (1.0)
Ketones			
Positive value	2/104 (1.9)	2/105 (1.9)	2/102 (2.0)
Specific gravity			
<1.001 or >1.035	1/104 (1.0)	1/105 (1.0)	0/102
Urine protein			
Positive value	54/104 (51.9)	63/105 (60.0)	63/102 (61.8)

HDL, high-density lipoprotein; LDL, low-density lipoprotein; ONR, outside normal range; ULN, upper limit of normal.

Supplementary Table S7. Mean Changes from Baseline at Final Evaluation for Selected Laboratory Tests: Safety Population

	Children			*Adolescents*		
	Placebo (n = 42)	*Fluoxetine (n = 45)*	*Desvenlafaxine (n = 43)*	*Placebo (n = 70)*	*Fluoxetine (n = 67)*	*Desvenlafaxine (n = 72)*
AST (IU/L)	–0.1	0.0	–0.7	0.0	–0.9	0.1
ALT (IU/L)	0.2	1.0	–0.1	–0.3	–1.3	–0.2
Alkaline phosphatase (IU/L)	0.1	–14.3	–12.3	–9.9	–6.2	–8.3
Total cholesterol (mg/dL)	1.4	4.7	–0.3	–5.4	1.0	–0.5
HDL cholesterol (mg/dL)	–0.6	1.8	0.4	–1.5	0.0	–0.1
LDL cholesterol (mg/dL)	3.5	5.3	–0.7	–5.4	2.4	–3.8
Triglycerides (mg/dL)	–4.4	–12.5	–0.2	7.6	–6.9	16.5
Prolactin (ng/mL)	1.0	0.5	0.2	0.7	0.8	1.2

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.