

**Supplemental Table 1.** Subgroup analysis of baseline HAM-D17 retardation score ( $\leq 7$  versus  $> 7$ ) effect on all scales.

| Baseline Patient Characteristic                               | Week | Duloxetine <sup>a</sup> |                         | SSRIs <sup>a</sup> |                         | Treatment Difference (95% CI) <sup>b</sup> | P-value            |
|---|------|-------------------------|-------------------------|--------------------|-------------------------|--|--------------------|
|   |      | n                       | LS Mean Change (95% CI) | n                  | LS Mean Change (95% CI) |  |                    |
| <b>Baseline HAM-D17 retardation score <math>\leq 7</math></b> |      |                         |                         |                    |                         |  |                    |
| BPI-SF average pain score                                     | 2    | 84                      | -1.5 (-1.9, -1.1)       | 81                 | -1.8 (-2.2, -1.4)       | -0.3 (-0.8, 0.3)                           | 0.315              |
|   | 4    | 102                     | -2.5 (-2.8, -2.1)       | 101                | -2.7 (-3.1, -2.3)       | -0.3 (-0.8, 0.3)                           | 0.357              |
|   | 8    | 70                      | -3.3 (-3.7, -2.8)       | 72                 | -3.0 (-3.4, -2.6)       | 0.2 (-0.4, 0.9)                            | 0.440              |
|   | 12   | 64                      | -3.4 (-3.9, -2.9)       | 79                 | -3.3 (-3.8, -2.9)       | 0.1 (-0.7, 0.8)                            | 0.854              |
| HAM-D17 total score   | 2    | 66                      | -3.5 (-4.5, -2.5)       | 75                 | -5.1 (-6.1, -4.2)       | -1.6 (-3.1, -0.2)                          | 0.027 <sup>d</sup> |
|   | 4    | 91                      | -7.3 (-8.4, -6.1)       | 98                 | -9.4 (-10.5, -8.3)      | -2.2 (-3.8, -0.5)                          | 0.010 <sup>d</sup> |
|   | 8    | 55                      | -10.5 (-12.0, -9.1)     | 69                 | -12.3 (-13.6, -11.0)    | -1.8 (-3.8, 0.2)                           | 0.082              |
|   | 12   | 51                      | -13.2 (-14.6, -11.7)    | 67                 | -14.0 (-15.2, -12.7)    | -0.8 (-2.8, 1.2)                           | 0.418              |
| GAF   | 12   | 65                      | 17.4 (14.8, 20.1)       | 74                 | 16.4 (13.9, 18.9)       | 1.1 (-2.7, 4.8)                            | 0.573              |
| SASS  | 12   | 54                      | 7.7 (6.1, 9.2)          | 69                 | 8.9 (7.5, 10.3)         | -1.2 (-3.4, 0.9)                           | 0.266              |
| EQ-5D   | 12   | 62                      | 0.2080 (0.1709, 0.2452) | 72                 | 0.2555 (0.2202, 0.2907) | -0.0474 (-0.1008, 0.0059)                  | 0.081              |
| Ability to work   | 0    | 120                     | 65.0%                   | 114                | 54.4%                   | --   | 0.11               |
|   | 12   | 74                      | 85.0% (74.6%, 91.6%)    | 77                 | 79.7% (66.7%, 88.4%)    | 1.450 (0.563, 3.733)                       | 0.441              |
| <b>Baseline HAM-D17 retardation score <math>&gt; 7</math></b> |      |                         |                         |                    |                         |  |                    |
| BPI-SF average pain score                                     | 2    | 117                     | -2.0 (-2.3, -1.6)       | 102                | -2.1 (-2.5, -1.7)       | -0.1 (-0.6, 0.4)                           | 0.748              |
|   | 4    | 127                     | -3.0 (-3.4, -2.6)       | 117                | -2.4 (-2.8, -2.0)       | 0.6 (0.1, 1.1)                             | 0.025 <sup>c</sup> |

|                     |    |     |                         |     |                         |                         |                    |
|---------------------|----|-----|-------------------------|-----|-------------------------|-------------------------|--------------------|
|                     | 8  | 105 | -3.8 (-4.2, -3.4)       | 91  | -3.1 (-3.6, -2.7)       | 0.7 (0.1, 1.3)          | 0.027 <sup>c</sup> |
|                     | 12 | 107 | -4.1 (-4.5, -3.7)       | 86  | -3.5 (-3.9, -3.0)       | 0.6 (0.0, 1.3)          | 0.045 <sup>c</sup> |
| HAM-D17 total score | 2  | 104 | -6.4 (-7.5, -5.4)       | 98  | -6.6 (-7.7, -5.6)       | -0.2 (-1.7, 1.3)        | 0.800              |
|                     | 4  | 115 | -12.0 (-13.3, -10.8)    | 111 | -11.2 (-12.5, -10.0)    | 0.8 (-1.0, 2.6)         | 0.394              |
|                     | 8  | 93  | -16.7 (-18.0, -15.3)    | 85  | -14.7 (-16.1, -13.3)    | 2.0 (0.0, 4.0)          | 0.047 <sup>c</sup> |
|                     | 12 | 92  | -19.0 (-20.4, -17.5)    | 81  | -17.2 (-18.7, -15.7)    | 1.8 (-0.4, 3.9)         | 0.102              |
| GAF                 | 12 | 99  | 22.4 (19.9, 24.9)       | 87  | 19.6 (17.0, 22.1)       | 2.8 (-0.8, 6.5)         | 0.129              |
| SASS                | 12 | 98  | 10.2 (8.5, 11.8)        | 85  | 8.5 (6.8, 10.3)         | 1.6 (-0.8, 4.1)         | 0.193              |
| EQ-5D               | 12 | 99  | 0.3695 (0.3340, 0.4050) | 86  | 0.3112 (0.2738, 0.3486) | 0.0583 (0.0053, 0.1113) | 0.031 <sup>c</sup> |
| Ability to work     | 0  | 144 | 30.6%                   | 135 | 24.4%                   | --                      | 0.285              |
|                     | 12 | 109 | 86.6% (76.4%, 92.7%)    | 90  | 74.6% (60.5%, 84.9%)    | 2.192 (1.097, 4.382)    | 0.026 <sup>c</sup> |

<sup>a</sup> For change from baseline, all values are presented as scores, except for Ability to Work, which is presented as a percentage.

<sup>b</sup> For treatment difference, Ability to Work is presented as an odds ratio (values >1 favor duloxetine). All other treatment differences presented are the least squares mean change difference between treatment groups (positive values indicate favorable outcome with duloxetine; negative values indicate favorable outcome with SSRIs).

<sup>c</sup> Statistically significant difference favoring duloxetine  $P < 0.05$ .

<sup>d</sup> Statistically significant difference favoring the SSRIs  $P < 0.05$ .

Abbreviations: BPI-SF, Brief Pain Inventory-Short Form (higher score indicates more pain)<sup>24</sup>; CI, confidence interval; EQ-5D, EuroQol – 5-Dimension Questionnaire for Quality of Life (lower score indicates less health)<sup>25</sup>; GAF, Global Assessment of Functioning Scale (lower score indicates greater severity of illness)<sup>26</sup>; HAM-D17, 17-Item Hamilton Rating Scale for Depression (higher score indicates more depression)<sup>27</sup>; LS, least squares, n, number of affected patients; SASS, Social Adaptation Self-Evaluation Scale (higher score indicates greater social adjustment)<sup>28</sup>; SSRIs, selective serotonin reuptake inhibitors.

**Supplemental Table 2.** Subgroup analysis of baseline HAM-D17 anxiety somatic score ( $\leq 6$  versus  $>6$ ) effect on all scales.

| Patient Characteristic  | Week | Duloxetine <sup>a</sup> |                            | SSRIs <sup>a</sup> |                            | Treatment Difference <sup>b</sup><br>(95% CI) | P-value |
|---|------|-------------------------|----------------------------|--------------------|----------------------------|---|---------|
|   |      | n                       | LS Mean Change<br>(95% CI) | n                  | LS Mean Change<br>(95% CI) |   |         |
| <b>Baseline HAM-D17 anxiety-somatic score <math>\leq 6</math></b> |      |                         |                            |                    |                            |   |         |
| BPI-SF average pain score   | 2    | 29                      | -1.7 (-2.6, -0.9)          | 28                 | -2.8 (-3.6, -2.0)          | -1.1 (-2.2, 0.1)                              | 0.083   |
|   | 4    | 63                      | -2.5 (-3.0, -2.1)          | 53                 | -2.8 (-3.3, -2.3)          | -0.3 (-0.9, 0.4)                              | 0.450   |
|   | 8    | 28                      | -3.7 (-4.3, -3.0)          | 24                 | -3.6 (-4.3, -3.0)          | 0.0 (-0.9, 1.0)                               | 0.967   |
|   | 12   | 29                      | -4.0 (-4.5, -3.4)          | 30                 | -3.8 (-4.3, -3.2)          | 0.2 (-0.6, 1.0)                               | 0.635   |
| HAM-D17 total score   | 2    | 25                      | -4.5 (-6.0, -3.0)          | 24                 | -3.6 (-5.2, -1.9)          | 1.0 (-1.2, 3.2)                               | 0.380   |
|   | 4    | 61                      | -7.2 (-8.4, -6.0)          | 51                 | -8.1 (-9.4, -6.9)          | -1.0 (-2.7, 0.8)                              | 0.273   |
|   | 8    | 19                      | -8.9 (-10.7, -7.1)         | 21                 | -9.4 (-11.3, -7.5)         | -0.5 (-3.2, 2.2)                              | 0.697   |
|   | 12   | 21                      | -11.2 (-13.3, -9.1)        | 21                 | -10.8 (-13.0, -8.6)        | 0.4 (-2.7, 3.5)                               | 0.807   |
| GAF   | 12   | 31                      | 16.8 (12.7, 20.8)          | 26                 | 17.6 (13.1, 22.1)          | -0.8 (-7.1, 5.4)                              | 0.791   |
| SASS  | 12   | 22                      | 8.0 (5.7, 10.4)            | 22                 | 10.7 (8.3, 13.2)           | -2.7 (-6.2, 0.8)                              | 0.129   |
| EQ-5D   | 12   | 23                      | 0.1793 (0.1276, 0.2310)    | 24                 | 0.1957 (0.1423, 0.2492)    | -0.0164 (-0.0907, 0.0579)                     | 0.659   |
| Ability to work   | 0    | 69                      | 52.2%                      | 61                 | 42.6%                      | --  | 0.296   |
|   | 12   | 40                      | 88.6% (63.0%, 97.2%)       | 30                 | 86.0% (56.9%, 96.6%)       | 1.256 (0.333, 4.740)                          | 0.737   |
| <b>Baseline HAM-D17 anxiety-somatic score <math>&gt;6</math></b>  |      |                         |                            |                    |                            |   |         |
| BPI-SF average pain score   | 2    | 172                     | -1.8 (-2.1, -1.5)          | 155                | -1.8 (-2.1, -1.5)          | 0.0 (-0.4, 0.4)                               | 0.984   |
|   | 4    | 166                     | -2.8 (-3.1, -2.5)          | 165                | -2.5 (-2.8, -2.1)          | 0.4 (-0.1, 0.8)                               | 0.133   |

|                     |    |     |                         |     |                         |                          |                    |
|---------------------|----|-----|-------------------------|-----|-------------------------|--------------------------|--------------------|
|                     | 8  | 147 | -3.5 (-3.9, -3.2)       | 139 | -3.0 (-3.3, -2.6)       | 0.6 (0.1, 1.1)           | 0.023 <sup>c</sup> |
|                     | 12 | 142 | -3.8 (-4.2, -3.5)       | 135 | -3.3 (-3.7, -2.9)       | 0.5 (0.0, 1.1)           | 0.067              |
| HAM-D17 total score | 2  | 145 | -5.4 (-6.2, -4.5)       | 149 | -6.3 (-7.2, -5.5)       | -1.0 (-2.2, 0.3)         | 0.127              |
|                     | 4  | 145 | -10.6 (-11.7, -9.5)     | 158 | -11.1 (-12.2, -10.0)    | -0.5 (-2.1, 1.1)         | 0.514              |
|                     | 8  | 129 | -15.3 (-16.5, -14.1)    | 133 | -14.6 (-15.7, -13.4)    | 0.7 (-1.0, 2.4)          | 0.401              |
|                     | 12 | 122 | -17.7 (-18.9, -16.5)    | 127 | -16.9 (-18.1, -15.7)    | 0.8 (-0.9, 2.6)          | 0.351              |
| GAF                 | 12 | 133 | 21.0 (19.0, 23.1)       | 135 | 18.0 (16.0, 20.0)       | 3.1 (0.1, 6.0)           | 0.040 <sup>c</sup> |
| SASS                | 12 | 130 | 8.9 (7.5, 10.2)         | 132 | 8.1 (6.8, 9.4)          | 0.7 (-1.2, 2.6)          | 0.466              |
| EQ-5D               | 12 | 138 | 0.3296 (0.2998, 0.3593) | 134 | 0.3041 (0.2742, 0.3341) | 0.0254 (-0.0185, 0.0694) | 0.256              |
| Ability to work     | 0  | 195 | 44.1%                   | 188 | 36.7%                   | --                       | 0.146              |
|                     | 12 | 143 | 86.5% (79.0%, 91.6%)    | 137 | 76.2% (66.5%, 83.7%)    | 2.008 (1.047, 3.851)     | 0.036 <sup>c</sup> |

<sup>a</sup> For change from baseline, all values are presented as scores, except for Ability to Work, which is presented as a percentage.

<sup>b</sup> For treatment difference, Ability to Work is presented as an odds ratio (values >1 favor duloxetine). All other treatment differences presented are the least squares mean change difference between treatment groups (positive values indicate favorable outcome with duloxetine; negative values indicate favorable outcome with SSRIs).

<sup>c</sup> Statistically significant difference favoring duloxetine  $P < 0.05$ .

Abbreviations: BPI-SF, Brief Pain Inventory-Short Form (higher score indicates more pain)<sup>24</sup>; CI, confidence interval; EQ-5D, EuroQol-5-Dimension Questionnaire for Quality of Life (lower score indicates less health)<sup>25</sup>; GAF, Global Assessment of Functioning Scale (lower score indicates greater severity of illness)<sup>26</sup>; HAM-D17, 17-Item Hamilton Rating Scale for Depression (higher score indicates more depression)<sup>27</sup>; LS, least squares; n, number of affected patients; SASS, Social Adaptation Self-Evaluation Scale (higher score indicates greater social adjustment)<sup>28</sup>; SSRIs, selective serotonin reuptake inhibitors.

**Supplemental Table 3.** Subgroup analysis of patient age (<65 versus ≥65) effect on all scales.

| Patient Characteristic    | Week | Duloxetine <sup>a</sup> |                         | SSRIs <sup>b</sup> |                         | Treatment Difference (95% CI) | P-value |
|---------------------------|------|-------------------------|-------------------------|--------------------|-------------------------|-------------------------------|---------|
|                           |      | n                       | LS Mean Change (95% CI) | n                  | LS Mean Change (95% CI) |                               |         |
| <b>Age &lt;65</b>         |      |                         |                         |                    |                         |                               |         |
| BPI-SF average pain score | 2    | 183                     | -1.9 (-2.1, -1.6)       | 166                | -2.0 (-2.3, -1.7)       | -0.1 (-0.5, 0.3)              | 0.550   |
|                           | 4    | 216                     | -2.9 (-3.1, -2.6)       | 195                | -2.5 (-2.8, -2.2)       | 0.3 (-0.1, 0.7)               | 0.100   |
|                           | 8    | 162                     | -3.6 (-3.9, -3.3)       | 146                | -3.2 (-3.5, -2.8)       | 0.4 (0.0, 0.9)                | 0.060   |
|                           | 12   | 158                     | -3.9 (-4.2, -3.5)       | 151                | -3.4 (-3.8, -3.1)       | 0.4 (-0.1, 0.9)               | 0.093   |
| HAM-D17 total score       | 2    | 155                     | -5.3 (-6.1, -4.6)       | 156                | -6.1 (-6.8, -5.3)       | -0.8 (-1.9, 0.3)              | 0.179   |
|                           | 4    | 190                     | -10.2 (-11.1, -9.3)     | 187                | -10.7 (-11.6, -9.8)     | -0.5 (-1.8, 0.8)              | 0.418   |
|                           | 8    | 134                     | -14.3 (-15.3, -13.3)    | 138                | -14.1 (-15.1, -13.1)    | 0.2 (-1.3, 1.6)               | 0.827   |
|                           | 12   | 126                     | -16.6 (-17.7, -15.6)    | 133                | -16.2 (-17.3, -15.2)    | 0.4 (-1.1, 1.9)               | 0.609   |
| GAF                       | 12   | 146                     | 20.0 (18.2, 21.9)       | 146                | 18.7 (16.8, 20.6)       | 1.3 (-1.4, 4.0)               | 0.346   |
| SASS                      | 12   | 138                     | 9.1 (7.9, 10.4)         | 140                | 8.9 (7.7, 10.2)         | 0.2 (-1.6, 2.0)               | 0.821   |
| EQ-5D                     | 12   | 143                     | 0.3049 (0.2778, 0.3319) | 144                | 0.3004 (0.2732, 0.3275) | 0.0045 (-0.0349, 0.0439)      | 0.822   |
| Ability to work           | 0    | 244                     | 48.4%                   | 221                | 42.5%                   | --                            | 0.226   |
|                           | 12   | 173                     | 85.0% (78.0%, 90.0%)    | 156                | 77.2% (68.3%, 84.2%)    | 1.669 (0.938, 2.970)          | 0.081   |
| <b>Age ≥65</b>            |      |                         |                         |                    |                         |                               |         |
| BPI-SF average pain score | 2    | 26                      | -1.4 (-2.2, -0.7)       | 18                 | -1.7 (-2.5, -0.8)       | -0.2 (-1.4, 0.9)              | 0.672   |
|                           | 4    | 20                      | -2.3 (-3.2, -1.4)       | 24                 | -2.8 (-3.6, -1.9)       | -0.5 (-1.8, 0.9)              | 0.494   |

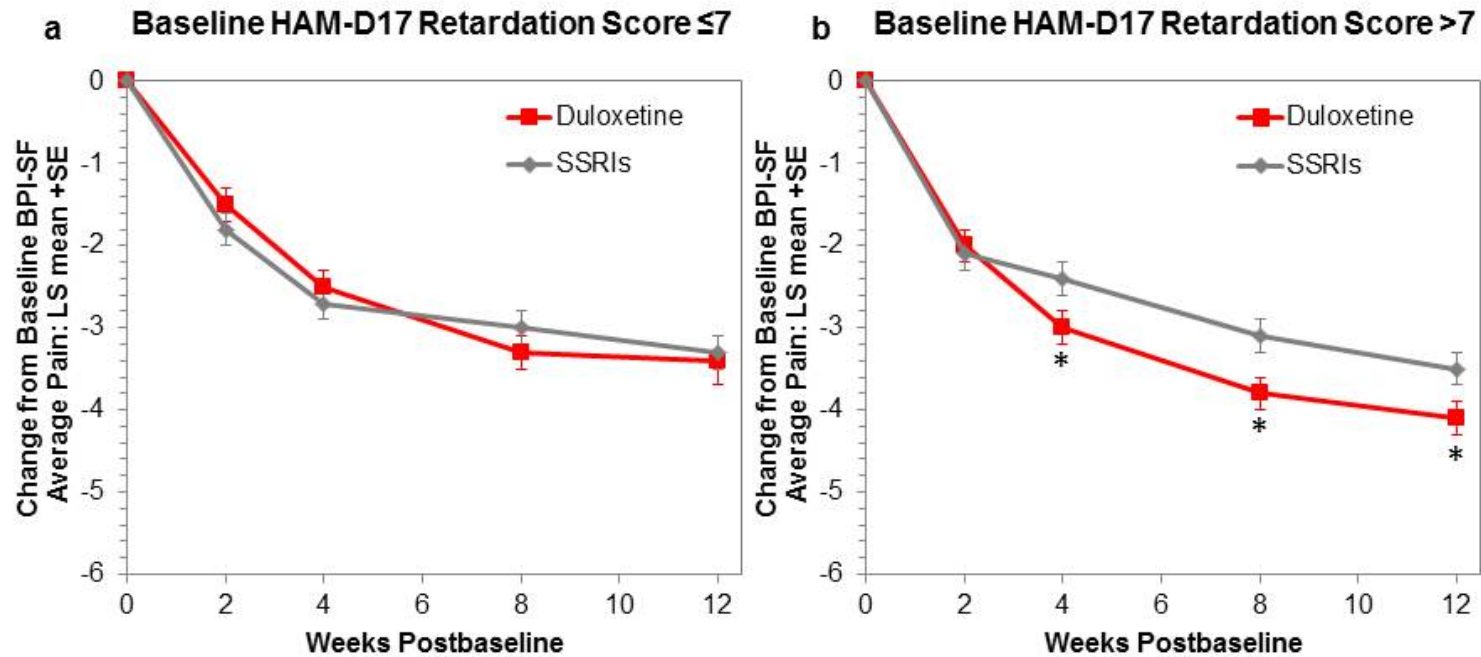
|                     |    |    |                         |    |                         |                          |                    |
|---------------------|----|----|-------------------------|----|-------------------------|--------------------------|--------------------|
|                     | 8  | 20 | -3.6 (-4.5, -2.6)       | 18 | -2.3 (-3.3, -1.3)       | 1.3 (-0.2, 2.8)          | 0.082              |
|                     | 12 | 21 | -3.8 (-4.8, -2.8)       | 14 | -3.1 (-4.3, -1.9)       | 0.7 (-1.0, 2.3)          | 0.406              |
| HAM-D17 total score | 2  | 15 | -3.4 (-6.6, -0.2)       | 17 | -5.3 (-8.1, -2.4)       | -1.9 (-6.4, 2.6)         | 0.400              |
|                     | 4  | 16 | -7.5 (-11.0, -4.1)      | 22 | -9.4 (-12.5, -6.3)      | -1.9 (-6.8, 3.0)         | 0.442              |
|                     | 8  | 14 | -12.2 (-15.4, -8.9)     | 16 | -10.8 (-13.8, -7.8)     | 1.3 (-3.3, 6.0)          | 0.569              |
|                     | 12 | 17 | -14.4 (-17.4, -11.5)    | 15 | -13.6 (-16.5, -10.8)    | 0.8 (-3.6, 5.2)          | 0.717              |
| GAF                 | 12 | 19 | 22.3 (16.6, 28.0)       | 15 | 12.7 (6.6, 18.9)        | 9.6 (0.6, 18.5)          | 0.037 <sup>c</sup> |
| SASS                | 12 | 15 | 8.2 (4.5, 12.0)         | 14 | 8.2 (4.5, 12.0)         | 0.0 (-5.6, 5.7)          | 0.992              |
| EQ-5D               | 12 | 19 | 0.2728 (0.2011, 0.3445) | 14 | 0.1588 (0.0787, 0.2389) | 0.1140 (-0.0011, 0.2290) | 0.052              |
| Ability to work     | 0  | 29 | 27.6%                   | 29 | 6.9%                    | --                       | 0.079              |
|                     | 12 | 18 | --                      | 11 | --                      | --                       | --                 |

<sup>a</sup> For change from baseline, all values are presented as scores.

<sup>b</sup> For treatment difference, Ability to Work is presented as an odds ratio (values >1 favor duloxetine). All other treatment differences presented are the least squares mean change difference between treatment groups (positive values indicate favorable outcome with duloxetine; negative values indicate favorable outcome with SSRIs).

<sup>c</sup> Statistically significant difference favoring duloxetine  $P < 0.05$ .

Abbreviations: BPI-SF, Brief Pain Inventory-Short Form (higher score indicates more pain)<sup>24</sup>; CI, confidence interval; EQ-5D, EuroQol – 5-Dimension Questionnaire for Quality of Life (lower score indicates less health)<sup>25</sup>; GAF, Global Assessment of Functioning Scale (lower score indicates greater severity of illness)<sup>26</sup>; HAM-D17, 17-Item Hamilton Rating Scale for Depression (higher score indicates more depression)<sup>27</sup>; LS, least squares; n, number of affected patients; SASS, Social Adaptation Self-Evaluation Scale (higher score indicates greater social adjustment)<sup>28</sup>; SSRIs, selective serotonin reuptake inhibitors.

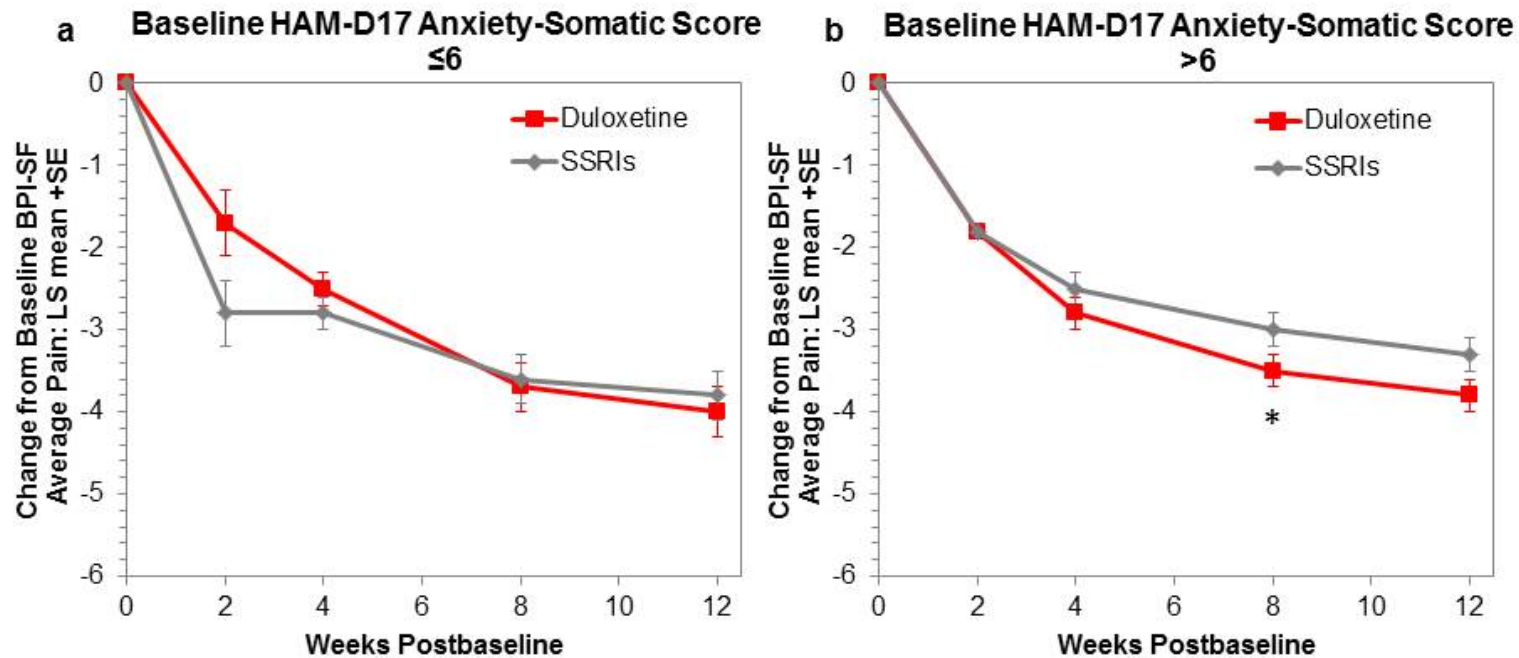


Supplemental Figure 1. Improvement in BPI-SF average pain scores as a function of baseline HAM-D17 retardation score ( $\leq 7$  [a] versus  $> 7$  [b]) for duloxetine- and SSRI-treated patients. Abbreviations: BPI-SF, Brief Pain Inventory- Short Form; HAM-D17, 17-Item Hamilton Rating Scale for Depression; LS, least squares; n, number of affected patients at postbaseline week 12; SE, standard error; SSRIs, selective serotonin reuptake inhibitors.

\* Statistically significant difference favoring duloxetine  $P < 0.05$ .

Number of patients at baseline – (a) HAM-D17 retardation score  $\leq 7$ : Duloxetine n=120; SSRIs n=114.

Number of patients at baseline – (b) HAM-D17 retardation score  $> 7$ : Duloxetine n=144; SSRIs n=135.



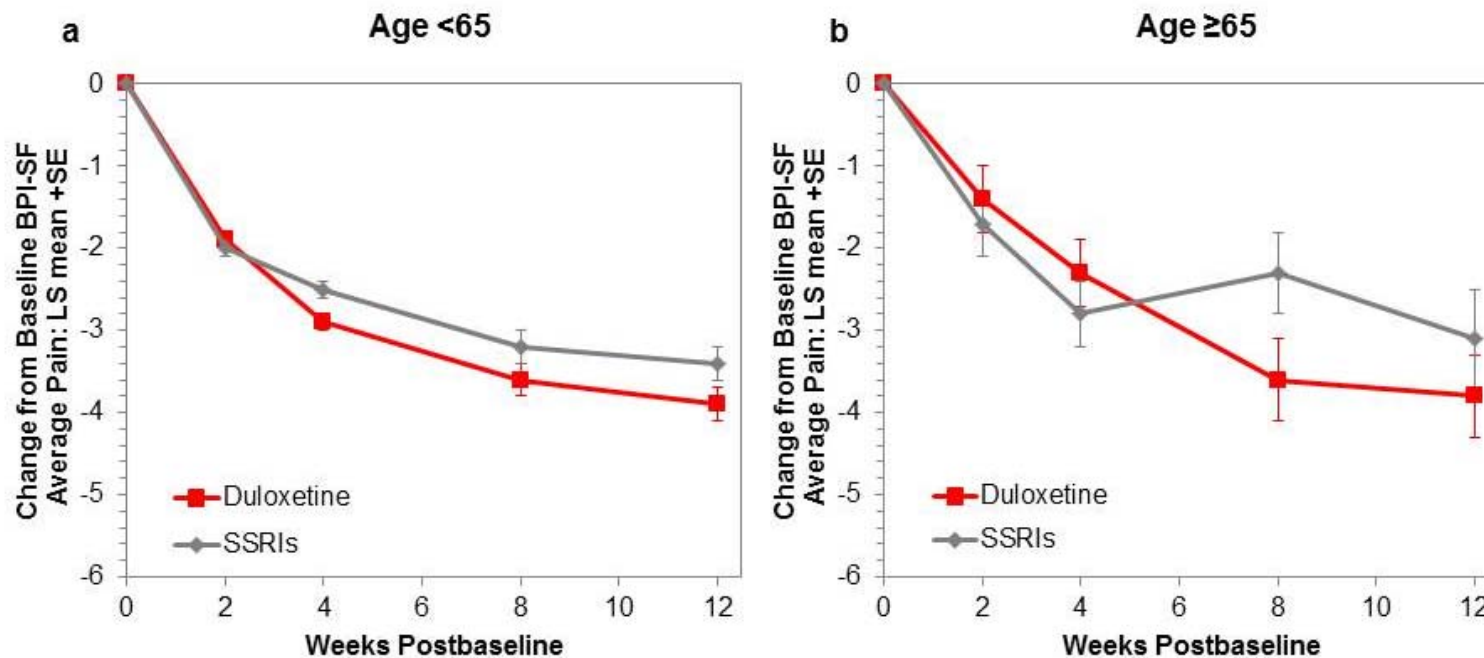
Supplemental Figure 2. Improvement in BPI-SF average pain scores as a function of baseline HAM-D17 anxiety-somatic score ( $\leq 6$  [a] versus  $> 6$  [b]) for duloxetine- and SSRI-treated patients. Abbreviations: BPI-SF, Brief Pain Inventory- Short Form; HAM-D17, 17-Item Hamilton Rating Scale for Depression; LS, least squares; n, number of affected patients at postbaseline week 12; SE, standard error; SSRIs, selective serotonin reuptake inhibitors.

\* Statistically significant difference favoring duloxetine  $P < 0.05$ .

Number of patients at baseline – (a) HAM-D17 anxiety-somatic score  $\leq 6$ : Duloxetine  $n = 69$ ; SSRIs  $n = 61$ .

Number of patients at baseline – (b) HAM-D17 anxiety-somatic score  $> 6$ : Duloxetine  $n = 195$ ; SSRIs  $n = 188$ .





Supplemental Figure 3. Improvement in BPI-SF average pain scores as a function of patient age (<65 [a] versus ≥65 [b]) for duloxetine- and SSRI-treated patients. Abbreviations: BPI-SF, Brief Pain Inventory-Short Form; LS, least squares; n, number of affected patients at postbaseline week 12; SE, standard error; SSRIs, selective serotonin reuptake inhibitors.

Number of patients at baseline – (a) Age <65: Duloxetine n=244; SSRIs n=221.

Number of patients at baseline – (b) Age ≥65: Duloxetine n=29; SSRIs n=29.