**SUPPLEMENTARY DIGITAL CONTENT**

**Trajectories of Function and Symptom Change in Desvenlafaxine Clinical Trials: Toward Personalized Treatment for Depression**

Sigal Zilcha-Mano, PhD,\* Xuemei Wang, MSc,† Dalia B. Wajsbrot, MSc,‡ Matthieu Boucher, PhD,§ Stuart A. Fine, BA,|| and Bret R. Rutherford, MD\*\*

From the \*University of Haifa, Haifa, Israel; †Syneos Health Inc, Raleigh, NC (at the time of the study); ‡Pfizer Inc, New York, NY; §Pfizer Canada Inc, Kirkland, QC, Canada (at the time of the study), and Department of Pharmacology and Therapeutics, McGill University, Montréal, QC, Canada; || Columbia University, New York, NY; \*\*Columbia University College of Physicians and Surgeons and New York State Psychiatric Institute, New York, NY.

Table S1: Desvenlafaxine studies for patients with major depressive disorder included in the pooled analysis. (Supplemental Digital Content 1.doc)

Table S2: Clinical and demographic characteristics of patients included in the pooled dataset. (Supplemental Digital Content 2.doc)

Table S3: Results from model selection for HRSD and for SDS for the placebo and desvenlafaxine groups. (Supplemental Digital Content 3.doc)

Table S4: Percentage of Patients Receiving Similar Ranking for HRSD and SDS (percentages are calculated within HRSD trajectories). (A) For the placebo arm; (B) For the desvenlafaxine arm. (Supplemental Digital Content 4.doc)

## Table S1. Desvenlafaxine Studies for Patients With Major Depressive Disorder Included in the Pooled Analysis

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study ID/ first author, yearRef[NCT identifier]**  | **Eligibility criteria†**  | **Study Duration (weeks)** | **Total Sample Size, N** | **Comparator** |  |
| **Desvenlafaxine 50 mg/d, n** | **Desvenlafaxine 100 mg/d, n** | **Other Treatment Arms\*** | **Placebo, n** |
| 306 / DeMartinis et al, 20071[NCT00072774] | HAMD17 ≥20HAMD17 (depressed mood) ≥2CGI-S ≥4 | 8  | 470 | – | 118 | Desvenlafaxine 200 mg/d, n = 116Desvenlafaxine 400 mg/d, n = 116 | 120 |
| 332 / Liebowitz et al, 20082‑[NCT00277823] | HAMD17 ≥20HAMD17 (depressed mood) ≥2CGI-S ≥4 | 8 | 451 | 151 | 148 | – | 152 |
| 333 / Boyer et al, 20083[NCT00300378] | HAMD17 ≥20HAMD17 (depressed mood) ≥2CGI-S ≥4 | 8  | 485 | 166 | 158 | – | 161 |
| 335 / Tourian et al, 20094[NCT00384033] | HAMD17 ≥20HAMD17 (depressed mood) ≥2CGI-S ≥4 | 8  | 616 | 148 | 150 | Duloxetine 60 mg/d, n = 157 | 161 |
| 4415 / Dunlop et al, 20115[NCT00824291] | MADRS total score ≥25 | 12 | 427 | 285 | – | – | 142 |
| 3359 / Iwata et al, 20136[NCT00798707] | HAMD17 ≥20HAMD17 (depressed mood) ≥2CGI-S ≥4 | 8  | 699 | 236 | – | Desvenlafaxine 25 mg/d, n = 232 | 231 |
| 3362 / Liebowitz et al, 20137[NCT00863798] | HAMD17 ≥20HAMD17 (depressed mood) ≥2CGI-S ≥4  | 8  | 673 | 224 | – | Desvenlafaxine 10 mg/d, n = 226 | 223 |
| 3364 / Clayton et al, 20138[NCT01121484] | MADRS total score ≥25 | 10  | 434 | 217 | – | – | 217 |
| 1028 / Clayton et al, 20159[NCT01432457] | HAMD17 ≥20HAMD17 (depressed mood) ≥2CGI-S ≥4 | 8  | 909 | 300 | 309 | – | 300 |
| **Total sample size** | **5164** | **1727** | **883** | **847** | **1707** |

\*Data from these treatment arms were not included in the present analysis, which only used desvenlafaxine 50 mg or 100 mg treatment arms.
†All patients had a DSM-VI diagnosis of MDD.

Abbreviations: CGI-S, Clinical Global Impressions– Severity of illness scale; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; NCT, ClinicalTrials.gov identifier.

**References**

1. DeMartinis NA, Yeung PP, Entsuah R, et al. A double-blind, placebo-controlled study of the efficacy and safety of desvenlafaxine succinate in the treatment of major depressive disorder*.* J Clin Psychiatry 2007;68:677–688.
2. Liebowitz MR, Manley AL, Padmanabhan SK, et al. Efficacy, safety, and tolerability of desvenlafaxine 50 mg/day and 100 mg/day in outpatients with major depressive disorder*.* Curr Med Res Opin 2008;24:1877–1890.
3. Boyer P, Montgomery S, Lepola U, et al. Efficacy, safety, and tolerability of fixed-dose desvenlafaxine 50 and 100 mg/day for major depressive disorder in a placebo-controlled trial*.* Int Clin Psychopharmacol 2008;23:243–253.
4. Tourian KA, Padmanabhan SK, Groark J, et al. Desvenlafaxine 50 and 100 mg/d in the treatment of major depressive disorder: an 8-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial and a post hoc pooled analysis of three studies*.* Clin Ther 2009;31 Pt 1:1405–1423.
5. Dunlop BW, Reddy S, Yang L, et al. Symptomatic and functional improvement in employed depressed patients: a double-blind clinical trial of desvenlafaxine versus placebo*.* J Clin Psychopharmacol 2011;31:569–576.
6. Iwata N, Tourian KA, Hwang E, et al. Efficacy and safety of desvenlafaxine 25 and 50 mg/day in a randomized, placebo-controlled study of depressed outpatients*.* J Psychiatr Pract 2013;19:5–14.
7. Liebowitz MR, Tourian KA, Hwang E, et al. A double-blind, randomized, placebo-controlled study assessing the efficacy and tolerability of desvenlafaxine 10 and 50 mg/day in adult outpatients with major depressive disorder*.* BMC Psychiatry 2013;13:94.
8. Clayton AH, Kornstein SG, Dunlop BW, et al. Efficacy and safety of desvenlafaxine 50 mg/d in a randomized, placebo-controlled study of perimenopausal and postmenopausal women with major depressive disorder*.* J Clin Psychiatry 2013;74:1010–1017.
9. Clayton AH, Tourian KA, Focht K, et al. Desvenlafaxine 50 and 100 mg/d versus placebo for the treatment of major depressive disorder: a phase 4, randomized controlled trial*.* J Clin Psychiatry 2015;76:562–569.

**Table S2.** Clinical and Demographic Characteristics of Patients Included in the analysis

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **Desvenlafaxine****(n = 2610)** | **Placebo****(n = 1707)** | **Total Sample****(N = 4317)** |
| Age, y | 42.84 ± 12.99 | 42.98 ± 12.68 | 42.89 ± 12.87 |
| Male, % | 35.4 | 33.8 | 34.8 |
| Baseline HRSD | 23.24 ± 2.95 | 23.18 ± 3.01 | 23.21 ± 2.97 |
| Baseline SDS\* | 18.49 ± 6.02 | 18.29 ± 6.58 | 18.41 ± 6.26 |
| CGI-S score at baseline |  |  |  |
| Mildly or moderately ill† | 67.2% | 67.4% | 67.3% |
| Markedly or severely ill | 32.8% | 32.6% | 32.7% |

\*Total sample size for SDS is 3228 because not all patients had SDS data.

†Even though this category is labeled “mildly or moderately ill,” it also includes 2 patients whose baseline CGI-S score was reported as “borderline mentally ill.”

CGI-S, Clinical Global Impressions - Severity;HRSD, Hamilton Rating Scale for Depression; SDS, Sheehan Disability Scale.

## Table S3. Results From Model Selection for HRSD and SDS for the Placebo and Desvenlafaxine Groups

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Score** | **No. of Trajectories** | **Growth Mixture Model** | **Placebo** |   | **Desvenlafaxine** |
| **BIC** | **% Patients in Each Trajectory Class** |  | **BIC** | **% Patients in Each Trajectory Class** |
| **1** | **2** | **3** | **4** |  | **1** | **2** | **3** | **4** |
| **HRSD** | 1 | Linear | 60,671 | 100 | – | – | – |  | 92,666 | 100 | – | – | – |
| Log-linear | 59,076 | 100 | – | – | – |  | 89,768 | 100 | – | – | – |
| Quadratic | 58,560 | 100 | – | – | – |  | 89,033 | 100 | – | – | – |
| Cubic | 58,047 | 100 | – | – | – |  | 88,101 | 100 | – | – | – |
| 2 | Linear | 60,603 | 45.4 | 54.6 | – | – |  | 92,564 | 58.8 | 41.2 | – | – |
| Log-linear | 59,009 | 58.3 | 41.7 | – | – |  | 89,694 | 44.1 | 55.9 | – | – |
| Quadratic | 58,480 | 52 | 48 | – | – |  | 88,883 | 36.7 | 63.3 | – | – |
| Cubic | 57,967 | 50 | 50 | – | – |  | 87,950 | 35.4 | 64.6 | – | – |
| 3 | Linear | 60,595 | 5.6 | 51.2 | 43.2 | – |  | 92,551 | 49.7 | 41.2 | 9.1 | – |
| Log-linear | 58,999 | 7.1 | 52 | 40.8 | – |  | 89,668 | 48.7 | 8.4 | 42.9 | – |
| Quadratic | 58,454 | 19.7 | 37.2 | 43.1 | – |  | 88,868 | 15.2 | 48 | 36.8 | – |
| Cubic | **57,955** | **21.8** | **34.4** | **43.8** | **–** |  | 87,929 | 18.2 | 50.7 | 31.1 | – |
| 4 | Linear | 60,618 | 5.6 | 0 | 45 | 49.3 |  | 92,564 | 47 | 41.9 | 10.7 | 0.4 |
| Log-linear | 59,022 | 7.1 | 47.5 | 45.3 | 0 |  | 89,678 | 0.3 | 48 | 8.4 | 43.3 |
| Quadratic | 58,466 | 35 | 5.9 | 27.9 | 31.2 |  | 88,850 | 19.3 | 37.9 | 30.5 | 12.3 |
| Cubic | 57,950 | 24.2 | 8.2 | 25 | 42.6 |  | **87,904** | **37.6** | **12.5** | **16.9** | **33** |
| **SDS** | 1 | Linear | 34,585 | 100 |  |  |  |  | 49,530 | 100 |  |  |  |
| Log-linear | 34,222 | 100 |  |  |  |  | 48,905 | 100 |  |  |  |
| Quadratic | 34,181 | 100 |  |  |  |  | 48,908 | 100 |  |  |  |
| Cubic | 34,158 | 100 |   |   |   |  | 48,822 | 100 |   |   |   |
| 2 | Linear | 34,536 | 48.2 | 51.8 |  |  |  | 49,486 | 69.5 | 30.5 |  |  |
| Log-linear | 34,186 | 46.8 | 53.2 |  |  |  | 48,847 | 9.9 | 90.1 |  |  |
| Quadratic | 34,111 | 49.7 | 50.3 |  |  |  | 48,826 | 29.3 | 70.7 |  |  |
| Cubic | 34,094 | 50.2 | 49.8 |   |   |  | 48,738 | 29.5 | 70.5 |   |   |
| 3 | Linear | 34,512 | 14.9 | 52.7 | 32.4 |  |  | 49,450 | 41.1 | 22.9 | 36 |  |
| Log-linear | 34,139 | 33 | 53.5 | 13.5 |  |  | 48,811 | 17 | 44.3 | 38.7 |  |
| Quadratic | 34,115 | 38 | 36.2 | 25.9 |  |  | 48,760 | 12.4 | 53.1 | 34.4 |  |
| Cubic | 34,098 | 37.1 | 39.4 | 23.5 |   |  | **48,655** | **53.8** | **33.2** | **13** |  |
| 4 | Linear | 34,512 | 43.3 | 25.5 | 8.9 | 22.3 |  | 49,434 | 45.4 | 9.1 | 31.4 | 14.1 |
| Log-linear | 34,148 | 26.7 | 8.8 | 22.2 | 42.3 |  | 48,798 | 47.8 | 8 | 14.5 | 29.7 |
| Quadratic | 34,113 | 22.1 | 40.8 | 31 | 6.1 |  | 48,733 | 43.4 | 15.4 | 33.4 | 7.9 |
| Cubic | **34,022** | **11.2** | **36.7** | **32.4** | **19.6** |  | 48,628 | 42.9 | 15.6 | 32.5 | 9 |

**Table S4.** Percentage of Patients Receiving Similar Ranking for HRSD and SDS (Percentages Are Calculated Within HRSD Trajectories)

|  |
| --- |
| 1. **Placebo Treatment**
 |
| **HRSD Trajectory** | **SDS Trajectory Responders** | **SDS Trajectory Non-responders** | **Total** |
| **Moderate SDS Score at BL** | **Severe SDS Score at BL** |
| **n** | **(%)** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** |
| Fast responders | 187 | (75) | 55 | (22) | 8 | (3) | 250 | (100) |
| Partial responders | 190 | (45) | 181 | (43) | 50 | (12) | 421 | (100) |
| Non-responders | 67 | (12) | 267 | (49) | 211 | (39) | 545 | (100) |
| **Total** | **444** | **(37)** | **503** | **(41)** | **269** | **(22)** | **1216** | **(100)** |
| 1. **Desvenlafaxine Treatment**
 |
| **HRSD Trajectory** | **SDS Trajectory Responders** |  | **SDS Trajectory Non-responders** |  | **Total** |
| **n** | **(%)** |  | **n** | **(%)** |  | **n** | **(%)** |
| Fast responders | 186 | (85) |  | 33 | (15) |  | 219 | (100) |
| Slow responders | 557 | (84) |  | 110 | (16) |  | 667 | (100) |
| Partial responders | 248 | (49) |  | 262 | (51) |  | 510 | (100) |
| Non-responders | 59 | (20) |  | 243 | (80) |  | 302 | (100) |
| **Total** | **1050** | **(62)** |  | **648** | **(38)** |  | **1698** | **(100)** |
| Shading represents agreement between HRSD and SDS trajectory assignments. Percentages are based on the total number of patients in each HRSD trajectory. Patients assigned to the low baseline SDS trajectory were excluded from this table.HRSD, Hamilton Rating Scale for Depression; SDS, Sheehan Disability Scale. |