**SUPPLEMENTAL DIGITAL CONTENT**

**SUPPLEMENTAL TABLE 3.** Predictive value of improvements in measures of disease severity after 2 weeks of treatment with placebo, stratified by a) fixed dose, b) flexible dose, and c) adjunctive regimen

a) Placebo fixed-dose monotherapy population

| **Early predictor** | **Outcome** | **Sensitivity (95% CI)** | **Specificity(95% CI)** | **Positive predictivevalue(95% CI)** | **Negativepredictivevalue(95% CI)** | **Falsepositiverate(95% CI)** | **Falsenegativerate(95% CI)** | **Yule’s Q(95% CI)** | **AUC(95% CI)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **MADRS** | **MADRS** |  |  |  |  |  |  |  |  |
| 15% | 50% improvement | 90 (82, 95) | 43 (36, 51) | 49 (42, 57) | 87 (78, 93) | 57 (49, 64) | 10 (5, 18) | 0.74 (0.71, 0.76) | 0.80 (0.73, 0.86) |
| 20% | 50% improvement | 86 (78, 92) | 51 (43, 58) | 52 (44, 59) | 85 (77, 92) | 49 (42, 57) | 14 (8, 22) | 0.73 (0.70, 0.75) |  |
| 25% | 50% improvement | 82 (74, 89) | 58 (50, 66) | 55 (47, 63) | 84 (76, 90) | 42 (35, 50) | 18 (11, 26) | 0.73 (0.71, 0.75) |  |
| 30% | 50% improvement | 80 (72, 87) | 66 (58, 73) | 59 (50, 67) | 84 (77, 90) | 34 (27, 42) | 20 (13, 28) | 0.77 (0.75, 0.79) |  |
|  |  |  |  |  |  |  |  |  |  |
| 15% | ≤12 pts | 89 (81, 95) | 41 (34, 48) | 43 (36, 50) | 88 (80, 94) | 59 (52, 66) | 11 (5, 19) | 0.70 (0.67, 0.74) | 0.79 (0.71, 0.86) |
| 20% | ≤12 pts | 85 (76, 92) | 48 (40, 55) | 45 (38, 53) | 86 (78, 92) | 52 (45, 60) | 15 (8, 24) | 0.68 (0.65, 0.70) |  |
| 25% | ≤12 pts | 81 (71, 88) | 55 (47, 62) | 47 (39, 55) | 85 (77, 91) | 45 (38, 53) | 19 (12, 29) | 0.67 (0.65, 0.69) |  |
| 30% | ≤12 pts | 79 (69, 86) | 61 (54, 69) | 51 (42, 59) | 85 (78, 91) | 39 (31, 46) | 21 (14, 31) | 0.71 (0.69, 0.73) |  |
| **MADRS**  | **HAM-D** |  |  |  |  |  |  |  |  |
| 15% | 50% improvement | 85 (77, 91) | 41 (33, 49) | 50 (42, 57) | 80 (69, 88) | 59 (51, 67) | 15 (9, 23) | 0.59 (0.56, 0.62) | 0.76 (0.68, 0.82) |
| 20% | 50% improvement | 81 (73, 88) | 48 (40, 56) | 52 (44, 60) | 79 (69, 87) | 52 (44, 60) | 19 (12, 27) | 0.60 (0.57, 0.62) |  |
| 25% | 50% improvement | 77 (68, 84) | 55 (47, 63) | 54 (46, 62) | 77 (68, 85) | 45 (37, 53) | 23 (16, 33) | 0.60 (0.57, 0.62) |  |
| 30% | 50% improvement | 74 (64, 82) | 63 (54, 70) | 58 (49, 66) | 78 (69, 85) | 37 (30, 46) | 26 (18, 36) | 0.65 (0.63, 0.67) |  |
|  |  |  |  |  |  |  |  |  |  |
| 15% | ≤7 pts | 88 (78, 95) | 37 (30, 44) | 33 (26, 40) | 90 (81, 96) | 63 (56, 70) | 12 (5, 22) | 0.62 (0.57, 0.67) | 0.78 (0.68, 0.85) |
| 20% | ≤7 pts | 87 (76, 94) | 44 (37, 51) | 35 (28, 43) | 90 (83, 96) | 56 (49, 63) | 13 (6, 24) | 0.67 (0.63, 0.71) |  |
| 25% | ≤7 pts | 84 (73, 92) | 51 (44, 58) | 38 (30, 46) | 90 (83, 95) | 49 (42, 56) | 16 (8, 27) | 0.69 (0.65, 0.72) |  |
| 30% | ≤7 pts | 81 (70, 89) | 58 (50, 65) | 40 (32, 49) | 90 (83, 94) | 42 (35, 50) | 19 (11, 30) | 0.70 (0.68, 0.73) |  |
| **CGI-S\*** | **CGI-S** |  |  |  |  |  |  |  |  |
| 1 pt | ≤2 | 80 (69, 88) | 56 (49, 63) | 42 (34, 50) | 88 (81, 93) | 44 (37, 51) | 20 (12, 31) |  |  |
| **CGI-S\*** | **HAM-D** |  |  |  |  |  |  |  |  |
| 1 pt | 50% improvement | 75 (65, 83) | 60 (52, 68) | 56 (48, 65) | 78 (69, 85) | 40 (32, 48) | 25 (17, 35) |  |  |
| 1 pt | ≤7 pts | 75 (63, 85) | 53 (46, 60) | 36 (28, 44) | 86 (78, 92) | 47 (40, 54) | 25 (15, 37) |  |  |
| \*1-point improvement at Week 2.AUC, area under the concentration-time curve; CGI-S, Clinical Global Impression – Severity Score; CI, confidence interval; HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; XR, extended release; Yule’s Q, Yule’s Q coefficient. |

b) Placebo flexible-dose monotherapy population

| **Early predictor** | **Outcome** | **Sensitivity (95% CI)** | **Specificity(95% CI)** | **Positive predictivevalue(95% CI)** | **Negativepredictivevalue(95% CI)** | **Falsepositiverate(95% CI)** | **Falsenegativerate(95% CI)** | **Yule’s Q(95% CI)** | **AUC(95% CI)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **MADRS** | **MADRS** |  |  |  |  |  |  |  |  |
| 15% | 50% improvement | 91 (85, 95) | 40 (31, 50) | 66 (59, 73) | 78 (65, 88) | 60 (50, 69) | 9 (5, 15) | 0.75 (0.72, 0.77) | 0.76 (0.70, 0.81) |
| 20% | 50% improvement | 88 (82, 93) | 46 (37, 56) | 68 (61, 75) | 76 (64, 85) | 54 (44, 63) | 12 (7, 18) | 0.74 (0.71, 0.76) |  |
| 25% | 50% improvement | 82 (74, 88) | 55 (46, 65) | 70 (63, 77) | 70 (59, 79) | 45 (35, 54) | 18 (12, 26) | 0.69 (0.67, 0.71) |  |
| 30% | 50% improvement | 76 (68, 83) | 66 (56, 74) | 74 (66, 81) | 68 (59, 77) | 34 (26, 44) | 24 (17, 32) | 0.72 (0.70, 0.74) |  |
|  |  |  |  |  |  |  |  |  |  |
| 15% | ≤12 pts | 92 (86, 96) | 36 (28, 44) | 56 (49, 63) | 83 (71, 92) | 64 (56, 72) | 8 (4, 14) | 0.73 (0.69, 0.76) | 0.76 (0.70, 0.82) |
| 20% | ≤12 pts | 89 (82, 94) | 41 (33, 50) | 58 (50, 65) | 80 (69, 89) | 59 (50, 67) | 11 (6, 18) | 0.69 (0.66, 0.72) |  |
| 25% | ≤12 pts | 83 (75, 89) | 50 (42, 59) | 60 (53, 68) | 77 (67, 85) | 50 (41, 58) | 17 (11, 25) | 0.67 (0.64, 0.69) |  |
| 30% | ≤12 pts | 79 (71, 86) | 61 (53, 70) | 65 (57, 72) | 76 (67, 84) | 39 (30, 47) | 21 (14, 29) | 0.71 (0.69, 0.73) |  |
| **MADRS**  | **HAM-D** |  |  |  |  |  |  |  |  |
| 15% | 50% improvement | 88 (82, 93) | 39 (29, 50) | 68 (61, 75) | 69 (55, 81) | 61 (50, 71) | 12 (7, 18) | 0.65 (0.62, 0.68) | 0.74 (0.68, 0.80) |
| 20% | 50% improvement | 86 (79, 91) | 45 (35, 56) | 70 (62, 76) | 69 (56, 80) | 55 (44, 65) | 14 (9, 21) | 0.67 (0.64, 0.70) |  |
| 25% | 50% improvement | 80 (73, 87) | 56 (45, 66) | 73 (65, 79) | 66 (55, 76) | 44 (34, 55) | 20 (14, 27) | 0.67 (0.65, 0.70) |  |
| 30% | 50% improvement | 74 (66, 81) | 65 (55, 74) | 76 (68, 82) | 63 (53, 72) | 35 (26, 45) | 26 (19, 34) | 0.68 (0.66, 0.70) |  |
|  |  |  |  |  |  |  |  |  |  |
| 15% | ≤7 pts | 95 (88, 99) | 32 (25, 40) | 41 (34, 49) | 93 (82, 98) | 68 (60, 75) | 5 (1, 12) | 0.80 (0.74, 0.85) | 0.74 (0.66, 0.81) |
| 20% | ≤7 pts | 91 (83, 96) | 36 (28, 44) | 42 (34, 49) | 89 (79, 95) | 64 (56, 72) | 9 (4, 17) | 0.71 (0.66, 0.75) |  |
| 25% | ≤7 pts | 85 (75, 92) | 44 (36, 52) | 43 (35, 51) | 85 (76, 92) | 56 (48, 64) | 15 (8, 25) | 0.63 (0.60, 0.69) |  |
| 30% | ≤7 pts | 80 (70, 88) | 53 (45, 61) | 46 (38, 55) | 84 (75, 91) | 47 (39, 55) | 20 (12, 30) | 0.64 (0.60, 0.66) |  |
| **CGI-S\*** | **CGI-S** |  |  |  |  |  |  |  |  |
| 1 pt | ≤2 | 86 (77, 92) | 52 (44, 59) | 48 (40, 56) | 87 (79, 93) | 48 (41, 56) | 14 (8, 23) |  |  |
| **CGI-S\*** | **HAM-D** |  |  |  |  |  |  |  |  |
| 1 pt | 50% improvement | 73 (64, 80) | 53 (42, 63) | 69 (61, 76) | 57 (46, 67) | 47 (37, 58) | 27 (20, 36) |  |  |
| 1 pt | ≤7 pts | 81 (71, 89) | 47 (39, 55) | 44 (36, 52) | 83 (74, 90) | 53 (45, 61) | 19 (11, 29) |  |  |
| \*1-point improvement at Week 2.AUC, area under the concentration-time curve; CGI-S, Clinical Global Impression – Severity Score; CI, confidence interval; HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; XR, extended release; Yule’s Q, Yule’s Q coefficient. |

c) Placebo adjunctive therapy population

| **Early predictor** | **Outcome** | **Sensitivity (95% CI)** | **Specificity(95% CI)** | **Positive predictivevalue(95% CI)** | **Negativepredictivevalue(95% CI)** | **Falsepositiverate(95% CI)** | **Falsenegativerate(95% CI)** | **Yule’s Q(95% CI)** | **AUC(95% CI)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **MADRS** | **MADRS** |  |  |  |  |  |  |  |  |
| 15% | 50% improvement | 91 (85, 95) | 44 (36, 52) | 60 (53, 67) | 83 (73, 91) | 56 (48, 64) | 9 (5, 15) | 0.76 (0.74, 0.79) | 0.78 (0.72, 0.83) |
| 20% | 50% improvement | 85 (78, 90) | 52 (44, 61) | 62 (55, 69) | 79 (69, 86) | 48 (39, 56) | 15 (10, 22) | 0.72 (0.70, 0.74) |  |
| 25% | 50% improvement | 82 (75, 88) | 62 (53, 70) | 67 (59, 74) | 79 (70, 86) | 38 (30, 47) | 18 (12, 25) | 0.76 (0.74, 0.78) |  |
| 30% | 50% improvement | 76 (68, 82) | 70 (62, 78) | 70 (62, 78) | 76 (68, 82) | 30 (22, 38) | 24 (18, 32) | 0.76 (0.75, 0.78) |  |
|  |  |  |  |  |  |  |  |  |  |
| 15% | ≤12 pts | 88 (80, 93) | 38 (30, 45) | 50 (43, 57) | 81 (70, 89) | 63 (55, 70) | 13 (7, 20) | 0.62 (0.58, 0.65) | 0.73 (0.66, 0.79) |
| 20% | ≤12 pts | 82 (74, 88) | 46 (38, 54) | 52 (45, 59) | 78 (68, 86) | 54 (46, 62) | 18 (12, 26) | 0.58 (0.55, 0.61) |  |
| 25% | ≤12 pts | 78 (69, 85) | 54 (46, 61) | 54 (47, 62) | 77 (68, 84) | 46 (39, 54) | 23 (15, 31) | 0.60 (0.57, 0.62) |  |
| 30% | ≤12 pts | 73 (64, 81) | 64 (56, 71) | 59 (51, 67) | 77 (69, 84) | 36 (29, 44) | 27 (19, 36) | 0.66 (0.64, 0.68) |  |
| **MADRS**  | **HAM-D** |  |  |  |  |  |  |  |  |
| 15% | 50% improvement | 86 (79, 91) | 42 (34, 51) | 61 (53, 68) | 74 (63, 83) | 58 (49, 66) | 14 (9, 21) | 0.63 (0.60, 0.65) | 0.72 (0.66, 0.78) |
| 20% | 50% improvement | 78 (70, 84) | 50 (41, 58) | 62 (54, 69) | 68 (58, 77) | 50 (42, 59) | 22 (16, 30) | 0.55 (0.53, 0.58) |  |
| 25% | 50% improvement | 74 (66, 81) | 59 (51, 68) | 65 (58, 73) | 69 (60, 77) | 41 (32, 50) | 26 (19, 34) | 0.62 (0.59, 0.64) |  |
| 30% | 50% improvement | 69 (61, 77) | 67 (59, 75) | 69 (60, 76) | 68 (59, 76) | 33 (25, 41) | 31 (23, 39) | 0.65 (0.63, 0.67) |  |
|  |  |  |  |  |  |  |  |  |  |
| 15% | ≤7 pts | 88 (78, 94) | 34 (27, 41) | 33 (27, 40) | 88 (79, 95) | 66 (59, 73) | 12 (6, 22) | 0.58 (0.53, 0.63) | 0.73 (0.64, 0.80) |
| 20% | ≤7 pts | 83 (72, 90) | 43 (36, 50) | 35 (28, 43) | 87 (78, 93) | 58 (50, 64) | 17 (10, 28) | 0.56 (0.52, 0.60) |  |
| 25% | ≤7 pts | 80 (69, 88) | 51 (43, 58) | 38 (30, 46) | 87 (80, 93) | 50 (42, 57) | 20 (12, 31) | 0.61 (0.57, 0.64) |  |
| 30% | ≤7 pts | 79 (68, 87) | 59 (52, 66) | 42 (34, 50) | 86 (81, 93) | 41 (34, 48) | 21 (13, 32) | 0.68 (0.66, 0.71) |  |
| **CGI-S\*** | **CGI-S** |  |  |  |  |  |  |  |  |
| 1 pt | ≤2 | 81 (70, 88) | 55 (48, 62) | 42 (34, 50) | 88 (81, 93) | 45 (38, 52) | 19 (12, 30) |  |  |
| **CGI-S\*** | **HAM-D** |  |  |  |  |  |  |  |  |
| 1 pt | 50% improvement | 73 (65, 80) | 65 (57, 73) | 69 (60, 76) | 70 (61, 78) | 35 (27, 43) | 27 (20, 35) |  |  |
| 1 pt | ≤7 pts | 79 (68, 87) | 55 (48, 62) | 40 (32, 48) | 87 (80, 93) | 45 (38, 52) | 21 (13, 32) |  |  |
| \*1-point improvement at Week 2.AUC, area under the concentration-time curve; CGI-S, Clinical Global Impression – Severity Score; CI, confidence interval; HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; XR, extended release; Yule’s Q, Yule’s Q coefficient. |