**SUPPLEMENTAL DIGITAL CONTENT**

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

a) Quetiapine XR fixed-dose monotherapy population

| **Early predictor** | **Outcome** | **Sensitivity  (95% CI)** | **Specificity  (95% CI)** | **Positive predictive value (95% CI)** | **Negative predictive value (95% CI)** | **False positive rate (95% CI)** | **False negative rate (95% CI)** | **Yule’s Q (95% CI)** | **P value versus placebo** | **AUC (95% CI)** | **P value versus placebo** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **MADRS** | **MADRS** |  |  |  |  |  |  |  |  |  |  |
| 15% | 50% improvement | 92 (89, 95) | 35 (29, 42) | 68 (64, 73) | 76 (66, 84) | 65 (58, 71) | 8 (5, 11) | 0.74 (0.72, 0.75) | 0.940 | 0.78 (0.74, 0.81) | 0.627 |
| 20% | 50% improvement | 88 (84, 92) | 43 (36, 50) | 70 (65, 75) | 71 (62, 79) | 57 (50, 64) | 12 (8, 16) | 0.71 (0.69, 0.72) | 0.222 |  |  |
| 25% | 50% improvement | 84 (80, 88) | 54 (47, 61) | 73 (68, 78) | 69 (61, 76) | 46 (39, 53) | 16 (12, 20) | 0.72 (0.71, 0.73) | 0.449 |  |  |
| 30% | 50% improvement | 78 (73, 83) | 64 (57, 71) | 77 (72, 81) | 66 (59, 73) | 36 (39, 43) | 22 (17, 27) | 0.73 (0.72, 0.74) | <0.001 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| 15% | ≤12 pts | 93 (89, 96) | 30 (24, 36) | 56 (51, 61) | 82 (73, 89) | 70 (64, 76) | 7 (4, 11) | 0.71 (0.68, 0.72) | 0.936 | 0.77 (0.73, 0.81) | 0.668 |
| 20% | ≤12 pts | 90 (85, 93) | 37 (31, 44) | 58 (53, 63) | 79 (70, 86) | 63 (56, 69) | 10 (7, 15) | 0.67 (0.65, 0.69) | 0.705 |  |  |
| 25% | ≤12 pts | 86 (82, 91) | 48 (42, 54) | 62 (56, 67) | 79 (72, 85) | 52 (46, 58) | 14 (9, 18) | 0.71 (0.70, 0.72) | 0.004 |  |  |
| 30% | ≤12 pts | 81 (76, 86) | 58 (51, 64) | 65(59, 70) | 76 (69, 82) | 42 (36, 49) | 19 (14, 24) | 0.70 (0.69, 0.72) | 0.647 |  |  |
| **MADRS** | **HAM-D** |  |  |  |  |  |  |  |  |  |  |
| 15% | 50% improvement | 92 (89, 95) | 34 (27, 41) | 68 (64, 73) | 74 (63, 83) | 66 (59, 73) | 8 (5, 11) | 0.71 (0.70, 0.73) | <0.001 | 0.77 (0.73, 0.80) | 0.845 |
| 20% | 50% improvement | 88 (84, 92) | 42 (35, 49) | 70 (65, 75) | 70 (60, 78) | 58 (51, 65) | 12 (8, 16) | 0.69 (0.68, 0.70) | <0.001 |  |  |
| 25% | 50% improvement | 84 (79, 88) | 53 (45, 60) | 74 (68, 78) | 68 (59, 75) | 47 (40, 55) | 16 (12, 21) | 0.70 (0.69, 0.72) | <0.001 |  |  |
| 30% | 50% improvement | 77 (72, 82) | 63 (56, 70) | 77 (71, 81) | 64 (57, 71) | 37 (30, 44) | 23 (18, 28) | 0.71 (0.70, 0.72) | <0.001 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| 15% | ≤7 pts | 93 (87, 97) | 23 (18, 27) | 34 (30, 39) | 88 (79, 94) | 77 (73, 82) | 7 (3, 13) | 0.59 (0.55, 0.63) | 0.263 | 0.72 (0.66, 0.77) | 0.376 |
| 20% | ≤7 pts | 89 (83, 94) | 29 (24, 34) | 36 (31, 41) | 86 (78, 92) | 71 (66, 76) | 11 (6, 17) | 0.55 (0.52, 0.58) | <0.001 |  |  |
| 25% | ≤7 pts | 87 (81, 92) | 38 (33, 44) | 38 (33, 44) | 87 (81, 92) | 62 (56, 67) | 13 (8, 19) | 0.62 (0.60, 0.64) | 0.002 |  |  |
| 30% | ≤7 pts | 80 (73, 86) | 47 (41, 52) | 40 (34, 46) | 84 (78, 89) | 53 (48, 59) | 20 (14, 27) | 0.56 (0.54, 0.58) | <0.001 |  |  |
| **CGI-S\*** | **CGI-S** |  |  |  |  |  |  |  |  |  |  |
| 1 pt | ≤2 | 84 (78, 88) | 39 (34, 45) | 48 (42, 53) | 78 (71, 85) | 61 (55, 66) | 16 (12, 22) |  |  |  |  |
| **CGI-S\*** | **HAM-D** |  |  |  |  |  |  |  |  |  |  |
| 1 pt | 50% improvement | 80 (74, 84) | 45 (38, 53) | 69 (64, 74) | 59 (50, 67) | 55 (47, 62) | 20 (16, 26) |  |  |  |  |
| 1 pt | ≤7 pts | 82 (74, 88) | 35 (30, 41) | 36 (30, 41) | 81 (74, 87) | 65 (59, 70) | 18 (12, 26) |  |  |  |  |
| \*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) Quetiapine XR flexible-dose monotherapy population

| **Early predictor** | **Outcome** | **Sensitivity  (95% CI)** | **Specificity  (95% CI)** | **Positive predictive value (95% CI)** | **Negative predictive value (95% CI)** | **False positive rate (95% CI)** | **False negative rate (95% CI)** | **Yule’s Q (95% CI)** | **P value versus placebo** | **AUC (95% CI)** | **P value versus placebo** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **MADRS** | **MADRS** |  |  |  |  |  |  |  |  |  |  |
| 15% | 50% improvement | 93 (88, 96) | 24 (15, 35) | 73 (66, 79) | 59 (41, 76) | 76 (65, 85) | 7 (4, 12) | 0.59 (0.54, 0.64) | <0.001 | 0.76 (0.71, 0.81) | 0.930 |
| 20% | 50% improvement | 91 (85, 95) | 34 (24, 46) | 75 (69, 81) | 63 (47, 77) | 66 (54, 76) | 9 (5, 15) | 0.67 (0.64, 0.70) | 0.003 |  |  |
| 25% | 50% improvement | 88 (83, 93) | 41 (30, 52) | 77 (70, 82) | 62 (47, 75) | 59 (48, 70) | 12 (7, 17) | 0.68 (0.65, 0.71) | 0.455 |  |  |
| 30% | 50% improvement | 82 (75, 87) | 59 (48, 70) | 82 (75, 87) | 59 (48, 70) | 41 (30, 52) | 18 (13, 25) | 0.73 (0.71, 0.75) | 0.409 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| 15% | ≤12 pts | 92 (87, 96) | 21 (13, 31) | 66 (59, 72) | 63 (44, 79) | 79 (69, 87) | 8 (4, 13) | 0.53 (0.47, 0.58) | <0.001 | 0.77 (0.71, 0.82) | 0.845 |
| 20% | ≤12 pts | 92 (86, 96) | 32 (22, 42) | 69 (62, 75) | 70 (54, 83) | 68 (58, 78) | 8 (4, 14) | 0.67 (0.64, 0.71) | 0.504 |  |  |
| 25% | ≤12 pts | 89 (83, 94) | 37 (27, 47) | 70 (63, 76) | 67 (53, 80) | 63 (53, 73) | 11 (6, 17) | 0.66 (0.62, 0.69) | 0.632 |  |  |
| 30% | ≤12 pts | 83 (76, 88) | 55 (44, 65) | 75 (68, 81) | 66 (54, 76) | 45 (35, 52) | 18 (13, 25) | 0.71 (0.68, 0.73) | 0.675 |  |  |
| **MADRS** | **HAM-D** |  |  |  |  |  |  |  |  |  |  |
| 15% | 50% improvement | 93 (88, 96) | 19 (10, 31) | 76 (70, 82) | 48 (28, 69) | 81 (69, 90) | 7 (4, 12) | 0.49 (0.42, 0.56) | <0.001 | 0.75 (0.69, 0.80) | 0.891 |
| 20% | 50% improvement | 90 (85, 94) | 31 (20, 44) | 78 (72, 84) | 53 (36, 70) | 69 (56, 80) | 10 (6, 15) | 0.60 (0.56, 0.65) | 0.018 |  |  |
| 25% | 50% improvement | 87 (81, 92) | 37 (25, 50) | 80 (73, 85) | 51 (36, 66) | 63 (50, 75) | 13 (8, 19) | 0.60 (0.56, 0.64) | 0.004 |  |  |
| 30% | 50% improvement | 79 (72, 84) | 56 (43, 69) | 83 (77, 89) | 49 (37, 61) | 44 (31, 57) | 21 (16, 28) | 0.65 (0.62, 0.68) | 0.145 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| 15% | ≤7 pts | 96 (91, 99) | 17 (11, 24) | 50 (43, 57) | 84 (64, 95) | 83 (76, 89) | 4 (1, 9) | 0.68 (0.59, 0.75) | 0.035 | 0.74 (0.67, 0.79) | 0.914 |
| 20% | ≤7 pts | 96 (91, 99) | 25 (18, 34) | 53 (46, 60) | 89 (74, 97) | 75 (66, 82) | 4 (1, 9) | 0.80 (0.74, 0.85) | 0.022 |  |  |
| 25% | ≤7 pts | 93 (86, 97) | 29 (22, 38) | 53 (46, 60) | 82 (68, 92) | 71 (62, 78) | 7 (3, 14) | 0.68 (0.63, 0.72) | 0.139 |  |  |
| 30% | ≤7 pts | 87 (79, 83) | 46 (37, 55) | 58 (50, 66) | 81 (70, 89) | 54 (45, 63) | 13 (7, 21) | 0.71 (0.68, 0.73) | 0.002 |  |  |
| **CGI-S\*** | **CGI-S** |  |  |  |  |  |  |  |  |  |  |
| 1 pt | ≤2 | 84 (76, 90) | 42 (33, 50) | 54 (46, 62) | 76 (65, 85) | 58 (50, 67) | 16 (10, 24) |  |  |  |  |
| **CGI-S\*** | **HAM-D** |  |  |  |  |  |  |  |  |  |  |
| 1 pt | 50% improvement | 77 (70, 83) | 45 (33, 58) | 80 (73, 86) | 41 (29, 54) | 55 (42, 67) | 23 (17, 30) |  |  |  |  |
| 1 pt | ≤7 pts | 86 (78, 92) | 42 (33, 51) | 56 (48, 64) | 78 (66, 87) | 58 (49, 67) | 14 (8, 22) |  |  |  |  |
| \*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) Quetiapine XR adjunctive therapy population

| **Early predictor** | **Outcome** | **Sensitivity  (95% CI)** | **Specificity  (95% CI)** | **Positive predictive value (95% CI)** | **Negative predictive value (95% CI)** | **False positive rate (95% CI)** | **False negative rate (95% CI)** | **Yule’s Q (95% CI)** | **P value versus placebo** | **AUC (95% CI)** | **P value versus placebo** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **MADRS** | **MADRS** |  |  |  |  |  |  |  |  |  |  |
| 15% | 50% improvement | 96 (93, 98) | 36 (29, 43) | 71 (67, 75) | 83 (73, 90) | 64 (57, 71) | 4 (2, 7) | 0.84 (0.83, 0.86) | <0.001 | 0.83 (0.80, 0.86) | 0.178 |
| 20% | 50% improvement | 93 (89, 95) | 46 (39, 53) | 74 (69, 78) | 79 (70, 86) | 54 (47, 61) | 7 (5, 11) | 0.82 (0.81, 0.83) | <0.001 |  |  |
| 25% | 50% improvement | 88 (84, 91) | 57 (50, 64) | 77 (73, 81) | 74 (67, 81) | 43 (36, 50) | 12 (9, 16) | 0.81 (0.81, 0.82) | <0.001 |  |  |
| 30% | 50% improvement | 84 (80, 88) | 64 (57, 71) | 80 (75, 84) | 71 (64, 78) | 36 (29, 43) | 16 (12, 20) | 0.82 (0.81, 0.82) | <0.001 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| 15% | ≤12 pts | 96 (93, 98) | 32 (26, 39) | 66 (61, 70) | 84 (75, 91) | 68 (61, 74) | 4 (2, 7) | 0.82 (0.80, 0.83) | <0.001 | 0.83 (0.79, 0.86) | 0.039 |
| 20% | ≤12 pts | 93 (90, 96) | 43 (36, 49) | 69 (64, 73) | 82 (74, 89) | 57 (51, 64) | 7 (4, 10) | 0.82 (0.81, 0.83) | <0.001 |  |  |
| 25% | ≤12 pts | 89 (85, 92) | 54 (47, 60) | 73 (68, 77) | 78 (71, 84) | 46 (40, 53) | 11 (8, 15) | 0.81 (0.80, 0.82) | <0.001 |  |  |
| 30% | ≤12 pts | 86 (81, 89) | 61 (54, 67) | 75 (70, 79) | 75 (68, 81) | 39 (33, 46) | 14 (11, 19) | 0.80 (0.79, 0.81) | <0.001 |  |  |
| **MADRS** | **HAM-D** |  |  |  |  |  |  |  |  |  |  |
| 15% | 50% improvement | 94 (90, 96) | 35 (28, 43) | 74 (70, 78) | 73 (62, 82) | 65 (57, 72) | 6 (4, 10) | 0.77 (0.76, 0.78) | <0.001 | 0.78 (0.74, 0.81) | 0.125 |
| 20% | 50% improvement | 90 (86, 93) | 42 (34, 50) | 75 (71, 79) | 68 (58, 77) | 58 (50, 66) | 10 (7, 14) | 0.73 (0.72, 0.74) | <0.001 |  |  |
| 25% | 50% improvement | 84 (80, 88) | 53 (45, 61) | 78 (73, 82) | 63 (55, 71) | 47 (39, 55) | 16 (12, 20) | 0.72 (0.71, 0.73) | <0.001 |  |  |
| 30% | 50% improvement | 80 (75, 84) | 59 (52, 67) | 79 (75, 84) | 60 (52, 67) | 41 (33, 48) | 20 (16, 25) | 0.71 (0.70, 0.72) | <0.001 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| 15% | ≤7 pts | 97 (94, 99) | 26 (21, 31) | 49 (44, 54) | 93 (85, 97) | 74 (69, 79) | 3 (1, 6) | 0.85 (0.82, 0.87) | <0.001 | 0.78 (0.74, 0.81) | 0.386 |
| 20% | ≤7 pts | 94 (90, 97 | 32 (27, 38) | 50 (45, 55) | 89 (81, 94) | 68 (62, 73) | 6 (3, 10) | 0.78 (0.76, 0.80) | <0.001 |  |  |
| 25% | ≤7 pts | 91 (87, 95) | 42 (37, 48) | 54 (48, 59) | 87 (80, 92) | 58 (52, 63) | 9 (5, 13) | 0.77 (0.75, 0.78) | <0.001 |  |  |
| 30% | ≤7 pts | 89 (84, 93) | 49 (44, 55) | 56 (51, 62) | 86 (80, 91) | 51 (45, 56) | 11 (7, 16) | 0.77 (0.76, 0.79) | <0.001 |  |  |
| **CGI-S\*** | **CGI-S** |  |  |  |  |  |  |  |  |  |  |
| 1 pt | ≤2 | 87 (82, 91) | 46 (41, 52) | 56 (51, 61) | 81 (75, 87) | 54 (48, 59) | 13 (9, 18) |  |  |  |  |
| **CGI-S\*** | **HAM-D** |  |  |  |  |  |  |  |  |  |  |
| 1 pt | 50% improvement | 80 (75, 84) | 54 (46, 61) | 77 (72, 81) | 57 (49, 65) | 46 (39, 54) | 20 (16, 25) |  |  |  |  |
| 1 pt | ≤7 pts | 89 (84, 93) | 46 (41, 52) | 55 (49, 60) | 85 (79, 90) | 54 (48, 59) | 11 (7, 16) |  |  |  |  |
| \*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. | | | | | | | | | | | |