

# Venlafaxine Efficacy Varies With CYP2D6 Phenotype in Patients Treated for Depression

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# Revised Abstract

**Background:** Venlafaxine (VEN) is primarily metabolized by CYP2D6 into O-desmethyl-venlafaxine (ODV). Individuals can be broadly classified as poor metabolizers (PMs) or extensive metabolizers (EMs) based on CYP2D6 activity. This analysis examines the relative efficacy of VEN in patients with major depressive disorder (MDD) classified as EMs or PMs based on plasma ODV to VEN ratio (ODV/VEN) following VEN administration.

**Methods:** Data from 4 double-blind, placebo-controlled efficacy studies of patients with MDD were pooled to assess VEN efficacy in VEN-treated EMs and PMs vs placebo. In those studies, blood samples were taken and plasma concentrations of VEN and ODV were determined to calculate ODV/VEN. Depression rating scale scores and remission rates (17-item Hamilton Rating Scale for Depression [HAM-D<sub>17</sub>] score  $\leq 7$ ) were compared for EMs and PMs, classified based on ODV/VEN, vs placebo using *t*-tests and the Fisher exact test, respectively. Distributions of percent improvement in HAM-D<sub>17</sub> scores were compared for VEN-treated EMs and PMs vs placebo using the Cochran-Mantel-Haenszel test.

**Results:** VEN-treated MDD patients, both EMs (n=415) and PMs (n=49), had significantly improved depression rating scale scores compared with placebo-treated patients (n=372; *P* values  $\leq 0.04$ ). Compared with PMs, VEN-treated EMs had significantly greater change from baseline on 4 of 5 depression rating scales (*P* values  $\leq 0.020$ ). For EMs, but not PMs, remission rate (EM, 41.4%; PM, 28.6%; placebo, 20.8%) and distribution of percent improvement in HAM-D<sub>17</sub> scores were significantly different from placebo (*P* values  $< 0.001$ ). Discontinuation rates did not differ significantly between EMs and PMs.

**Conclusions:** VEN treatment in EMs was associated with greater efficacy in MDD on virtually all measures compared with PMs, with no significant tolerability differences.

## Introduction

- One of the major enzymes of the cytochrome P450 drug metabolizing system, CYP2D6, shows a high degree of genetic polymorphism and variability in activity<sup>1</sup>
- Individuals can be broadly classified as PMs or EMs based on CYP2D6 activity<sup>1</sup>
- Preliminary studies have found an association between metabolizer genotype or phenotype and tolerability of antidepressants metabolized by CYP2D6, with PMs more likely to experience poor tolerability compared with EMs.<sup>2</sup> Most, however, found no differences in antidepressant efficacy between EMs and PMs
- The antidepressant VEN is a serotonin-norepinephrine reuptake inhibitor metabolized primarily by CYP2D6 into ODV.<sup>3</sup> Plasma ODV/VEN ratios can be used reliably to distinguish CYP2D6 EMs from PMs<sup>4</sup>
- The objective of this analysis was to examine the relative efficacy of VEN in patients with MDD classified as EMs or PMs, based on their plasma ODV/VEN ratios

## Methods

### Study Design

- Data from 4 short-term (6 to 12 weeks) trials, representing all Wyeth-sponsored, randomized, double-blind, placebo-controlled MDD studies for which ODV and VEN plasma concentrations were available, were pooled for analysis
  - Two studies used fixed doses of VEN immediate release (IR; 75 to 375 mg/d)<sup>5,6</sup>
  - Two used flexible dosing (VEN extended release [ER] or IR, 75 to 150 mg/d and VEN ER 25 to 225 mg/d, respectively)<sup>7,8</sup>

### Patients

- Adult outpatients (18 years or older, up to age 65 in 2 studies) who met the *Diagnostic and Statistical Manual of Mental Disorders* criteria for MDD and had a minimum baseline score of 20 on the 21-item Hamilton Rating Scale for Depression
- Exclusion criteria were designed to select a population of medically stable patients with MDD

## Assessments and Statistical Analysis

- Blood samples drawn at various time points, ranging from 10 minutes to 55 hours postdose on study days 14, 42, 56, and 84, or on the last day of full-dose treatment
- Plasma concentrations of ODV and VEN were determined, and ODV/VEN ratios were calculated for each time point
- CYP2D6 EM and PM phenotypes were determined based on the ratio of ODV/VEN concentrations, using decision rules generated in an analysis of the relationship between ODV/VEN ratios and CYP2D6 metabolizer status<sup>4</sup>
- The primary outcome measure for all studies was the HAM-D<sub>17</sub>; other efficacy assessments included the 6-item Hamilton Rating Scale for Depression (HAM-D<sub>6</sub>; Bech version), the Montgomery Åsberg Depression Rating Scale (MADRS), and the Clinical Global Impressions– Improvement (CGI-I) and Severity (CGI-S) Scales.
- Data from the final on-therapy evaluation were analyzed
- Distribution of percent improvement in HAM-D<sub>17</sub> scores (<20%, 20% to 49%, 50% to 69%, ≥70%) was assessed using the Cochran-Mantel-Haenszel test
  - The lower cutoff (20%) is generally used as a minimal threshold for improvement
  - The upper cutoff (70%) is commensurate with remission in this patient population: a 70% reduction from the baseline mean HAM-D<sub>17</sub> total score of 22 would be ≤7

# Results

## Patients

- A total of 836 patients were included in the analysis (placebo, n=372; VEN, n=464). Based on ODV/VEN ratio, 415 (89%) patients in the VEN treatment group were classified as EMs and 49 (11%) were classified as PMs
- Baseline demographic and clinical characteristics were comparable between VEN-treated EMs and PMs, and placebo-treated patients (**Table 1**)
- There were no significant main effects or interactions of VEN formulation (IR vs ER) on efficacy. Therefore, efficacy analyses were conducted using pooled data from studies using both formulations
- Among VEN-treated patients, there was no statistically significant difference between EMs and PMs in raw mean VEN dose or total (ODV + VEN) plasma concentrations. Consistent with the criteria used to determine metabolizer status, EMs and PMs had statistically significant differences in mean plasma concentrations of ODV and VEN (both  $P<0.001$ ) (**Table 2**)

## Efficacy

- Both EM and PM VEN-treated patients had statistically greater changes from baseline on the HAM-D<sub>17</sub>, HAM-D<sub>6</sub>, MADRS, and CGI-S scales and significantly greater improvement on the CGI-I scale compared with the placebo group (all comparisons,  $P\leq 0.037$ )
  - Significant differences between VEN-treated EMs and PMs were observed for HAM-D<sub>17</sub>, HAM-D<sub>6</sub>, MADRS, and CGI-I scale scores (all comparisons,  $P\leq 0.020$ )
  - **Figure 1** shows the change from baseline at final evaluation for HAM-D<sub>17</sub> and MADRS scores by metabolizer status
    - The magnitude of the difference between VEN-treated EMs and PMs in improvement on each scale (HAM-D<sub>17</sub>, 2.67; MADRS, 3.98) was similar to that between VEN-treated PMs and placebo (HAM-D<sub>17</sub>, 2.40; MADRS, 3.18)
  - The distribution of percent improvement in HAM-D<sub>17</sub> total scores from baseline to final evaluation was significantly different from placebo for VEN-treated EMs ( $P<0.001$ ), but not PMs (**Figure 2**). The distribution was skewed toward ≥70% improvement for EMs relative to placebo
    - The distribution of percent improvement in HAM-D<sub>17</sub> total scores was significantly different for VEN-treated EMs compared with VEN-treated PMs ( $P=0.016$ ; **Figure 2**)
- Significantly greater percentages of VEN-treated EMs achieved response or remission based on both HAM-D<sub>17</sub> and MADRS scales compared with placebo-treated patients (all comparisons,  $P<0.001$ ; **Figure 3**)
  - VEN-treated EMs had significantly higher rates of HAM-D<sub>17</sub> and MADRS response and MADRS remission compared with VEN-treated PMs (all comparisons,  $P\leq 0.015$ )
  - For VEN-treated PMs, HAM-D<sub>17</sub> and MADRS response and remission rates did not differ significantly compared with placebo

**Table 1. Demographic and Baseline Characteristics**

Demographics				
Characteristic	Venlafaxine		Placebo n=372	P Value
	EM n=415	PM n=49		
<b>Age (years)</b>				0.697*
Mean (SD)	40.6 (10.6)	41.8 (10.7)	40.4 (11.2)	
Range	18-72	19-66	18-77	
Median	40	41	39	
<b>Sex, n (%)</b>				0.073 <sup>†</sup>
Female	250 (60)	34 (69)	203 (55)	
Male	165 (40)	15 (31)	169 (45)	
<b>Ethnic origin, n (%)</b>				0.230 <sup>†</sup>
Black	27 (7)	2 (4)	18 (5)	
Hispanic	14 (3)	1 (2)	4 (1)	
Other	7 (2)	0	11 (3)	
White	367 (88)	46 (94)	339 (91)	
Baseline Clinical Characteristics				
Variable	Venlafaxine		Placebo	P Value*
	EM	PM		
<b>HAM-D<sub>17</sub></b>				0.433
N	415	49	366	
Mean (SD)	22.32 (3.21)	22.82 (3.32)	22.20 (3.12)	
<b>HAM-D<sub>6</sub></b>				0.182
N	415	49	366	
Mean (SD)	12.60 (1.76)	12.61 (1.72)	12.38 (1.58)	
<b>MADRS</b>				0.778
N	414	49	362	
Mean (SD)	28.14 (5.85)	28.57 (5.93)	27.99 (5.21)	
<b>CGI-S</b>				0.663
N	413	49	361	
Mean (SD)	4.30 (0.59)	4.22 (0.65)	4.30 (0.56)	

Abbreviations: CGI-S, Clinical Global Impressions–Severity; EM, extensive metabolizer; HAM-D<sub>6</sub>, 6-item Hamilton Rating Scale for Depression; HAM-D<sub>17</sub>, 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery Åsberg Depression Rating Scale; PM, poor metabolizer; SD, standard deviation.

\*One-way analysis of variance with treatment sequence as factor.

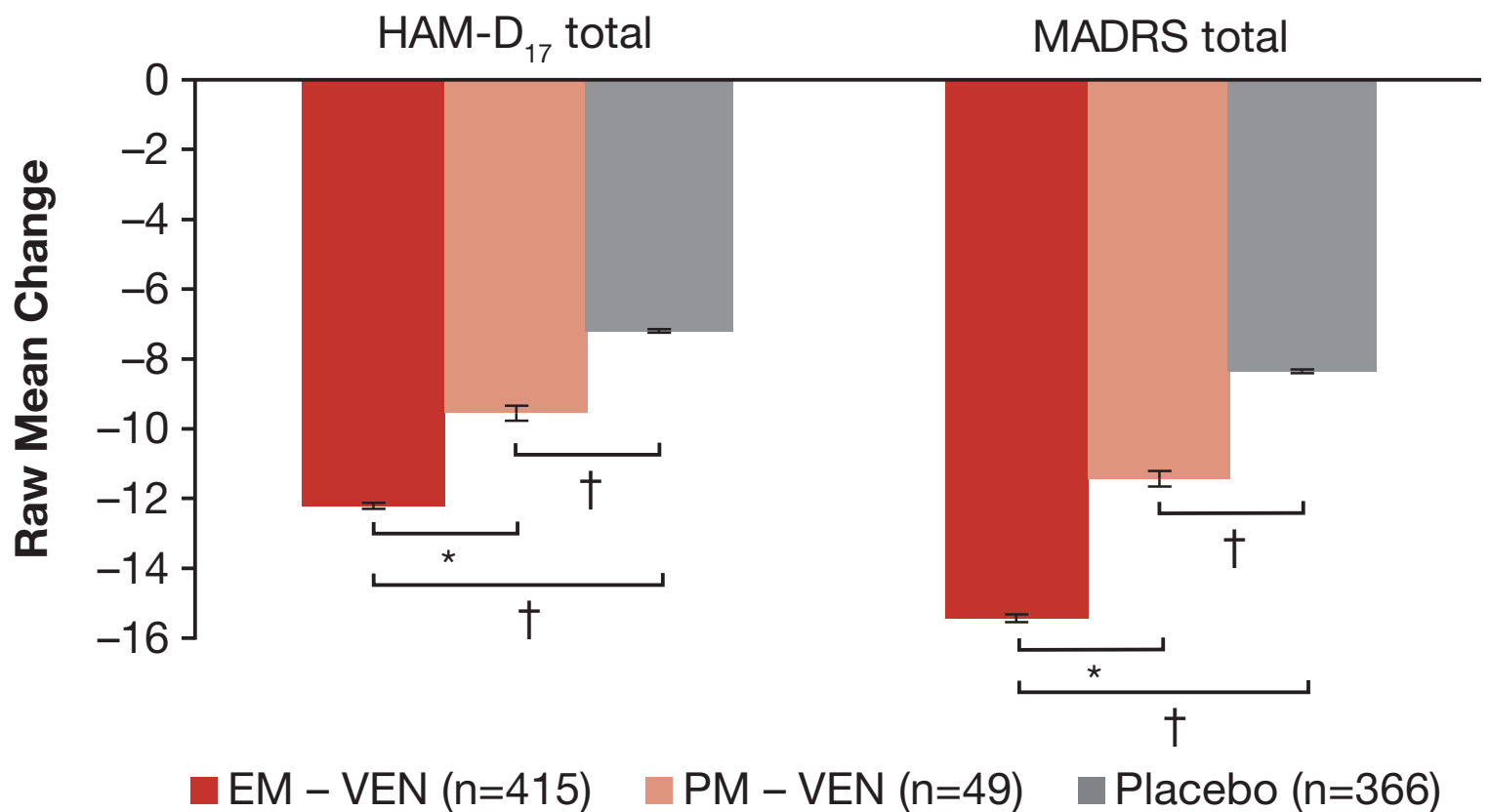
<sup>†</sup>Fisher exact test P value (2 tail).

**Table 2. Dose and Plasma Concentrations by Metabolizer Status**

	P Value (t-test)	EM n=415	PM n=49
<b>Dose, mg</b>	0.963		
Mean (SD)		129.08 (68.30)	128.60 (60.47)
Median		129.75	132.69
Range		19.74-339.62	22.97-316.35
<b>Study Day, Relative to First Dose</b>	0.989		
Mean (SD)		41.11 (24.42)	41.16 (23.47)
<b>ODV Concentration, ng/mL</b>	<0.001		
Mean (SD)		221.37 (169.32)	109.97 (94.55)
<b>VEN Concentration, ng/mL</b>	<0.001		
Mean (SD)		77.08 (78.54)	276.76 (234.01)
<b>Total Concentration (ODV+VEN), ng/mL</b>	0.056		
Mean (SD)		298.44 (232.72)	386.73 (305.85)

Abbreviations: EM, extensive metabolizer; ODV, O-desmethylvenlafaxine; PM, poor metabolizer; SD, standard deviation; VEN, venlafaxine.

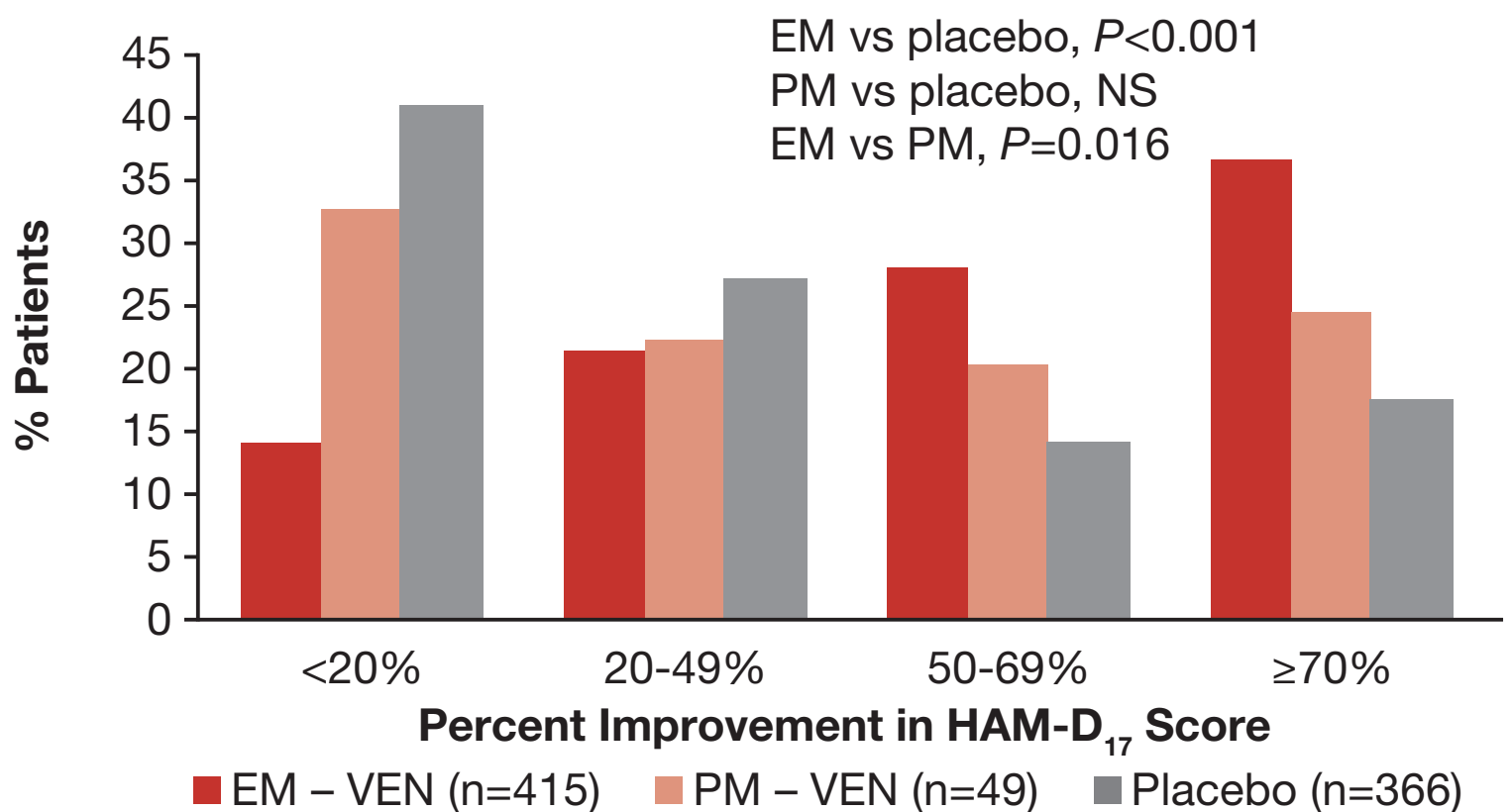
**Figure 1. Change From Baseline to Final Evaluation in Depression Scale Scores by Metabolizer Status**



Abbreviations: EM, extensive metabolizer; HAM-D<sub>17</sub>, 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery Åsberg Depression Rating Scale; PM, poor metabolizer; VEN, venlafaxine.

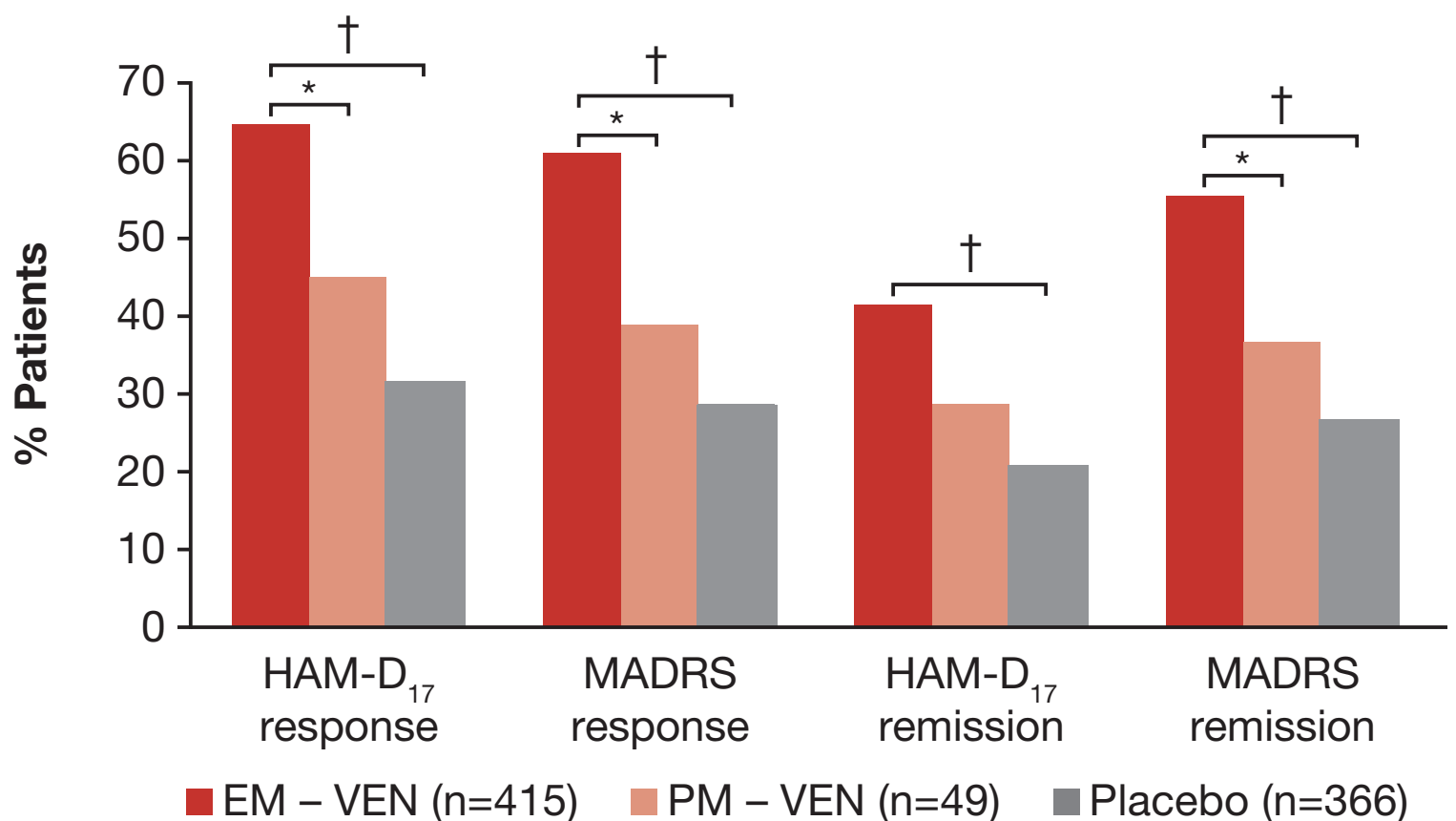
\*P value ≤ 0.02, EM vs PM; †P value ≤ 0.04, VEN vs placebo.

**Figure 2. Distribution of Metabolizer Groups by Percent Change in HAM-D<sub>17</sub> Total Scores at Final On-Therapy Evaluation, Cochran-Mantel-Haenszel Test**



Abbreviations: EM, extensive metabolizer; HAM-D<sub>17</sub>, 17-item Hamilton Rating Scale for Depression; NS, not significant; PM, poor metabolizer; VEN, venlafaxine.

**Figure 3. Response and Remission Rates by Metabolizer Status**



Abbreviations: EM, extensive metabolizer; HAM-D<sub>17</sub>, 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery Åsberg Depression Rating Scale; PM, poor metabolizer; VEN, venlafaxine.

Response is defined as ≥50% decrease from baseline score.

HAM-D<sub>17</sub> remission is defined as total score ≤ 7.

MADRS remission is defined as total score ≤ 12.

\*P value ≤ 0.02, EM vs PM; †P value < 0.001, VEN vs placebo

## Safety and Tolerability

- Neither overall discontinuation rate nor the rate of discontinuations due to adverse events (AEs) differed significantly between VEN-treated EMs and PMs (**Table 3**)
- Three AEs were reported by a significantly higher percentage of VEN-treated PM patients compared with EM patients (increased alkaline phosphatase [EM: 0.2%, PM: 4.1%;  $P=0.031$ ], sweating [EM: 13.3%, PM: 24.5%;  $P=0.050$ ], and insomnia [EM: 22.4%, PM: 38.8%;  $P=0.020$ ])
- The overall number of patients reporting AEs did not differ significantly between VEN-treated EMs (94%) and PMs (98%)

**Table 3. Number (%) of Discontinuations by Primary Reason**

Conclusion Status Reason	Overall P Value*	EM vs PM P Value	Venlafaxine		Placebo n=372	Total n=836
			EM n=415	PM n=49		
Discontinued	<0.001	0.839	69 (16.6)	7 (14.3)	144 (38.7)	220 (26.3)
Adverse reaction	0.926	1.000	18 (4.3)	2 (4.1)	18 (4.8)	38 (4.5)
Failed to return	<0.001	0.238	17 (4.1)	0	45 (12.1)	62 (7.4)
Other medical event	0.393	0.361	3 (0.7)	1 (2.0)	4 (1.1)	8 (1.0)
Other nonmedical event	0.201	0.285	2 (0.5)	1 (2.0)	5 (1.3)	8 (1.0)
Patient/subject request	0.028	1.000	3 (0.7)	0	12 (3.2)	15 (1.8)
Protocol violation	0.237	1.000	3 (0.7)	0	8 (2.2)	11 (1.3)
Unsatisfactory response, efficacy	<0.001	0.747	23 (5.5)	3 (6.1)	52 (14.0)	78 (9.3)

Abbreviations: EM, extensive metabolizer; PM, poor metabolizer.

\*Fisher exact test P value (2 tail).

## Conclusions

- Antidepressant response to VEN varies with CYP2D6 metabolizer phenotype; VEN-treated EM patients had significantly greater improvement compared with VEN-treated PMs on a wide range of efficacy measures
- VEN-treated EMs had a significantly different distribution of percent improvement in HAM-D<sub>17</sub> total scores compared with placebo, whereas PMs did not
- There were no important differences in VEN safety and tolerability between EMs and PMs

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