Supplementary Data

Supplementary Data S1: Exclusion Criteria and Prohibited Treatments

Exclusion criteria

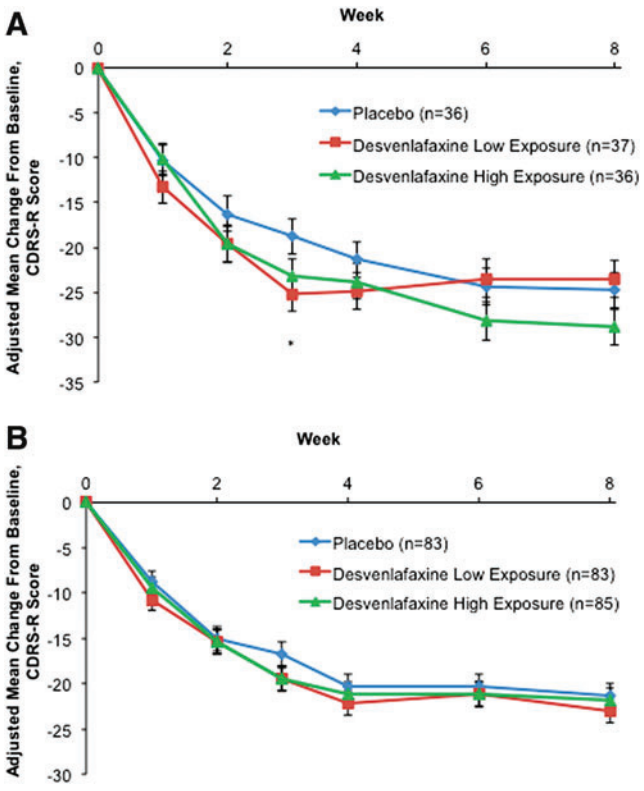
Patients were excluded from the study if they were not in a generally healthy medical condition, as determined by the investigator, had any major acute illness within 90 days before the screening visit, had a history of seizure disorder other than a single childhood febrile seizure, had a history or 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, or obsessive-compulsive disorder; current generalized anxiety disorder, panic disorder, social anxiety disorder, or attention-deficit/hyperactivity disorder considered a primary diagnosis (or causing a higher degree of stress or impairment than MDD); history or presence of borderline personality disorder, clinically important personality disorder, or history of recurrent, intentional self-injurious behavior; or 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 3 or more times the 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, previous clinically significant adverse event related to venlafaxine or desvenlafaxine, or history of failure to respond to an adequate course of treatment for MDD with 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 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 drug; formal psychotherapy for



SUPPLEMENTARY FIG. S1. Adjusted mean (standard error) change from baseline in CDRS-R score; MMRM analysis, ITT population: **(A)** children (7–11 years), **(B)** adolescents (12–17 years). CDRS-R, Children's Depression Rating Scale-Revised; ITT, intent-to-treat; MMRM, mixed-effects model for repeated measures. *$p = 0.021$, desvenlafaxine low exposure versus placebo.

SUPPLEMENTARY TABLE S1. TITRATION, TREATMENT PERIOD, AND TAPER DOSING

	Titration (baseline/day 1–7) dose, mg	*Treatment (week 1–8) dose, mg*	*Taper[a] (week 8–9) dose, mg*
Baseline body weight, kg			
Desvenlafaxine low exposure group			
≥20 and <35	10	20	10
≥35 and <70	10	25	10
≥70	20	35	20
Desvenlafaxine high exposure group			
≥20 and <35	10	25	10
≥35 and <70	10	35	10
≥70	20	50	20

[a]For patients not entering the open-label extension study, a 1-week blinded taper phase followed the week 8 visit.

Supplementary Table S2. Criteria for Potentially Clinically Important Vital Signs, Electrocardiogram Results, and Laboratory Findings

Vital signs		
Supine pulse (years)	*Females*	*Males*
6–7	*<68 >126*	*<68 >126*
8–9	*<63 >121*	*<63 >121*
10–11	*<63 >121*	*<63 >121*
12–13	*<63 >121*	*<58 >116*
14–15	*<58 >116*	*<54 >110*
16–17	*<54 >110*	*<50 >104*
18	*<50 >104*	<45 >99
Temperature	*Increase of ≥2°F and temperature ≥101°F*	
Weight	*Increase of ≥7% or decrease of ≥3.5% in body weight*	
Supine systolic BP, supine diastolic BP	*Elevation of second supine BP reading at three consecutive visits as per below*	
Sustained diastolic BP	*An increase of 10 mm Hg from the baseline value AND elevation of the second supine diastolic BP reading at three consecutive visits as per below*	

	Height (cm)	*Systolic BP (mm Hg)*	*Diastolic BP (mm Hg)*
Females (years)			
6	*<111.6*	*>110*	*>73*
	111.6–118.6	*>113*	*>74*
	>118.6	*>115*	*>76*
7	*<118.1*	*>112*	*>74*
	118.1–125.6	*>115*	*>76*
	>125.6	*>116*	*>77*
8	*<123.9*	*>114*	*>75*
	123.9–131.9	*>116*	*>77*
	>131.9	*>118*	*>78*
9	*<129.0*	*>115*	*>76*
	129.0–137.4	*>118*	*>78*
	>137.4	*>120*	*>79*
10	*<133.7*	*>117*	*>77*
	133.7–142.8	*>120*	*>79*
	>142.8	*>122*	*>80*
11	*<139.4*	*>119*	*>78*
	139.4–149.2	*>122*	*>80*
	>149.2	*>124*	*>81*
12	*<146.5*	*>121*	*>79*
	146.5–156.4	*>124*	*>81*
	>156.4	*>126*	*>82*
13	*<152.7*	*>123*	*>80*
	152.7–162.0	*>126*	*>82*
	>162.0	*>128*	*>83*
14	*<156.0*	*>125*	*>81*
	156.0–164.9	*>127*	*>83*
	>164.9	*>129*	*>84*
15	*<157.5*	*>126*	*>82*
	157.5–166.3	*>129*	*>84*
	>166.3	*>130*	*>85*
16	*<158.2*	*>127*	*>83*
	158.2–166.9	*>130*	*>85*
	>166.9	*>132*	*>86*
17	*<158.6*	*>127*	*>83*
	158.6–167.3	*>130*	*>85*
	>167.3	*>132*	*>86*
Males (years)			
6	*<112.2*	*>112*	*>73*
	112.2–119.1	*>115*	*>75*
	>119.1	*>117*	*>76*
7	*<118.4*	*>113*	*>75*
	118.4–125.7	*>117*	*>77*
	>125.7	*>119*	*>78*

(*continued*)

SUPPLEMENTARY TABLE S2. (CONTINUED)

	Height (cm)	*Systolic BP (mm Hg)*	*Diastolic BP (mm Hg)*
8	*<124.3*	*>114*	*>77*
	124.3–132.1	*>118*	*>79*
	>132.1	*>120*	*>80*
9	*<129.6*	*>116*	*>78*
	129.6–137.9	*>119*	*>80*
	>137.9	*>121*	*>81*
10	*<134.4*	*>117*	*>79*
	134.4–143.3	*>121*	*>81*
	>143.3	*>123*	*>82*
11	*<139.0*	*>119*	*>79*
	139.0–148.5	*>123*	*>81*
	>148.5	*>125*	*>82*
12	*<144.3*	*>122*	*>80*
	144.3–154.4	*>125*	*>82*
	>154.4	*>127*	*>83*
13	*<151.1*	*>124*	*>80*
	151.1–161.7	*>128*	*>82*
	>161.7	*>130*	*>83*
14	*<158.7*	*>127*	*>81*
	158.7–169.5	*>130*	*>83*
	>169.5	*>132*	*>84*
15	*<164.8*	*>129*	*>82*
	164.8–175.3	*>133*	*>84*
	>175.3	*>135*	*>85*
16	*<168.5*	*>132*	*>83*
	168.5–178.6	*>135*	*>85*
	>178.6	*>137*	*>87*
17	*<170.4*	*>134*	*>86*
	170.4–180.2	*>138*	*>87*
	>180.2	*>140*	*>89*
Orthostatic changes	*Decrease of ≥15 mm Hg diastolic last supine to first standing or decrease of ≥20 mm Hg systolic last supine to first standing or increase of pulse ≥20 bpm*		
Electrocardiogram			
Heart rate	*Same criteria as for BP above*		
PR interval	≥200 milliseconds		
QT interval	≥480 milliseconds		
QRS interval	≥120 milliseconds		
QTcX	≥500 milliseconds		
	>470 milliseconds (females) and >450 milliseconds (males) or increase of ≥60 milliseconds		
	≥470 milliseconds (females) and ≥450 milliseconds (males)		
	≥30 milliseconds change from baseline		
Rhythm	*Any rhythm other than sinus rhythm*		
Overall evaluation	*Anything other than normal*		
Laboratory test results			
Hemoglobin	<95 or >165 g/L (females) or <115 or >185 g/L (males)		
Hematocrit	<0.32 or >0.50 (females) or <0.37 or >0.55 (males)		
White blood cell count	$<2.8\times10^9$/L or $>16\times10^9$/L		
Platelet count	$<75\times10^9$/L or $>700\times10^9$/L		
Sodium	<126 or >156 mmol/L		
Potassium	<2.5 or >6.5 mmol/L		
Calcium	<2.046 or >2.994 mmol/L		
Chloride	<90 or >118 mmol/L		
Glucose, fasting/ nonfasting/unknown	<2.22 or ≥11.10 mmol/L		
Uric acid	>0.4758 mmol/L (females) or >0.5948 mmol/L (males)		
Total protein	<45 or ≥100 g/L		
Albumin	<25 g/L		
Total bilirubin	*≥1.5 × ULN*		
ALT/SGPT	*≥3 × ULN*		
AST/SGOT	*≥3 × ULN*		
Alkaline phosphatase	*≥3 × ULN*		
Blood urea nitrogen	*≥1.5 × ULN*		
Creatinine	*≥1.5 × ULN*		

(*continued*)

SUPPLEMENTARY TABLE S2. (CONTINUED)

	Height (cm)	*Systolic BP (mm Hg)*	*Diastolic BP (mm Hg)*
Bicarbonate	*Increase or decrease from baseline of >4 mmol/L and ONR*		
Total cholesterol, fasting/ nonfasting/unknown	≥7.758 mmol/L		
Total cholesterol, fasting/ nonfasting/unknown	*Increase ≥1.29 mmol/L and value ≥6.21 mmol/L*		
HDL cholesterol, fasting/ nonfasting/unknown	*Decrease >0.21 mmol/L and value ≤1.16 mmol/L*		
LDL cholesterol direct, fasting/nonfasting/ unknown	*Increase ≥0.78 mmol/L and value ≥4.14 mmol/L*		
LDL cholesterol Friedewald, fasting/ nonfasting/unknown	*Increase ≥0.78 mmol/L and value ≥4.14 mmol/L*		
Triglycerides, fasting/ nonfasting/unknown	*≥2.258 mmol/L*		
Triglycerides, fasting/ nonfasting/unknown	*Increase ≥1.13 and ≥3.39 mmol/L*		
Prolactin	*≥40 μg/L*		
Urinalysis			
Specific gravity	<1.001 or >1.035		
pH	≤4 or ≥9		
Protein/albumin	Positive value		
Glucose/sugar	Positive value		
Hemoglobin/blood	Positive value		
Ketones	Positive value		

Pfizer criteria in italics, European Medicines Evaluation Agency criteria in bold.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ONR, outside normal range; QTcB, QT correction using Bazett formula; QTcF, QT correction using the Fridericia formula; QTcX, either QTcB or QTcF; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; ULN, upper limit of normal range.

MDD, fluoxetine, antipsychotic drugs, or investigational drugs or devices within 30 days of first dose of study drug; antidepressants other than fluoxetine, venlafaxine, or desvenlafaxine, monoamine oxidase inhibitors (MAOIs), anxiolytics, benzodiazepines and non-benzodiazepines, sumatriptan, naratriptan, zolmitriptan (or other drugs indicated for the treatment of migraine with a similar mechanism of action), or tryptophan supplements within 14 days of first dose of study drug; and herbal products intended to treat anxiety, insomnia or depression, sedative-hypnotic drugs, other psychotropic drugs or substances, or nonpsychopharmacologic drugs 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 drug. MAOIs were also prohibited for 7 days after last dose of study drug. 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 Analysis

Interim analysis

A partially unblinded interim analysis was conducted by an independent party and reviewed by the Data Monitoring Committee after 75% of patients had the opportunity to complete the 8-week double-blind phase (including both subjects who have completed and those who have discontinued the 8-week treatment 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. Based on the results of the interim analysis, the sample size was increased from 333 to 360 total subjects (an additional 9 subjects were randomized to each of the 3 treatment groups).

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, 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, 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 by a weighted average over patterns, where the weight was based on the proportion of completers, following the approach by Hedeker and Gibbons (2006).

The results of all sensitivity analyses were consistent with those of the primary analysis.

Reference

Hedeker D, Gibbons RD: Missing data in longitudinal studies. In: Longitudinal Data Analysis. Hoboken, NJ: John Wiley & Sons, Inc., 2006, pp. 279–312.

Supplementary Table S3. Occurrence of Prespecified TEAEs of Clinical Importance (Tier-1 TEAEs), Safety Population

	Placebo (n = *120*)	*Desvenlafaxine low exposure* (n = *122*)	*Desvenlafaxine high exposure* (n = *121*)
Agranulocytosis	0	1 (0.8)	1 (0.8)
Hematochezia	0	1 (0.8)	0
Contusion	0	1 (0.8)	0
Laceration	0	2 (1.6)	3 (2.5)
Blood pressure increase	0	0	1 (0.8)
Blood pressure orthostatic abnormal	1 (0.8)	2 (1.6)	2 (1.7)
Akathisia	0	1 (0.8)	0
Aggression	0	2 (1.6)	0
Hypomania	0	1 (0.8)	0
Self-injurious behavior	2 (1.7)	3 (2.5)	1 (0.8)
Suicidal ideation	1 (0.8)	1 (0.8)	2 (1.7)
Suicide attempt	1 (0.8)	1 (0.8)	0
Epistaxis	0	0	2 (1.7)
Ecchymosis	0	1 (0.8)	0

TEAE, treatment-emergent adverse event.

Supplementary Table S4. Summary of Suicidal Ideation and Behavior Reported on the Columbia-Suicide Severity Rating Scale at Baseline and at Any Postbaseline Assessment, Safety Population

	Placebo (n = *120*)	*Desvenlafaxine low exposure* (n = *122*)	*Desvenlafaxine high exposure* (n = *121*)
Baseline			
Number assessed	120	122	121
Suicidal behavior and/or ideation *n* (%)	12 (10.0)	8 (6.6)	13 (10.7)
Suicidal behavior	0	0	0
Suicidal ideation	12 (10.0)	8 (6.6)	13 (10.7)
Wish to be dead	12 (10.0)	8 (6.6)	13 (10.7)
Nonspecific active suicidal thoughts	6 (5.0)	1 (0.8)	3 (2.5)
Active suicidal ideation with any methods (no plan) without intent to act	0	1 (0.8)	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 (0.8)	0	1 (0.8)
Any postbaseline assessment			
Number assessed	119	120	121
Suicidal behavior and/or ideation *n* (%)	19 (16.0)	10 (8.3)	20 (16.5)
Suicidal behavior	1 (0.8)	1 (0.8)	0
Completed suicide	0	0	0
Suicide attempt	1 (0.8)	1 (0.8)	0
Preparatory acts toward imminent suicidal behavior	1 (0.8)	0	0
Aborted attempt	0	0	0
Interrupted attempt	0	0	0
Preparatory acts or behavior	1 (0.8)	0	0
Suicidal ideation	19 (16.0)	10 (8.3)	20 (16.5)
Wish to be dead	18 (15.1)	10 (8.3)	20 (16.5)
Nonspecific active suicidal thoughts	12 (10.1)	5 (4.2)	10 (8.3)
Active suicidal ideation with any methods (no plan) without intent to act	5 (4.2)	1 (0.8)	5 (4.1)
Active suicidal ideation with some intent to act, without specific plan	1 (0.8)	0	0
Active suicidal ideation with specific plan and intent	2 (1.7)	1 (0.8)	0
Self-injurious behavior, no suicidal intent	4 (3.4)	3 (2.5)	3 (2.5)

SUPPLEMENTARY TABLE S5. MEAN CHANGES FROM BASELINE AT FINAL EVALUATION FOR SELECTED LABORATORY TESTS, SAFETY POPULATION

	Children			*Adolescents*		
	Placebo (n = 36)	*Desvenlafaxine low exposure (n = 37)*	*Desvenlafaxine high exposure (n = 36)*	*Placebo (n = 84)*	*Desvenlafaxine low exposure (n = 85)*	*Desvenlafaxine high exposure (n = 85)*
AST (U/L)	–0.8	–0.7	–0.9	–0.8	1.5	–0.4
ALT (U/L)	1.1	–0.4	–1.5	–1.6	1.8	–0.03
Alkaline phosphatase (U/L)	–10.5	–2.9	–12.2	–8.7	–12.6	–6.7
Total cholesterol/lipid (mg/dL)	–4.5	–1.9	–1.4	–3.8	–2.9	1.2
HDL cholesterol (mg/dL)	–4.0	–0.9	–0.5	–2.4	–0.5	0.1
LDL cholesterol (mg/dL)	0.6	–2.7	–4.7	–3.2	–2.6	2.1
Triglycerides/lipid (mg/dL)	–6.9	27.6	29.5	9.2	0.5	–9.9

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