**Supplementary Table 2a. Evaluating biological factors as potential mediators of clinical response to adjunctive minocycline treatment**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| IL-6 change (week 12 – baseline) | | | | | | | | | | | | | | | | | | | |
|  | Low\* | | | |  | | High\* | | | | |  | | | | Interaction$ | |  | β coefficient  95%CI | |
|  | Placebo | | Minocycline | |  | | Placebo | Minocycline | | | | |  | | |  |
| MADRS change b  Mean (SD) | -12.71 (10.81) | | -16.09 (10.21) | |  | | -10.62 (10.97) | -15.38 (8.97) | | | | |  | | | χ2 (1)= 0.002  *p* = 0.967 | |  | 0.10  -4.59-4.79 | |
| *n#* | 17 | | 11 | |  | | 13 | 16 | | | | |  | | |  | |  |  | |
|  |  | |  | |  | |  |  | | | | |  | | |  | |  |  | |
| PGI change  Mean (SD) | -0.12 (1.22) | | -1.09 (0.83) | |  | | -0.15 (1.52) | -0.93 (1.39) | | | | |  | | | χ2 (1)= 0.252  *p* = 0.616 | |  | -0.14  -0.70-0.42 | |
| *n* | 17 | | 11 | |  | | 13 | 15 | | | | |  | | |  | |  |  | |
|  |  | |  | |  | |  |  | | | | |  | | |  | |  |  | |
| CGI-I change  Mean (SD) | -0.06 (1.69) | | -1.45 (1.13) | |  | | -0.15 (1.57) | -1.00 (1.36) | | | | |  | | | χ2 (1)= 0.000  *p* = 0.995 | |  | 0.00  -0.54-0.55 | |
| *n* | 17 | | 11 | |  | | 13 | 15 | | | | |  | | |  | |  |  | |
|  |  | |  | |  | |  |  | | | | |  | | |  | |  |  | |
| HAMA change  Mean (SD) | -6.35 (6.63) | | -4.36 (5.30) | |  | | -4.69 (6.06) | -10.20 (5.35) | | | | |  | | | **χ2** (1)**= 4.527**  ***p* = 0.033$** | |  | **3.75**  **0.30-7.20** | |
| n | 17 | | 11 | |  | | 13 | 15 | | | | |  | | |  | |  |  | |
|  |  | |  | |  | |  |  | | | | |  | | |  | |  |  | |
| LIFE-RIFT change  Mean (SD) | -0.76 (3.03) | | -3.00 (2.72) | |  | | -1.38 (3.57) | -4.33 (3.04) | | | | |  | | | χ2 (1)= 0.751  *p* = 0.386 | |  | 0.50  -0.60-1.64 | |
| *n* | 17 | | 11 | |  | | 13 | 15 | | | | |  | | |  | |  |  | |
|  |  | |  | |  | |  |  | | | | |  | | |  | |  |  | |
| Q-LES-Q-SF change  Mean (SD) | 0.05 (0.11) | | 0.12 (0.10) | |  | | 0.02 (0.15) | 0.14 (0.15) | | | | |  | | | χ2 (1)= 1.151  *p* = 0.283 | |  | -0.03  -0.10-0.03 | |
| *n* | 17 | | 11 | |  | | 13 | 15 | | | | |  | | |  | |  |  | |
|  | | | | | | | | | | | | | | | | | | | |
| LBP change (week 12 – baseline) | | | | | | | | | | | | | | | | | | | |
|  | Low | | | |  | | High | | |  | | | | Interaction$ | | | |  | β coefficient  95%CI | |
|  | Placebo | | Minocycline | |  | | Placebo | Minocycline |  | | | | |  |
| MADRS change b  Mean (SD) | -11.36 (12.37) | | -14.43 (9.39) | |  | | -12.19 (9.50) | -17.00 (9.41) | |  | | | | χ2 (1)= 0.769  *p* = 0.380 | | | |  | 1.61  -1.99-5.22 | |
| *n#* | 14 | | 14 | |  | | 16 | 13 | |  | | | |  | | | |  |  | |
|  |  | |  | |  | |  |  | |  | | | |  | | | |  |  | |
| PGI change  Mean (SD) | -0.14 (1.83) | | -1.00 (0.82) | |  | | -0.13 (0.72) | -1.00 (1.47) | |  | | | | χ2 (1)= 0.366  *p* = 0.545 | | | |  | -0.18  -0.78-0.41 | |
| *n* | 14 | | 13 | |  | | 16 | 13 | |  | | | |  | | | |  |  | |
|  |  | |  | |  | |  |  | |  | | | |  | | | |  |  | |
| CGI-I change  Mean (SD) | -0.36 (2.10) | | -1.31 (1.03) | |  | | 0.13 (0.99) | -1.08 (1.50) | |  | | | | χ2 (1)= 0.060  *p* = 0.807 | | | |  | 0.09  -0.62-0.79 | |
| *n* | 14 | | 13 | |  | | 15 | 13 | |  | | | |  | | | |  |  | |
|  |  | |  | |  | |  |  | |  | | | |  | | | |  |  | |
| HAMA change  Mean (SD) | -5.36 (6.28) | | -7.85 (6.03) | |  | | -5.88 (6.58) | -7.62 (6.20) | |  | | | | χ2 (1)= 1.095  *p* = 0.295 | | | |  | 1.69  -1.48-4.86 | |
| *n* | 14 | | 13 | |  | | 16 | 13 | |  | | | |  | | | |  |  | |
|  |  | |  | |  | |  |  | |  | | | |  | | | |  |  | |
| LIFE-RIFT change  Mean (SD) | -1.07 (4.01) | | -3.15 (3.24) | |  | | -1.00 (2.50) | -4.38 (2.57) | |  | | | | χ2(1) = 0.016  *p* = 0.900 | | | |  | 0.08  -1.21-1.37 | |
| *n* | 14 | | 13 | |  | | 16 | 13 | |  | | | |  | | | |  |  | |
|  |  | |  | |  | |  |  | |  | | | |  | | | |  |  | |
| Q-LES-Q-SF change  Mean (SD) | 0.03 (0.14) | | 0.14 (0.16) | |  | | 0.42 (0.12) | 0.13 (0.10) | |  | | | | χ2 (1)= 0.413  *p* = 0.512 | | | |  | 0.02  -0.04-0.09 | |
| *n* | 14 | | 13 | |  | | 16 | 13 | |  | | | |  | | | |  |  | |
|  |  |  | |  | |  | |  | | |  | | | |  | |  | |  |
| BDNF change (week 12 – baseline) | | | | | | | | | | | | | | | | | | | |
|  | Low | | |  | | High | | | | |  | | | | Interaction$ | |  | | β coefficient  95%CI |
|  | Placebo | Minocycline | |  | | Placebo | | Minocycline | | |  | | | |  | |
| MADRS change b  Mean (SD) | -11.94 (11.97) | -12.80 (10.53) | |  | | -11.58 (9.10) | | -17.35 (8.39) | | |  | | | | χ2 (1)= 0.031  *p* = 0.861 | |  | | -0.08  -0.92-0.77 |
| *n#* | 18 | 10 | |  | | 12 | | 17 | | |  | | | |  | |  | |  |
|  |  |  | |  | |  | |  | | |  | | | |  | |  | |  |
| PGI change  Mean (SD) | 0.17 (1.38) | -0.80 (1.69) | |  | | -0.58 (1.16) | | -1.13 (0.72) | | |  | | | | χ2 (1)= 1.458  *p* = 0.227 | |  | | 0.08  -0.05-0.20 |
| *n* | 18 | 10 | |  | | 12 | | 16 | | |  | | | |  | |  | |  |
|  |  |  | |  | |  | |  | | |  | | | |  | |  | |  |
| CGI-I change  Mean (SD) | -0.06 (1.85) | -0.90 (1.73) | |  | | -0.17 (1.27) | | -1.38 (0.89) | | |  | | | | χ2 (1)= 0.022  *p* = 0.881 | |  | | 0.01  -0.12-0.14 |
| *n* | 17 | 10 | |  | | 12 | | 16 | | |  | | | |  | |  | |  |
|  |  |  | |  | |  | |  | | |  | | | |  | |  | |  |
| HAMA change  Mean (SD) | -6.00 (7.00) | -5.80 (6.73) | |  | | -5.08 (5.45) | | -8.94 (5.35) | | |  | | | | χ2 (1)= 0.019  *p* = 0.892 | |  | | 0.04  -0.58-0.67 |
| *n* | 18 | 10 | |  | | 12 | | 16 | | |  | | | |  | |  | |  |
|  |  |  | |  | |  | |  | | |  | | | |  | |  | |  |
| LiIFE-RIFT change  Mean (SD) | -0.61 (2.97) | -2.00 (2.75) | |  | | -1.67 (3.63) | | -4.88 (2.53) | | |  | | | | χ2 (1)= 2.455  *p* = 0.117 | |  | | 0.19  -0.05-0.43 |
| *n* | 18 | 10 | |  | | 12 | | 16 | | |  | | | |  | |  | |  |
|  |  |  | |  | |  | |  | | |  | | | |  | |  | |  |
| Q-LES-Q-SF change  Mean (SD) | 0.04 (0.14) | 0.06 (0.09) | |  | | 0.03 (0.11) | | 0.18 (0.13) | | |  | | | | χ2 (1)= 0.558  *p* = 0.455 | |  | | -0.01  -0.02-0.01 |
| *n* | 18 | 10 | |  | | 12 | | 16 | | |  | | | |  | |  | |  |
| *Abbreviations*: MADRS, Montgomery-Asberg Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale ; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire ; LIFE-RIFT, Range of Impaired Functioning Tool ; PGI, Patient Global Impression ; CGI-I, Clinical Global Impression–Improvement.  b Change reflects the difference from week 12 (endpoint) to baseline (absolute values)  \* Low and High values were presented based on median for descriptive purpose only. All mediator analyses included the biological marker as continuous variables.  $ three-way interaction between potential predictor (changes in levels of marker), log of follow-up time, and treatment group.  *#* Differential sample sizes reflect the entire cohort (intention to treat) compared to those who provided complete biological data (per protocol). | | | | | | | | | | | | | | | | | | | |

**Supplementary Table 2b. Evaluating potential non-specified effects of biological factors on clinical response**

|  |  |  |  |
| --- | --- | --- | --- |
| Clinical measures | Biological factors | Main effect | β coefficient  95% CI |
| MADRS | IL-6 | χ2 = 1.254  *p* = 0.263 | 0.44  -0.33 – 1.20 |
|  | LBP | χ2 = 0.141  *p* = 0.707 | -0.24  -1.50 – 1.02 |
|  | BDNF | χ2 = 0.138  *p* = 0.710 | -0.05  -0.32 – 0.22 |
|  |  |  |  |
| PGI | IL-6 | χ2 = 0.847  *p* = 0.357 | 0.06  -0.07 – 0.18 |
|  | LBP | χ2 = 0.507  *p* = 0.477 | 0.07  -0.13 – 0.28 |
|  | BDNF | χ2 = 0.508  *p* = 0.476 | -0.01  -0.04 – 0.02 |
|  |  |  |  |
| CGI-I | IL-6 | χ2 = 0.932  *p* = 0.334 | 0.06  -0.06 – 0.19 |
|  | LBP | χ2 = 0.003  *p* = 0.959 | -0.00  -0.18 – 0.17 |
|  | BDNF | χ2 = 0.394  *p* = 0.530 | -0.01  -0.05 – 0.03 |
|  |  |  |  |
| HAMA | IL-6 | χ2 = 0.33  *p* = 0.566 | -0.174  -0.77 – 0.42 |
|  | LBP | χ2 = 1.003  *p* = 0.317 | -0.62  -1.84 – 0.60 |
|  | BDNF | χ2 = 0.097  *p* = 0.755 | -0.03  -0.20 – 0.15 |
|  |  |  |  |
| LIFE-RIFT | IL-6 | χ2 = 3.235  *p* = 0.072 | 0.27  -0.02 – 0.57 |
|  | LBP | χ2 = 0.158  *p* = 0.691 | -0.10  -0.57 – 0.38 |
|  | BDNF | **χ2 = 9.109**  ***p* = 0.003** | **-0.11**  **-0.18 – -0.04** |
|  |  |  |  |
| Q-LES-Q-SF | IL-6 | χ2 = 1.847  *p* = 0.174 | -0.01  -0.02 – 0.00 |
|  | LBP | χ2 = 0.267  *p* = 0.605 | 0.01  -0.02 – 0.03 |
|  | BDNF | χ2 = 2.171  *p* = 0.141 | 0.00  -0.00 – 0.01 |
| *Abbreviations*: MADRS, Montgomery-Asberg Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale ; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire ; LIFE-RIFT, Range of Impaired Functioning Tool ; PGI, Patient Global Impression ; CGI-I, Clinical Global Impression–Improvement. | | | |