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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Effexor XR® / Venlafaxine HCl

PROTOCOL NO.: 0600B2-396-US

PROTOCOL TITLE: Double-Blind, Placebo-Controlled Study of Venlafaxine ER in Children and Adolescents with Generalized Anxiety Disorder

Study Centres: A total of 39 centres in the United States participated in this study (37 centres enrolled subjects).

Study Initiation Date and Completion Dates: August 2000 to September 2001.

Phase of Development: Phase 3

Study Objective: To compare the anxiolytic efficacy and safety of venlafaxine extended release (ER) with placebo in children and adolescents with generalized anxiety disorder (GAD).

METHODS

Study Design: This was a multicenter, parallel-group, randomised, double-blind, placebo-controlled, flexible-dose, outpatient study in children and adolescents with GAD. Following a 7 ± 3 day single-blind placebo lead-in period, eligible subjects received venlafaxine ER or placebo for up to 8 weeks, followed by a taper period of up to 14 days. Subjects were to return for a post study evaluation 4 to 10 days after taking the last dose of study medication, regardless of the length of time the study medication was taken. The overall duration of a subjects’ study participation was 11 to 13 weeks.

Number of Subjects (Planned and Analysed): Of 272 subjects screened, 165 completed the single-blind placebo lead-in period and were randomised, and a total of 164 subjects received at least one dose of study medication.

Diagnosis and Main Criteria for Inclusion: Male and female outpatient children (6-11 years of age) or adolescents (12–17 years of age), who met the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM-IV) and Columbia-Kiddie Schedule for Affective Disorders and Schizophrenia GAD Subsection (C-KIDDIE-SADS GAD) criteria for GAD, and had the following scores at prestudy screening and baseline (Study Day -1):
• a total score of ≥20 on the Severity component and a total score of ≥7 on the Impairment component of the C-KIDDIE-SADS GAD,

• a score of ≥4 on 3 items of the C-KIDDIE-SADS GAD Severity component (severity of anxiety and worry, difficulty controlling the worry, and severity of associated symptoms),

• a score of ≥4 on 2 other items of the Severity component of the C-KIDDIE-SADS GAD (frequency of anxiety and worry during the average week, and frequency of associated symptoms during the average week),

• a score of ≥4 on one item of the Impairment component of the C-KIDDIE-SADS GAD (global impairment in functioning),

• a Childhood Depression Rating Scale-Revised (CDRS-R) score <45, and

• a Clinical Global Impressions – Severity of Illness (CGI-S) score of ≥4, and anxiety symptoms for at least 6 months before entry into the study.

**Study Treatment:** Venlafaxine ER (37.5 mg and 75 mg) was supplied as capsules, to be taken once per day with food in the morning. Evening dosing was permitted if medically indicated. Subjects unable to tolerate the minimum daily dose for their weight category were discontinued from the study. Eligible subjects received venlafaxine ER at daily doses (number of 37.5 mg and/or 75 mg capsules) that were based on the weight of subjects (3 weight ranges 25-39 kg, 40-49 kg, ≥ 50 kg) and included pre-specified dose increases for each weight class during the following weeks on on-therapy: Week 2, Weeks 3 and 4, and for the remaining weeks of the 8-week treatment period. All doses were based on weight and supported by pharmacokinetic data of venlafaxine in children and adolescents which suggested that children and adolescents from study 0600A-126-US. Upon completion of the 8-week treatment period, or early termination, daily doses of ≥75 mg were tapered in one or two 7-day steps.

**Efficacy Evaluations:** To determine efficacy the following determinations were made:

• C-KIDDIE-SADS GAD (complete) at prestudy, baseline (Day -1), and Study Days 28 and 56.

• C-KIDDIE-SADS GAD (9 delineated items) on Study Days 7, 14, 21, 42, and 49.

• Paediatric Anxiety Rating Scale (PARS) at baseline (Day -1) and Study Days 7, 14, 21, 28, 42, 49, and 56.

• Hamilton Rating Scale for Anxiety (HAM-A) at baseline (Day -1) and Study Days 28 and 56.

• Self Report for Childhood Anxiety Related Disorder (SCARED) Parent and Patient forms at baseline (Day -1) and Study Days 28 and 56.
Clinical Global Impressions-Severity (CGI-S) at prestudy visit and baseline (Day -1) and CGI-S and Clinical Global Impressions-Improvement (CGI-I) at Study Days 7, 14, 21, 28, 42, 49, and 56.

The primary efficacy variable was the C-KIDDIE-SADS GAD (9 delineated items). Secondary efficacy variables were the C-KIDDIE-SADS GAD complete, Severity component (5 delineated items) and Impairment component (4 delineated items) total scores, the PARS total score, the HAM-A total score, the SCARED Parent and Patient total scores, and the CGI-S and CGI-I scores.

Safety Evaluations: The following safety variables were assessed during this study: adverse events (AEs), physical examinations including height (at prestudy and Study Day 56), screening clinical laboratory (urine drug screen, thyroid stimulation hormone, and serum pregnancy test for all females of childbearing potential), vital signs including weight (at prestudy [including temperature], baseline [Day -1], on Days 7, 14, 21, 28, 42, and 49, Day 56 [including temperature], and at the poststudy visit), clinical safety laboratory determinations (at prestudy and on Day 56, including pregnancy testing for all females of childbearing potential), and electrocardiograms (ECGs) (at prestudy, baseline [Day –1], and on Day 56).

Statistical Methods: Unless otherwise noted, all tests of hypotheses were 2-sided and were at least at the 5% level of significance.

Efficacy analyses: A student t-test was used to test for comparability in the randomly assigned treatment groups with respect to age, weight, and the baseline total scores of the C-KIDDIE-SADS GAD (complete, 9 delineated items, and subscales), PARS, HAM-A, and SCARED scales. Fisher's exact test was used to compare the distribution of nominal attributes (eg, ethnic origin, sex). These statistical comparisons of baseline data were used to check the performance of the randomization with respect to comparability of the treatment groups.

Changes from baseline for the primary and secondary efficacy variables (ie, C-KIDDIE-SADS GAD [9 delineated items and complete], PARS, HAM-A, CGI-S, and SCARED scales) were analyzed at each time point using a parametric 2-way analysis of covariance (ANCOVA) with treatment and investigator as factors and the associated baseline as the covariate. The CGI-I was analyzed by using the same model as the CGI-S, except that there was no baseline CGI-I to enter into the model. The assumptions of the primary ANCOVA model (ie, normality, homogeneity of variance, and parallelism of slopes) were tested.

For each scale, the total score was the mean of all items multiplied by the total number of items in the scale. If more than 50% of the items were missing from a scale, then the total score for that time point was not used in the analysis and was treated as missing. On the C-KIDDIE-SADS GAD subscales, if 3 or more of the individual Severity items or 2 or more of the Impairment items were missing, then the total score for that time point was not used in the analysis. On the C-KIDDIE-SADS GAD (Complete), if 3 or more of the individual Severity items, 2 or more of the Impairment items, or 50% or more of the total 29 items were
missing, then the total score for that time point was not used in the analysis. Instead, the most recent previous total score and subscale scores were carried forward and used in the analysis. In this approach the score for a missing item was the score on that item from the most recent administration of the scale. However, an item score from the baseline period was never carried into the double-blind period. Exploratory analyses to address missing data were performed by using Entsuah RANKing procedure (ETRANK) procedures.

In addition to a last-observation-carried-forward (LOCF) analysis in which the last observation for a dropout was carried forward into all subsequent time periods, analyses of the observed data at each time point were employed, using the ETRANK. In this analysis, different statistical weights are assigned to subjects’ efficacy data at each time point, and thus subjects who withdrew before completion of the study were statistically weighted more heavily at early time points than subjects who remained in the study, dependent on the subjects’ reason for withdrawal (eg, intolerance, lack of therapeutic effect, etc). Subjects who completed the study; however, had more statistical weight assigned at the final time point than subjects who withdrew before the final time point. The scoring systems generated were either categorical, time-related ranks, or observed levels, and were used to obtain a p-value or empirical significance level with time point descriptive statistics.

The LOCF and observed data analyses (ETRANK) were applied to the primary (C-KIDDIE-SADS GAD, 9 delineated items) and secondary variables. These 2 forms of analyses were done on the intent-to-treat (ITT) subjects. ITT was defined as follows: all subjects who had been randomly assigned to double-blind therapy, had a baseline evaluation for the primary efficacy variable, took at least 1 dose of their assigned study medication, and had at least 1 post-baseline evaluation for the primary efficacy variable, either during therapy or within 3 days of the last day of treatment.

Responder status was assessed for 3 of the scales. Patients whose total score (for the C-KIDDIE-SADS GAD [9 delineated items] or PARS scales) decreased by 50% or more from baseline were considered responders. On the CGI scale, subjects who attained a score of 1 or 2 on the GCI-I were considered responders. Methods based on categorical data analysis were applied to the response data.

Safety analyses: Fisher’s exact test was used for comparisons among groups of the proportion of subjects who discontinued from the study, both overall and for specific reasons, and for comparison of the incidence of AEs.

For laboratory test results, vital signs, weight, and ECG data, the paired test was used to test for significant changes in mean values over time within treatment groups. Comparisons between groups were made by 2-way ANCOVA with treatment and investigator serving as the factors and baseline values as the covariate. Categorical analyses were used to assess changes within and differences between treatment groups. The within-treatment trend with respect to time was also assessed. Additionally, each individual laboratory determination was classified as to whether it was of potential clinical importance based on pre-established criteria. No interim analyses were performed.
RESULTS

Subject Disposition and Demography: Subject disposition is summarised in Table 1.

Of 272 subjects screened, 165 subjects (92 children, 6–11 years old, and 72 adolescents, 12-17 years old) completed the single-blind placebo lead-in period and were randomised to receive placebo (82 subjects, 45 children and 37 adolescents) or venlafaxine ER (82 subjects, 46 children and 36 adolescents) during the 8-week double-blind treatment period, not including 1 subject that was given study medication but failed to return after the baseline (Day -1) visit (“no data” subject). Thus, a total of 164 subjects who received at least 1 dose of study medication were included in all safety analyses. Of these 164 subjects, 4 subjects did not meet the ITT criteria and were not included in the primary efficacy evaluation. Overall 160 subjects were analyzed for efficacy (ITT), and 129 subjects completed the 8-week double-blind treatment period as per protocol.

Subject disposition and reasons for discontinuation are summarised in Table 1. A slightly higher percentage of subjects discontinued from the venlafaxine ER group, with the most common reasons for discontinuation being failure to return and protocol violation.

Table 1. Subject Disposition and Subjects Analysed

<table>
<thead>
<tr>
<th>Population Subset</th>
<th>Placebo</th>
<th>Venlafaxine ER</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entered placebo lead-in period</td>
<td>84</td>
<td>81</td>
<td>165</td>
</tr>
<tr>
<td>Entered double blind</td>
<td>84</td>
<td>80</td>
<td>165</td>
</tr>
<tr>
<td>Enrolled</td>
<td>84</td>
<td>80</td>
<td>164</td>
</tr>
<tr>
<td>Assessed for safety</td>
<td>84</td>
<td>80</td>
<td>164</td>
</tr>
<tr>
<td>Analysed for efficacy (Intent to treat)</td>
<td>82</td>
<td>78</td>
<td>161</td>
</tr>
<tr>
<td>Discontinued</td>
<td>16</td>
<td>18</td>
<td>34</td>
</tr>
<tr>
<td>Double blind treatment period, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any reason</td>
<td>16 (19)</td>
<td>18 (23)</td>
<td>34</td>
</tr>
<tr>
<td>Adverse reaction</td>
<td>2 (2)</td>
<td>2 (3)</td>
<td>4</td>
</tr>
<tr>
<td>Failed to return</td>
<td>5 (6)</td>
<td>5 (6)</td>
<td>10</td>
</tr>
<tr>
<td>Other event</td>
<td>2 (2)</td>
<td>3 (4)</td>
<td>5</td>
</tr>
<tr>
<td>Subject request unrelated to study</td>
<td>2 (2)</td>
<td>3 (4)</td>
<td>5</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>3 (4)</td>
<td>2 (3)</td>
<td>5</td>
</tr>
<tr>
<td>Unsatisfactory response-lack of efficacy</td>
<td>2 (2)</td>
<td>3 (4)</td>
<td>5</td>
</tr>
</tbody>
</table>

n (%) = number of subjects (percentage).

Demographic and baseline characteristics for all subjects are summarized in Table 2. Overall demography and baseline characteristics were similar in both the treatment groups.
# Table 2.  **Demographic Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo n=84</th>
<th>Venlafaxine ER n=80</th>
<th>p-value/Statistical Test$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>11.1</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>2.5</td>
<td>3.2</td>
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<td>Range</td>
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</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>46 (55)</td>
<td>28 (35)</td>
<td>0.011$^c$</td>
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<tr>
<td>Male</td>
<td>38 (45)</td>
<td>52 (65)</td>
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</tr>
<tr>
<td><strong>Ethnic origin, n (%)</strong></td>
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<td></td>
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<td>Arabic</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0.547$^c$</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
<td>1 (1)</td>
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<tr>
<td>Black</td>
<td>7 (8)</td>
<td>7 (9)</td>
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<td>Hispanic</td>
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<td>13 (16)</td>
<td></td>
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<td>Native American</td>
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<td>Other</td>
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<td>0 (0)</td>
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</tr>
<tr>
<td>White</td>
<td>60 (71)</td>
<td>58 (73)</td>
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<td><strong>Body weight, kg</strong></td>
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<td>Mean</td>
<td>51.7</td>
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<tr>
<td>SD</td>
<td>20.7</td>
<td>17.1</td>
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<tr>
<td>Range</td>
<td>23.0-105.0</td>
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<tr>
<td><strong>Height, cm</strong></td>
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</tr>
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<td>Mean</td>
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<td>148.0</td>
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<tr>
<td>SD</td>
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<tr>
<td>Range</td>
<td>112.0-172.0</td>
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<tr>
<td><strong>Duration of episode, weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>168</td>
<td>179</td>
<td>0.616$^c$</td>
</tr>
<tr>
<td>SD</td>
<td>127</td>
<td>149</td>
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<tr>
<td>Range</td>
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<td>27.0-697.0</td>
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<tr>
<td><strong>Duration of current episode, weeks (%)</strong></td>
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<td>&lt;5</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.797$^c$</td>
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<td>25-48</td>
<td>10 (12)</td>
<td>7 (9)</td>
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<td>49-96</td>
<td>24 (29)</td>
<td>23 (29)</td>
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<tr>
<td>&gt;96</td>
<td>50 (60)</td>
<td>50 (63)</td>
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<tr>
<td><strong>Baseline Scores</strong></td>
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<tr>
<td>C-KIDDIE-SADS GAD (9-delineated items)</td>
<td></td>
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<td>0.571$^t$</td>
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<tr>
<td>Mean</td>
<td>39.7</td>
<td>39.3</td>
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<td>SD</td>
<td>4.7</td>
<td>3.7</td>
<td></td>
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<tr>
<td>Range</td>
<td>28.0-52.0</td>
<td>32.0-48.0</td>
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<tr>
<td>C-KIDDIE-SADS GAD (complete / total score)</td>
<td>n=83</td>
<td>n=80</td>
<td>0.418$^d$</td>
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<tr>
<td>Mean</td>
<td>74.3</td>
<td>73.6</td>
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<td>SD</td>
<td>6.0</td>
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<td>57.0-91.0</td>
<td>61.0-85.0</td>
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<tr>
<td>C-KIDDIE-SADS subscale Impairment (4-items)</td>
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<td>0.373$^d$</td>
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<tr>
<td>Mean</td>
<td>16.2</td>
<td>15.9</td>
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<td>Range</td>
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$^a$: C and t indicate p-value for chi-square or paired t test, respectively.

Abbreviations:  SD= Standard Deviation; n (%) = number of subjects (percentage); C-KIDDIE-SADS GAD = Columbia-Kidddie-Schedule for Affective Disorders and Schizophrenia GAD subsection; CGI = Clinical Global Impressions; PARS = Paediatric Anxiety Rating Scale; HAM-A = Hamilton Psychiatric Rating Scale for Anxiety; SCARED = Self Report for Childhood Anxiety Related Disorder Parent or Patient form
### Table 2. Demographic Characteristics (continued)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo</th>
<th>Venlafaxine ER</th>
<th>p-value/Statistical Testa</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-KIDDIE-SADS subscale Severity (5 items)</td>
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</tr>
<tr>
<td>Mean</td>
<td>23.5</td>
<td>23.4</td>
<td>0.865</td>
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<tr>
<td>SD</td>
<td>3.0</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>17.0-31.0</td>
<td>18.0-29.0</td>
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<tr>
<td>PARS</td>
<td></td>
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<tr>
<td>Mean</td>
<td>23.7</td>
<td>23.8</td>
<td>0.841c</td>
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<tr>
<td>SD</td>
<td>3.2</td>
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<td>Range</td>
<td>9.0-31.0</td>
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<td>HAM-A</td>
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<td>Mean</td>
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<td>36.2</td>
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<td>Range</td>
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<td>SCARED Patient</td>
<td>N=84</td>
<td>N=79</td>
<td>0.845c</td>
</tr>
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<td>Mean</td>
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<td>Range</td>
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<td>3.0-71.0</td>
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<td>CGI-Severity</td>
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<tr>
<td>Mean</td>
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<td>4.5</td>
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<td>SD</td>
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<td>Range</td>
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<td>CGI-Severity, n (%)</td>
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<tr>
<td>0</td>
<td>54 (64)</td>
<td>47 (59)</td>
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<td>4</td>
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</tr>
<tr>
<td>6</td>
<td>6 (7)</td>
<td>4 (5)</td>
<td></td>
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C and t indicate p-value for chi-square or paired t test, respectively.

Abbreviations: SD= Standard Deviation; n (%) = number of subjects (percentage); C-KIDDIE-SADS GAD = Columbia-Kiddie-Schedule for Affective Disorders and Schizophrenia GAD subsection; CGI = Clinical Global Impressions; PARS = Paediatric Anxiety Rating Scale; HAM-A = Hamilton Psychiatric Rating Scale for Anxiety; SCARED = Self Report for Childhood Anxiety Related Disorder Parent or Patient form.

Most subjects were white (71–73%), had a mean weight of 51.7 kg (range: 23–105 kg) and 48.6 kg (range 25.0-94.0 kg) for placebo and venlafaxine ER, respectively, and had a current GAD episode at baseline with a duration of at least 6 months (Table 2). The demographic and baseline characteristics of the subjects in the total population did not differ appreciably from those of the ITT population. Fifty-seven (57, 71%) of the 80 venlafaxine ER-treated subjects and 62 (74%) of the 84 placebo subjects received some type of concomitant therapy, most frequently nonsteroidal anti-inflammatory drugs, analgesics/antipyretics, and antihistamines.
Efficacy Results:

Primary Efficacy Variables: Results of the LOCF analyses for the mean scores on the C-KIDDIE-SADS GAD (9 delineated items) total score, the primary efficacy variable, showed marginally significant improvement (p = 0.06) in subjects treated with venlafaxine ER compared with subjects treated with placebo at Week 8 of treatment (Table 3).

The primary endpoint analysis of the observed data using the ETRANK ranking procedure showed that a significant (p = 0.041) advantage for venlafaxine ER over placebo, with the subjects in the venlafaxine ER group (mean = 3.88) having an approximately 3-point lower C-KIDDIE-SADS GAD (9 delineated items) total score at Week 8 than the placebo group (mean = 26.94).

Table 3  Comparison Between Treatment Groups For C-KIDDIE-SADS GAD (9 Delineated Items) (Intent-To-Treat Subjects) - LOCF Analysis

<table>
<thead>
<tr>
<th>Time On Therapy</th>
<th>Treatment Group</th>
<th>Number of subjects</th>
<th>Mean Score</th>
<th>Change from Baseline</th>
<th>Adj Change from Baseline</th>
<th>Std. Error</th>
<th>Adj Means (95 % CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Placebo</td>
<td>82</td>
<td>39.7</td>
<td></td>
<td></td>
<td></td>
<td>39.5 (39.5, 39.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Venlafaxine ER</td>
<td>78</td>
<td>39.3</td>
<td></td>
<td></td>
<td></td>
<td>39.5 (39.5, 39.5)</td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>Placebo</td>
<td>81</td>
<td>35.2</td>
<td>-4.4</td>
<td>-4</td>
<td>0.8</td>
<td>35.5 (34.0, 37.0)</td>
<td>0.276</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine ER</td>
<td>74</td>
<td>34.6</td>
<td>-4.7</td>
<td>-5</td>
<td>0.8</td>
<td>34.5 (33.0, 36.0)</td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>Placebo</td>
<td>82</td>
<td>31.2</td>
<td>-8.4</td>
<td>-7.9</td>
<td>1.01</td>
<td>31.6 (29.6, 33.6)</td>
<td>0.486</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine ER</td>
<td>77</td>
<td>30.4</td>
<td>-8.9</td>
<td>-8.8</td>
<td>1</td>
<td>30.7 (28.8, 32.7)</td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>Placebo</td>
<td>82</td>
<td>29.9</td>
<td>-9.8</td>
<td>-9.1</td>
<td>1.06</td>
<td>30.3 (28.1, 32.5)</td>
<td>0.257</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine ER</td>
<td>78</td>
<td>28.1</td>
<td>-11.2</td>
<td>-10.7</td>
<td>1.04</td>
<td>28.8 (26.7, 30.9)</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>Placebo</td>
<td>82</td>
<td>29.6</td>
<td>-10.1</td>
<td>-9.6</td>
<td>1.03</td>
<td>29.9 (27.7, 32.1)</td>
<td>0.088</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine ER</td>
<td>78</td>
<td>27.2</td>
<td>-12.1</td>
<td>-11.9</td>
<td>1.04</td>
<td>27.6 (25.5, 29.7)</td>
<td></td>
</tr>
<tr>
<td>Week 6</td>
<td>Placebo</td>
<td>82</td>
<td>28.6</td>
<td>-11.1</td>
<td>-11.8</td>
<td>1.11</td>
<td>27.7 (25.3, 30.1)</td>
<td>0.180</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine ER</td>
<td>78</td>
<td>25.6</td>
<td>-13.6</td>
<td>-13.8</td>
<td>1.18</td>
<td>25.7 (23.4, 28.0)</td>
<td></td>
</tr>
<tr>
<td>Week 7</td>
<td>Placebo</td>
<td>82</td>
<td>26</td>
<td>-13.7</td>
<td>-13.9</td>
<td>1.2</td>
<td>25.6 (23.1, 28.1)</td>
<td>0.342</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine ER</td>
<td>78</td>
<td>23.7</td>
<td>-15.6</td>
<td>-15.3</td>
<td>1.16</td>
<td>24.2 (21.8, 26.6)</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>Placebo</td>
<td>82</td>
<td>26.7</td>
<td>-13</td>
<td>-12.6</td>
<td>1.17</td>
<td>26.9 (24.4, 29.4)</td>
<td>0.060</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine ER</td>
<td>78</td>
<td>23.5</td>
<td>-15.8</td>
<td>-15.5</td>
<td>1.12</td>
<td>24.0 (21.6, 26.4)</td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>Placebo</td>
<td>82</td>
<td>26.8</td>
<td>-12.9</td>
<td>-12.7</td>
<td>1.17</td>
<td>26.8 (24.3, 29.3)</td>
<td>0.075</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine ER</td>
<td>78</td>
<td>23.6</td>
<td>-15.5</td>
<td>-15.5</td>
<td>1.12</td>
<td>24.0 (21.6, 26.4)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI=Confidence Interval; C-KIDDIE-SADS GAD = Columbia-Kiddie-Schedule for Affective Disorders and Schizophrenia GAD subsection; LOCF = last-observation-carried-forward

Secondary Efficacy Variables: With regard to secondary outcome measures, treatment with venlafaxine ER was significantly (p < 0.05) better than treatment with placebo according to the results of the LOCF analyses for the mean scores on the C-KIDDIE-SADS GAD Severity component at Weeks 4 and 8, or the CGI-S at Weeks 2, 3, and 8, on the CGI-I at Weeks 3, 6, 7, and 8, and on the SCARED subject at Week 4. The observed cases analyses revealed a significant benefit of venlafaxine ER over placebo for the C-KIDDIE-SADS GAD Severity subscale at Week 8 (p = 0.05), CGI-S at Week 3 (p < 0.03), and CGI-I at Week 3 (p < 0.03).
Moreover, based on the CGI-I score, significantly more subjects in the venlafaxine ER group were reported to have been “much improved” or “very much improved” (ie, responders) at weeks 6, 7, and 8 (LOCF) compared with subjects in the placebo group (p = 0.008, 0.010, and 0.008, respectively). In the observed-cases analysis (CGI-I score), significantly more subjects in the venlafaxine ER group were reported responders at Week 8 compared with the placebo group (p = 0.044).

**Safety Results:** One (1) or more AEs were reported by 67 (84%) of the 80 subjects treated with venlafaxine ER and 73 (87%) of the 84 subjects treated with placebo. Overall, TEAEs were reported during the on-therapy period for 66 (83%) subjects treated with venlafaxine ER and 69 (82%) subjects in the placebo group. Six (6) subjects reported other AEs that were considered of clinical interest: 3 subjects in each treatment group. Table 4 presents the most common TEAEs that occurred in at least 5% of the subjects.

**Table 4. Commonly Reported TEAEs (≥5% In Either Treatment Groups)**

<table>
<thead>
<tr>
<th>Body System</th>
<th>TEAE</th>
<th>Placebo (n=84)</th>
<th>Venlafaxine ER (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>69 (82)</td>
<td>66 (83)</td>
<td></td>
</tr>
<tr>
<td>Body as a whole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11 (13)</td>
<td>12 (15)</td>
<td></td>
</tr>
<tr>
<td>Accidental injury</td>
<td>7 (8)</td>
<td>11 (14)</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>5 (6)</td>
<td>5 (6)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>3 (4)</td>
<td>4 (5)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>29 (35)</td>
<td>21 (26)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>11 (13)</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>2 (2)</td>
<td>7 (9)</td>
<td></td>
</tr>
<tr>
<td>Digestive system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>3 (4)</td>
<td>12 (15)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (6)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>4 (5)</td>
<td>7 (9)</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2 (2)</td>
<td>4 (5)</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3 (4)</td>
<td>4 (5)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (5)</td>
<td>10 (13)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (5)</td>
<td>7 (9)</td>
<td></td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (1)</td>
<td>5 (6)</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 (7)</td>
<td>6 (8)</td>
<td></td>
</tr>
<tr>
<td>Nervousness</td>
<td>1 (1)</td>
<td>6 (8)</td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>1 (1)</td>
<td>6 (8)</td>
<td></td>
</tr>
<tr>
<td>Respiratory system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough increased</td>
<td>5 (6)</td>
<td>5 (6)</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>7 (8)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>7 (8)</td>
<td>5 (6)</td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>6 (7)</td>
<td>5 (6)</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>5 (6)</td>
<td>9 (11)</td>
<td></td>
</tr>
<tr>
<td>Urogenital system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysmenorrhoea</td>
<td>5 (11)</td>
<td>2 (7)</td>
<td></td>
</tr>
<tr>
<td>Adverse event associated with miscellaneous factors</td>
<td>Allergic reaction other than</td>
<td>5 (6)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>drug</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on the number of girls: placebo: n = 46; Venlafaxine ER: n = 28.
Abbreviations: n (%) = number of subjects (percentage); TEAE= treatment-emergent adverse event.
AEs were the primary or a secondary cause for discontinuation of double-blind treatment (on-therapy period) for 3 (4%) subjects in the venlafaxine ER-treated group and for 2 (2%) subjects in the placebo group. Table 5 summarises the AEs leading to discontinuation.

**Table 5. Summary Of Adverse Events Leading To Discontinuation**

<table>
<thead>
<tr>
<th>Treatment Body system</th>
<th>Age / Sex</th>
<th>Mean Daily Dose (mg/day)</th>
<th>Total Daily Dose At Onset (mg/day)</th>
<th>Days On Therapy At Onset</th>
<th>Adverse Event Preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine ER</td>
<td>16/M</td>
<td>123.1 1.73</td>
<td>0</td>
<td>64&lt;sup&gt;c&lt;/sup&gt; (post therapy)</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Body as a whole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13/M</td>
<td>108.1 2.07</td>
<td>150.0</td>
<td>34</td>
<td>Flu syndrome</td>
</tr>
<tr>
<td></td>
<td>7/M</td>
<td>53.5 1.76</td>
<td>75.0</td>
<td>29</td>
<td>Abnormal/changed behaviour</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Oppositional defiant behaviour&lt;sup&gt;d&lt;/sup&gt;)</td>
</tr>
<tr>
<td></td>
<td>12/F</td>
<td>98.7 2.28</td>
<td>187.5</td>
<td>14</td>
<td>Neuritis</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11/M</td>
<td>NA</td>
<td>NA</td>
<td>3</td>
<td>Infection (Mononucleosis)</td>
</tr>
<tr>
<td></td>
<td>11/M</td>
<td>NA</td>
<td>NA</td>
<td>10</td>
<td>Nervousness (Increased irritability)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body as a whole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11/M</td>
<td>NA</td>
<td>NA</td>
<td>3</td>
<td>Infection (Mononucleosis)</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>Nervousness (Increased irritability)</td>
</tr>
</tbody>
</table>

<sup>a</sup>: Age in years at study entry (baseline, day –1).  
<sup>b</sup>: Calculated by using baseline weight.  
<sup>c</sup>: Onset of adverse event was 1 or more days after the last full dose of study drug.  
<sup>d</sup>: Adverse event verbatim was incorrectly recorded as “Oppositional deviant behaviour” on the database; an erratum was generated.

No subjects died during this study. One (1) venlafaxine ER-treated subject and 1 placebo-treated subject had serious adverse events during the study.

**Laboratory results:** For the placebo group, the mean total protein values at Week 8 (-1.98 g/L) and at the final on therapy evaluations (-1.6 g/L) were significantly decreased from baseline values. The adjusted mean changes at Week 8 were significantly different between the 2 treatment groups.

At the Week 8 evaluation, the venlafaxine ER group had a significant increase from baseline values in mean total cholesterol values (0.20868 mmol/L). This mean increase was significantly different from the decrease (-0.00355 mmol/L) in the placebo group at this time point. At Week 8, the mean high-density lipoprotein (HDL) values were significantly decreased from baseline for the placebo group (-0.057 mmol/L), but not for the venlafaxine ER group (-0.015 mmol/L). The adjusted mean HDL decreases in were significantly different between the 2 treatment groups. The low-density lipoprotein (LDL) cholesterol values at Week 8 and at the final on-therapy evaluation were significantly increased from baseline (0.161 and 0.170 mmol/L, respectively) in the venlafaxine ER group. These mean increases in LDL cholesterol values for the venlafaxine-treated subjects were significantly different from the mean decreases (-0.033 and -0.090 mmol/L, respectively) in the placebo-treated subjects.

**Vitals signs results:** In the venlafaxine ER group, increases from baseline in mean supine pulse rate were significant at most time points and ranged from 2.33 to 6.77 beats/min during the study and were 4.92 and 4.08 beats/min at final on-therapy and poststudy evaluations, respectively. The mean increases at the final on-therapy evaluation were significantly different between the 2 treatment groups. In the venlafaxine ER group, changes in mean
supine diastolic blood pressure (SDBP) ranged from −0.04 to 3.15 mm Hg during the study and were 2.12 and 1.33 mm Hg at the final on-therapy and poststudy evaluations, respectively. The mean increase from baseline at final on-therapy was significant. At Week 3, 6, and final on-therapy, the mean changes in supine systolic blood pressure (SSBP) were significantly different between the 2 treatment groups. In the venlafaxine ER group, changes in mean supine SSBP ranged from −0.07 to 3.09 mm Hg during the study and were 1.83 and 0.40 mm Hg for final on-therapy and poststudy, respectively. The mean increases in SSBP from baseline and at Weeks 3 and 6 were significant. At Weeks 2, 3, 5, 6, Month 2 and final on-therapy the mean changes were significantly different between the 2 treatment groups.

**Weight results:** Mean weight for the venlafaxine ER group showed significant decreases from baseline at Week 2 through Month 2 (−0.15 to −0.91 kg) and at the final on-therapy evaluation (−0.66 kg). Mean weight for the placebo group showed significant increases from baseline at Week 6 through month 2 and at the final on therapy (0.72 kg) and poststudy (1.15 kg) evaluations. The mean decreases for the venlafaxine ER group were significantly different from the mean increases for the placebo group at Week 2 through Month 2 and at the final on-therapy and poststudy evaluations.

**ECG results:** Mean heart rate increases from baseline at Week 8 and at the final on-therapy evaluation for the venlafaxine ER group (2.67 and 2.38 beats/min, respectively) were significantly different from the mean decreases (−2.82 and −2.59 beats/min, respectively) for the placebo group. At Week 8 and at the final on-therapy evaluation for the venlafaxine ER group, the mean QT interval was significantly decreased (5.78 and 5.57 ms, respectively) from baseline. The changes in QT interval were significantly different between the 2 treatment groups, but when the QT interval was corrected for heart rate, there were no significant changes in the mean QTc. The mean PR interval showed a significant decrease (−2.71 ms) for the venlafaxine group at the final on-therapy evaluation, but there was no difference in mean PR interval changes between the 2 treatment groups. There were no significant changes in mean QRS intervals for either treatment group.

**CONCLUSION(S):** Venlafaxine ER was shown to be more efficacious than placebo in the short-term treatment of GAD in children and adolescents based on Week 8 results (LOCF) of the C-KIDDIE-SADS GAD total score (9 delineated items) in ANCOVA and ETRANK analyses. The results of the secondary analyses (C-KIDDIE-SADS GAD severity component, CGI-S, and CGI-I) and the responder analyses (CGI-I), support the benefits of venlafaxine ER over placebo for treatment of GAD in children and adolescents. The AEs observed in venlafaxine ER-treated children and adolescents in this study were similar to AEs observed in adult subjects in premarketing studies for GAD. Venlafaxine ER is a safe, well tolerated, and efficacious treatment for GAD in children and adolescents.