**Supplementary Table 3a. Evaluating potential moderator effects of biological factors (i.e. factor measurements at baseline) on clinical response to adjunctive minocycline treatment**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| IL6 at baseline | | | | | | | |
|  | Placebo | |  | Minocycline | | Interaction$ | β coefficient  95%CI |
|  | Low\* | High\* |  | Low\* | High\* |
| MADRS change  Mean (SD) | -9.75 (11.89) | -15.77 (9.82) |  | -14.14 (9.13) | -15.57 (9.18) | χ2 (1)= 0.708  *p* = 0.400 | 1.64  -2.18-5.46 |
| *n#* | 16 | 13 |  | 14 | 14 |  |  |
|  |  |  |  |  |  |  |  |
| PGI change  Mean (SD) | -0.63 (1.29) | -1.42 (0.79) |  | -0.21 (1.42) | -0.73 (1.33) | χ2 (1)= 0.560  *p* = 0.454 | 0.16  -0.26-0.58 |
| *n* | 16 | 12 |  | 14 | 15 |  |  |
|  |  |  |  |  |  |  |  |
| CGI-I change  Mean (SD) | -0.06 (1.34) | -1.50 (1.17) |  | -0.15 (1.95) | -1.00 (1.31) | χ2 (1)= 0.049  *p* = 0.825 | 0.05  -0.37-0.46 |
| *n* | 16 | 12 |  | 13 | 15 |  |  |
|  |  |  |  |  |  |  |  |
| HAMA change  Mean (SD) | -4.63 (6.48) | -10.08 (5.82) |  | -6.79 (6.20) | -7.33 (8.24) | **χ2** (1)**= 5.345**  ***p* = 0.021$** | **3.59**  **0.55-6.63** |
| *n* | 16 | 12 |  | 14 | 15 |  |  |
|  |  |  |  |  |  |  |  |
| LIFE-RIFT change  Mean (SD) | -0.38 (3.26) | -5.00 (2.34) |  | -1.79 (3.14) | -3.07 (3.24) | χ2 (1)= 2.858  *p* = 0.091 | 0.86  -0.14-1.86 |
| *n* | 16 | 12 |  | 14 | 15 |  |  |
|  |  |  |  |  |  |  |  |
| Q-LES-Q-SF change  Mean (SD) | 4.46 (12.93) | 16.22(13.74) |  | 2.93 (12.96) | 10.95 (11.97) | **χ2** (1)**= 5.188**  ***p* = 0.023$** | **-0.05**  **-0.09-0.01** |
| *n* | 16 | 12 |  | 14 | 15 |  |  |
|  |  |  |  |  |  |  |  |
| LBP at baseline | | | | | | | |
|  | Placebo | |  | Minocycline | | Interaction$ | β coefficient  95%CI |
|  | Low | High |  | Low | High |
| MADRS change  Mean (SD) | -9.40 (8.10) | -18.27(10.23) |  | -14.20(12.7) | -12.42 (7.13) | χ2 (1)= 1.800  *p* = 0.180 | 2.84  -1.31-6.99 |
| *n#* | 15 | 15 |  | 15 | 12 |  |  |
|  |  |  |  |  |  |  |  |
| PGI change  Mean (SD) | 0.27 (1.10) | -1.44 (0.81) |  | -0.53 (1.46) | -0.45 (1.37) | χ2(1) = 0.655  *p* = 0.418 | 0.25  -0.36-0.86 |
| *n* | 15 | 16 |  | 15 | 11 |  |  |
|  |  |  |  |  |  |  |  |
| CGI-I change  Mean (SD) | 0.20 (1.15) | -1.63 (1.02) |  | -0.43 (1.99) | -0.64 (1.36) | χ2 (1)= 0.594  *p* = 0.441 | 0.30  -0.47-1.08 |
| *n* | 15 | 16 |  | 14 | 11 |  |  |
|  |  |  |  |  |  |  |  |
| HAMA change  Mean (SD) | -5.07 (6.09) | -10.63(8.11) |  | -6.20 (6.74) | -5.55 (4.68) | χ2 (1)= 2.419  *p* = 0.120 | 2.50  -0.65-5.65 |
| *n* | 15 | 16 |  | 15 | 11 |  |  |
|  |  |  |  |  |  |  |  |
| LIFE-RIFT change  Mean (SD) | -0.47 (3.02) | -4.88 (2.68) |  | -1.60 (3.44) | -2.55 (2.98) | χ2 (1)= 1.194  *p* = 0.275 | 0.78  -0.62-2.19 |
| *n* | 15 | 16 |  | 15 | 11 |  |  |
|  |  |  |  |  |  |  |  |
| Q-LES-Q-SF change  Mean (SD) | 2.98 (13.31) | 13.39(12.71) |  | 4.52 (12.57) | 13.15 (13.58) | χ2 (1)= 0.004  *p* = 0.950 | -0.00  -0.07-0.07 |
| *n* | 15 | 16 |  | 15 | 11 |  |  |
|  |  |  |  |  |  |  |  |
| BDNF at baseline | | | | | | | |
|  | Placebo | |  | Minocycline | | Interaction$ | β coefficient  95%CI |
|  | Low | High |  | Low | High |
| MADRS change  Mean (SD) | -12.50 (10.23) | -13.25 (8.75) |  | -11.19(11.47) | -17.60 (9.58) | χ2 (1)= 0.408  *p* = 0.523 | -0.34  -1.40-0.71 |
| *n#* | 14 | 12 |  | 16 | 15 |  |  |
|  |  |  |  |  |  |  |  |
| PGI change  Mean (SD) | 0.00 (1.18) | -1.00 (0.82) |  | -0.25 (1.48) | -1.07 (1.44) | χ2 (1)= 0.991  *p* = 0.320 | 0.78  -0.08-0.23 |
| *n* | 14 | 13 |  | 16 | 14 |  |  |
|  |  |  |  |  |  |  |  |
| CGI-I change  Mean (SD) | -0.07 (1.59) | -1.08 (0.82) |  | -0.13 (1.68) | -1.36 (1.55) | χ2 (1)= 0.144  *p* = 0.704 | 0.03  -0.13-0.19 |
| *n* | 14 | 13 |  | 15 | 14 |  |  |
|  |  |  |  |  |  |  |  |
| HAMA change  Mean (SD) | -4.71 (5.69) | -7.92 (7.98) |  | -6.44 (6.94) | -9.14 (6.79) | χ2 (1)= 0.167  *p* = 0.683 | 0.13  -0.51-0.78 |
| *n* | 14 | 13 |  | 16 | 14 |  |  |
|  |  |  |  |  |  |  |  |
| LIFE-RIFT change  Mean (SD) | -1.00 (3.46) | -4.23 (3.14) |  | -1.06 (3.13) | -.3.64 (2.92) | χ2 (1)= 0.988  *p* = 0.320 | 0.12  -0.11-0.35 |
| *n* | 14 | 13 |  | 16 | 14 |  |  |
|  |  |  |  |  |  |  |  |
| Q-LES-Q-SF at change  Mean (SD) | 3.19 (13.14) | 12.91 (7.92) |  | 4.24 (12.79) | 13.65(16.43) | χ2 (1)= 0.102  *p* = 0.749 | -0.00  -0.01-0.01 |
| *n* | 14 | 13 |  | 16 | 14 |  |  |
| *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.  \*Low and High indicate the data was dichotomised as low and high based on median for descriptive purposes only. All biological markers were considered continuous for modelling.  $three-way interaction between potential predictor (baseline at levels of biomarkers), changes in clinical measurement 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 3b. 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 3c. 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. | | | |