

## Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

**eTable 1. Adverse Events**

| Adverse events   | Minocycline (n=81) |           | Placebo (n=87) |        | p-value |
|--|--------------------|-----------|----------------|--------|---------|
|  | N                  | (%)       | N              | (%)    |         |
| Number of subjects with at least one AE                | 68                 | (84.0)    | 63             | (72.4) | 0.106   |
| Number of subjects with at least two AE                | 56                 | (69.1)    | 45             | (41.7) | 0.032   |
| Number of subjects with at least one sAE               | 6                  | (7.4)     | 7              | (8.0)  | 0.987   |
| Total number of AEs                                    | 265                | (52.8)    | 237            | (47.2) | 0.211   |
| Total number of sAEs                                   | 6*                 | (2.3)     | 7*             | (3.0)  | 0.838   |
| Severity of AE   |                    |           |                |        | 0.021   |
| Mild   | 194                | (73.2)    | 147            | (62.0) |         |
| Moderate   | 65                 | (24.5)    | 79             | (33.3) |         |
| Severe   | 6                  | (2.3)     | 11             | (4.6)  |         |
| Relation to study medication?                          |                    |           |                |        | 0.145   |
| Yes  | 27                 | (10.2)    | 21             | (8.9)  |         |
| No   | 53                 | (20.0)    | 65             | (27.4) |         |
| Unknown  | 185                | (69.8)    | 151            | (63.7) |         |
| Severity of sAE  |                    |           |                |        | 0.065   |
| Mild   | 0                  | (0.0)     | 2              | (28.6) |         |
| Moderate   | 3                  | (50.0)    | 0              | (0.0)  |         |
| Severe   | 3                  | (50.0)    | 5              | (71.4) |         |
| Leads to permanent or serious disability or invalidity | 1                  | (16.7)    | 0              | (0.0)  |         |
| Leads to inpatient treatment or extends it             | 5                  | (83.3)    | 6              | (85.7) |         |
| Fatal or life threatening                              | 0                  | (0.0)     | 1**            | (14.3) |         |
| <b>Type of (S)AE</b>                                   |                    |           |                |        |         |
|  | Minocycline        | Placebo   |                |        |         |
| Number of (S)AEs                                       | 265                | 237       |                |        |         |
|  | n (%)              | n (%)     |                |        |         |
| Headache   | 33 (11.9)          | 43 (16.5) |                |        |         |
| Flu-like symptoms                                      | 30 (10.8)          | 17 ( 6.5) |                |        |         |
| Dyspepsia/indigestion                                  | 25 ( 9.0)          | 19 ( 7.3) |                |        |         |
| Flatulence and diarrhea                                | 15 ( 5.4)          | 26 (10.0) |                |        |         |
| Skin problems  | 22 ( 7.9)          | 15 ( 5.7) |                |        |         |
| Dizziness  | 20 ( 7.2)          | 7 ( 2.7)  |                |        |         |
| Nausea   | 12 ( 4.3)          | 12 ( 4.6) |                |        |         |
| Psychiatric symptoms, exacerbation                     | 10 ( 3.6)          | 10 ( 3.8) |                |        |         |
| Tiredness  | 11 ( 4.0)          | 9 ( 3.4)  |                |        |         |
| Blood parameters changes                               | 12 ( 4.3)          | 6 ( 2.3)  |                |        |         |
| Insomnia   | 4 ( 1.4)           | 9 ( 3.4)  |                |        |         |
| Other neurological symptoms                            | 10 ( 3.6)          | 4 ( 1.5)  |                |        |         |
| General pain/joint pain                                | 8 ( 2.9)           | 5 ( 1.9)  |                |        |         |
| Hyperhidrosis  | 4 ( 1.4)           | 6 ( 2.3)  |                |        |         |
| Back pain  | 4 ( 1.4)           | 6 ( 2.3)  |                |        |         |

| <u>Type of (S)AE</u>   |             |          |
|--|-------------|----------|
|  | Minocycline | Placebo  |
| Fungal infection   | 5 ( 1.8)    | 1 ( 0.4) |
| Teeth problems   | 3 ( 1.1)    | 3 ( 1.1) |
| Sore throat/cold   | 2 ( 0.7)    | 3 ( 1.1) |
| Visual impairments   | 3 ( 1.1)    | 1 ( 0.4) |
| Tinnitus   | 3 ( 1.1)    | 1 ( 0.4) |
| Urological problems  | 3 ( 1.1)    | 1 ( 0.4) |
| Chest palpitation/pain   | 0 ( 0.0)    | 3 ( 1.1) |
| Hypertension   | 2 ( 0.7)    | 1 ( 0.4) |
| Constipation   | 0 ( 0.0)    | 3 ( 1.1) |
| Irritable cough  | 0 ( 0.0)    | 2 ( 0.8) |
| Insect bites   | 1 ( 0.4)    | 1 ( 0.4) |
| Increased appetite   | 0 ( 0.0)    | 2 ( 0.8) |
| Drowsiness   | 2 ( 0.7)    | 0 ( 0.0) |
| Allergic conjunctivitis, intermittent  | 1 ( 0.4)    | 0 ( 0.0) |
| Allergic reaction  | 1 ( 0.4)    | 0 ( 0.0) |
| Head impact with sloping roof frontal left side                                  | 0 ( 0.0)    | 1 ( 0.4) |
| Rear-end collision   | 0 ( 0.0)    | 1 ( 0.4) |
| Biliary pancreatitis with choledocholithiasis                                    | 0 ( 0.0)    | 1 ( 0.4) |
| Blood spotting in stool, fresh reddish blood, a.e. due to injuries in anal canal | 0 ( 0.0)    | 1 ( 0.4) |
| Cholecystitis, cholecystectomy   | 1 ( 0.4)    | 0 ( 0.0) |
| Colon carcinoma (incidental finding)   | 0 ( 0.0)    | 1 ( 0.4) |
| Intake of ibuprofen, novalgin, tilidine  | 1 ( 0.4)    | 0 ( 0.0) |
| Panic attack   | 1 ( 0.4)    | 0 ( 0.0) |
| Somewhat increased symptoms of pre-existing asthma                               | 1 ( 0.4)    | 0 ( 0.0) |
| Folliculitis   | 1 ( 0.4)    | 0 ( 0.0) |
| Stye on left eye   | 0 ( 0.0)    | 1 ( 0.4) |
| Facial swelling of unknown origin  | 1 ( 0.4)    | 0 ( 0.0) |
| Granulopenia   | 1 ( 0.4)    | 0 ( 0.0) |
| Hoarseness   | 1 ( 0.4)    | 0 ( 0.0) |
| Light blood in stool   | 1 ( 0.4)    | 0 ( 0.0) |
| Herpes labialis  | 0 ( 0.0)    | 1 ( 0.4) |
| Itching and burning in the vagina  | 1 ( 0.4)    | 0 ( 0.0) |
| Itching of both eyes   | 0 ( 0.0)    | 1 ( 0.4) |
| Small laceration on the head during gardening                                    | 0 ( 0.0)    | 1 ( 0.4) |
| Lump on the wrist  | 1 ( 0.4)    | 0 ( 0.0) |
| Concentration problems   | 1 ( 0.4)    | 0 ( 0.0) |
| Temporary visual perception problems (duration 15 min)                           | 1 ( 0.4)    | 0 ( 0.0) |
| Eyelid swelling on the right   | 0 ( 0.0)    | 1 ( 0.4) |
| Lymphoma   | 1 ( 0.4)    | 0 ( 0.0) |
| Metallic taste in the mouth  | 1 ( 0.4)    | 0 ( 0.0) |
| Nosebleed  | 0 ( 0.0)    | 1 ( 0.4) |
| Norovirus infection  | 1 ( 0.4)    | 0 ( 0.0) |
| Sleep apnea syndrome   | 0 ( 0.0)    | 1 ( 0.4) |
| Swelling of the right eyelid   | 0 ( 0.0)    | 1 ( 0.4) |
| Vision problems with dry eyes  | 0 ( 0.0)    | 1 ( 0.4) |
| Stenting of femoral artery in case of known PAOD                                 | 0 ( 0.0)    | 1 ( 0.4) |
| Symptomatic cholecystolithiasis  | 0 ( 0.0)    | 1 ( 0.4) |
| Tendinitis of the right long biceps tendon                                       | 0 ( 0.0)    | 1 ( 0.4) |
| Tendovaginitis of the right wrist  | 1 ( 0.4)    | 0 ( 0.0) |
| <u>Type of (S)AE</u>   |             |          |

|  | Minocycline | Placebo  |
|--|-------------|----------|
| Bicycle accident with subsequent hospitalization for 1 night with fracture of zygomatic bone | 1 ( 0.4)    | 0 ( 0.0) |
| Varicose vein surgery  | 1 ( 0.4)    | 0 ( 0.0) |
| Whitish tongue coating   | 0 ( 0.0)    | 1 ( 0.4) |
| Recurrence of menstruation, under constant use of an oral contraceptive                      | 0 ( 0.0)    | 1 ( 0.4) |
| Tick bite  | 0 ( 0.0)    | 1 ( 0.4) |
| Cerebral aneurysm hemorrhage   | 0 ( 0.0)    | 1 ( 0.4) |

**eTable 1** Adverse Events

\* no relation to study medication

\*\* incidental finding

**eTable 2. Exploratory Endpoints**

| End points               | Pre-treatment mean (SD) |                    | Post-treatment mean (SD) |                    | Difference of week 6 and baseline between Placebo and Minocycline (95% CI) |  | p-values |
|--------------------------|-------------------------|--------------------|--------------------------|--------------------|--|--|----------|
|                          | Minocycline             | Placebo            | Minocycline              | Placebo            |  |  |          |
| <b>Anhedonia</b>         | 20.2 (4.3)<br>N=81      | 20.4 (4.4)<br>N=87 | 12.8 (6.5)<br>N=69       | 13.2 (7.6)<br>N=75 | 0.76 (-1.34 to 2.86)   |  | 0.48     |
| <b>Sickness behavior</b> | 8.8 (1.8)<br>N=81       | 9.0 (2.2)<br>N=87  | 6.2 (2.7)<br>N=69        | 6.2 (3.1)<br>N=75  | -0.005 (-0.85 to 0.84)   |  | 0.99     |
| <b>Fear, suicidality</b> | 6.1 (1.5)<br>N=81       | 6.1 (1.7)<br>N=87  | 4.2 (2.0)<br>N=69        | 4.2 (2.2)<br>N=75  | -0.01 (-0.62 to 0.60)  |  | 0.98     |
| <b>HAMD6</b>             | 11.4 (2.2)<br>N=81      | 11.4 (2.1)<br>N=87 | 7.4 (3.5)<br>N=69        | 7.6 (6.7)<br>N=71  | 0.33 (-0.77 to 1.42)   |  | 0.56     |

**eTable 2** Exploratory outcome measures. The difference between the two treatment groups are based on the least square differences for the change of the outcome measures from baseline to week 6 based on linear mixed effects models for repeated measures.

**eTable 3. Exploratory Subgroup Analysis**

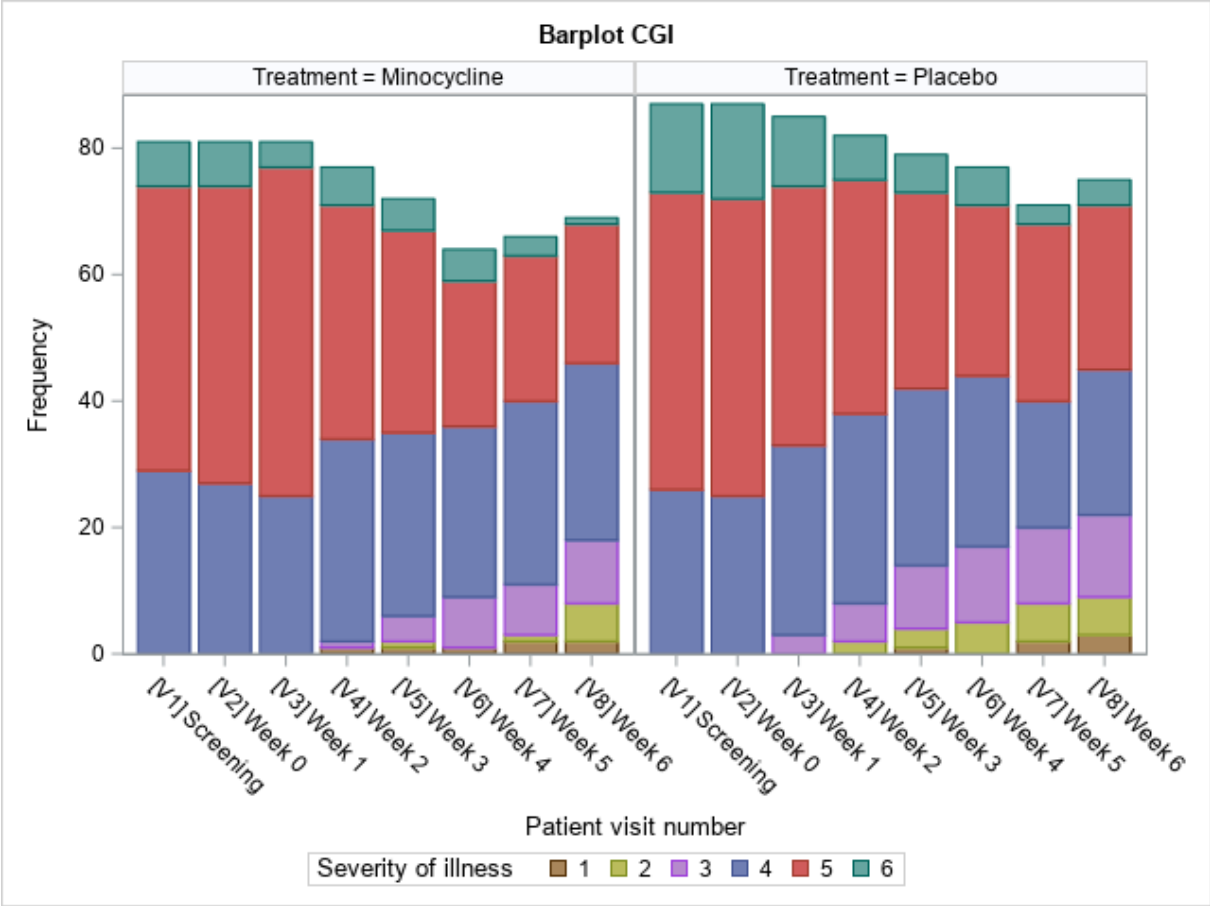
|                        | Subgroup | Pre-treatment mean (SD) for MADRS |                    | Post-treatment mean (SD) For MADRS |                    | Difference of week 6 and baseline between Placebo and Minocycline | 95% CI |  | p-values |
|------------------------|----------|-----------------------------------|--------------------|------------------------------------|--------------------|---|--------|--|----------|
|                        |          | Minocycline                       | Placebo            | Minocycline                        | Placebo            |   |        |  |          |
| Gender                 | Male     | 27.0 (4.9)<br>N=50                | 26.4 (4.7)<br>N=39 | 19.7 (7.6)<br>N=42                 | 18.8 (8.3)<br>N=31 | 0.76 (-2.70 to 4.22)  |        |  | 0.6642   |
|                        | Female   | 25.4 (4.7)<br>N=31                | 26.8 (5.4)<br>N=48 | 14.4 (7.3)<br>N=27                 | 15.3 (9.5)<br>N=44 | 3.21 (-0.48 to 6.90)  |        |  | 0.0877   |
| CTQ sum score          | 0        | 26.8 (6.0)<br>N=32                | 26.5 (5.0)<br>N=39 | 16.3 (8.7)<br>N=28                 | 18. (9.9)<br>N=32  | 2.55 (-.140 to 6.51)  |        |  | 0.2041   |
|                        | 1        | 26.2 (4.1)<br>N=18                | 25.8 (5.1)<br>N=25 | 20.1 (8.3)<br>N=15                 | 19.7 (8.7)<br>N=23 | 0.34 (-4.63 to 5.31)  |        |  | 0.8937   |
|                        | 2        | 25.5 (4.7)<br>N=13                | 27.5 (5.3)<br>N=8  | 17.2 (7.0)<br>N=11                 | 17.6 (7.5)<br>N=8  | -0.73 (-7.95 to 6.50)   |        |  | 0.8428   |
|                        | 3,4 or 5 | 26.9 (3.8)<br>N=15                | 27.9 (5.4)<br>N=15 | 17.7 (6.7)<br>N=12                 | 19.3 (8.7)<br>N=12 | 2.36 (-3.73 to 8.45)  |        |  | 0.7605   |
| CTQ- Physical abuse    | Yes      | 24.8 (4.3)<br>N=12                | 25.6 (7.3)<br>N=13 | 19.2 (4.6)<br>N=10                 | 18.5 (8.7)<br>N=11 | -0.49 (-7.01 to 6.04)   |        |  | 0.8833   |
|                        | No       | 24.1 (5.4)<br>N=68                | 25.1 (7.3)<br>N=72 | 17.3 (8.3)<br>N=58                 | 18.8 (9.1)<br>N=64 | 1.95 (-0.80 to 4.69)  |        |  | 0.1635   |
| CTQ- Emotional abuse   | Yes      | 23.6 (4.2)<br>N=31                | 25.3 (6.4)<br>N=23 | 17.5 (6.5)<br>N=25                 | 18.9 (7.6)<br>N=23 | 0.86 (-3.52 to 5.24)  |        |  | 0.6976   |
|                        | No       | 24.5 (5.8)<br>N=49                | 25.1 (7.6)<br>N=62 | 17.6 (8.7)<br>N=43                 | 18.7 (9.6)<br>N=52 | 1.91 (-1.20 to 5.02)  |        |  | 0.2273   |
| CTQ- Sexual abuse      | Yes      | 25.9 (3.6)<br>N=12                | 27.4 (3.7)<br>N=7  | 15.7 (8.3)<br>N=10                 | 16.6 (6.4)<br>N=7  | 0.62 (-7.03 to 8.26)  |        |  | 0.8737   |
|                        | No       | 26.5 (5.1)<br>N=67                | 26.6 (5.2)<br>N=80 | 17.9 (7.9)<br>N=57                 | 19.0 (9.2)<br>N=68 | 1.52 (-1.19 to 4.23)  |        |  | 0.5752   |
| CTQ- Emotional neglect | Yes      | 26.8 (4.0)<br>N=36                | 26.9 (5.5)<br>N=40 | 18.2 (7.3)<br>N=30                 | 19.4 (8.8)<br>N=35 | 1.63 (-2.12 to 5.37)  |        |  | 0.3924   |
|                        | No       | 26.1 (5.6)<br>N=43                | 26.4 (4.8)<br>N=47 | 17.0 (8.5)<br>N=37                 | 18.2 (9.2)<br>N=35 | 1.40 (-2.07 to 4.87)  |        |  | 0.4272   |
| CTQ-                   | Yes      | 25.9 (4.3)<br>N=12                | 27.9 (5.6)<br>N=14 | 19.2 (4.6)<br>N=10                 | 18.5 (8.7)<br>N=11 | -0.49 (-7.01 to 6.04)   |        |  | 0.8833   |

|                          |                                     |                    |                    |                    |                    |                             |       |      |        |
|--------------------------|-------------------------------------|--------------------|--------------------|--------------------|--------------------|-----------------------------|-------|------|--------|
| <b>Physical neglect</b>  | <b>No</b>                           | 26.5 (5.0)<br>N=68 | 26.4 (5.0)<br>N=73 | 17.3 (8.3)<br>N=58 | 18.8 (9.1)<br>N=64 | -0.30 (-0.80<br>to 4.69)    |       |      | 0.1635 |
| <b>MADRS at baseline</b> | <b>Larger than the median value</b> | 30.7 (3.3)<br>N=37 | 30.7 (3.5)<br>N=44 | 20.5 (8.7)<br>N=31 | 21.1 (8.8)<br>N=39 | 1.77 (-1.91<br>to 5.44)     |       |      | 0.3436 |
|                          | <b>Smaller than median value</b>    | 22.8 (2.3)<br>N=44 | 22.4 (2.3)<br>N=43 | 15.3 (6.2)<br>N=38 | 16.2 (8.7)<br>N=36 | 1.22 (-2.28<br>to 4.73<br>) |       |      | 0.4913 |
| <b>CRP at baseline</b>   | <b>Larger than the median value</b> | 26.1 (5.0)<br>N=47 | 26.4 (5.0)<br>N=36 | 16.5 (8.6)<br>N=40 | 16.3 (9.4)<br>N=30 | 1.21 (-2.35<br>to 4.77)     |       |      | 0.5033 |
|                          | <b>Smaller than median value</b>    | 26.8 (4.6)<br>N=34 | 26.9 (5.1)<br>N=50 | 19.2 (6.6)<br>N=29 | 20.4 (8.4)<br>N=45 | 0.96 (-2.61<br>to 4.52)     |       |      | 0.5967 |
| <b>BMI at baseline</b>   | <b>Larger than the median value</b> | 26.3 (5.1)<br>N=45 | 27.0 (5.2)<br>N=40 | 18.2 (8.7)<br>N=39 | 19.1 (8.6)<br>N=40 | 0.68 (-2.87<br>To           |       | 4.23 | 0.7039 |
|                          | <b>Smaller than median value</b>    | 26.5 (4.6)<br>N=36 | 26.3 (5.0)<br>N=47 | 16.9 (6.7)<br>N=30 | 18.4 (9.4)<br>N=35 | 2.28                        | -.133 | 5.88 | 0.2149 |

**eTable 3** Exploratory subgroup analysis for the primary end point MADRS. MADRS = Montgomery Asberg Depression Rating Scale, BMI= body mass index, CTQ= Childhood Trauma Questionnaire. The presence of emotional, physical and sexual abuse as well as emotional and physical neglect are defined as at least moderate severity of abuse or neglect based on Häuser et al. (2011). The difference between the two treatment groups in each subgroup are based on the least square differences for the change of MADRS from baseline to week 6 based on linear mixed effects models for repeated measures.

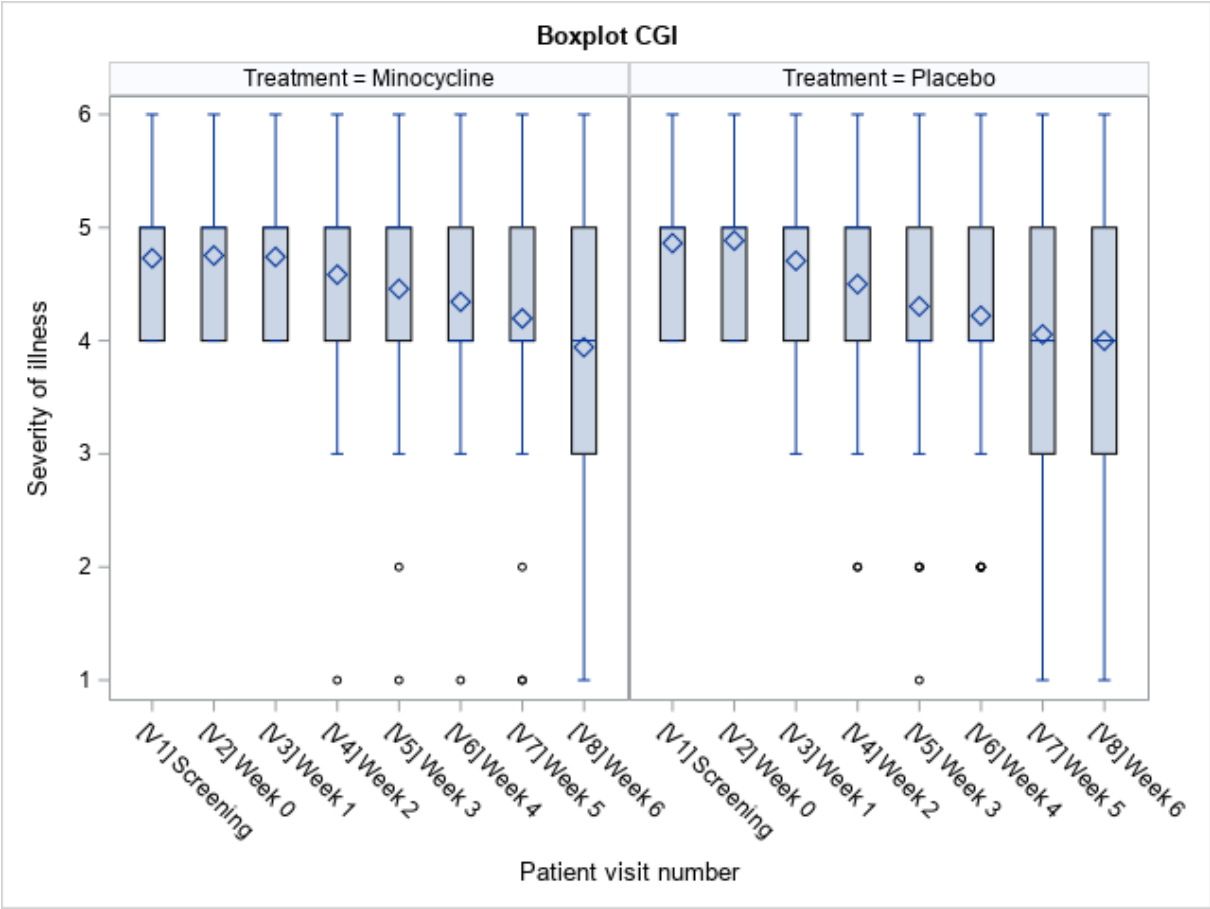
eFigure 1. CGI

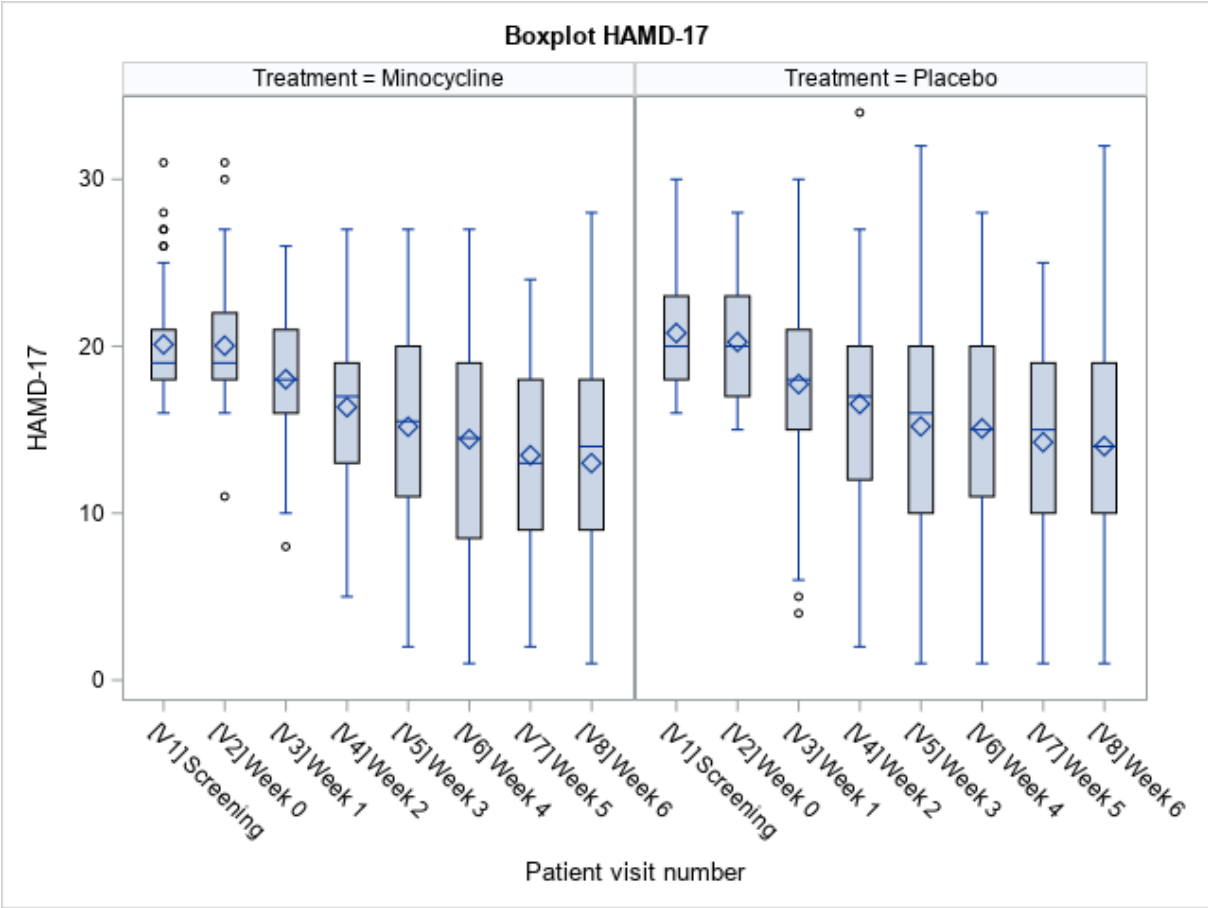
A. Barplot CGI





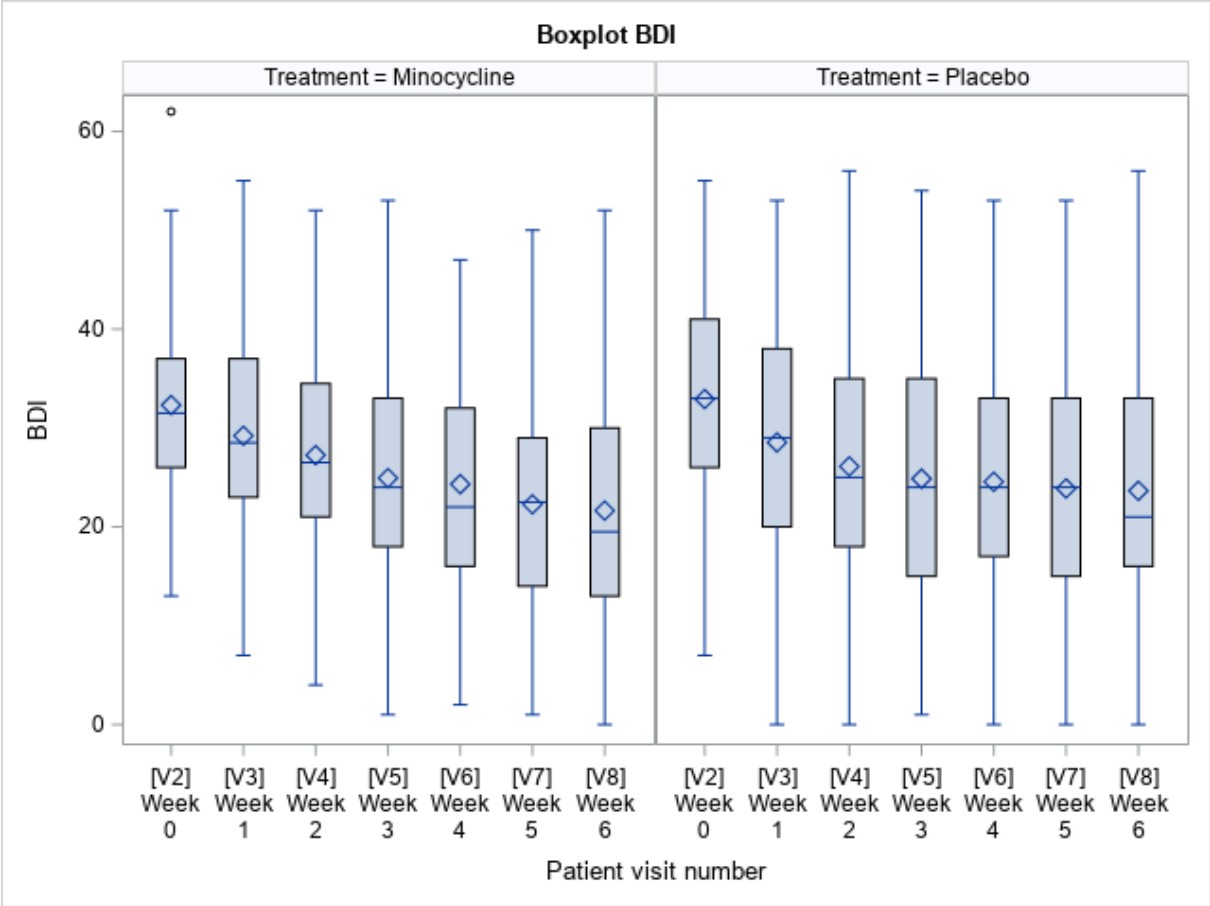
**B. Boxplot CGI**



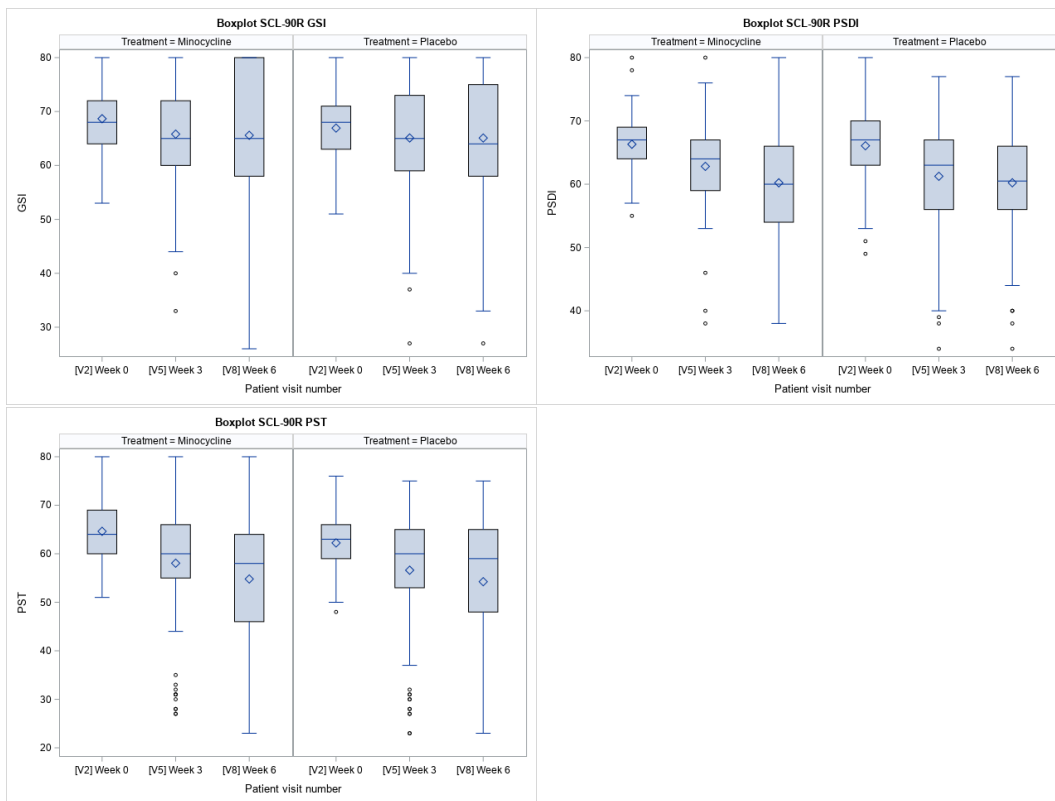


eFigure 2. Boxplot HAMD-17

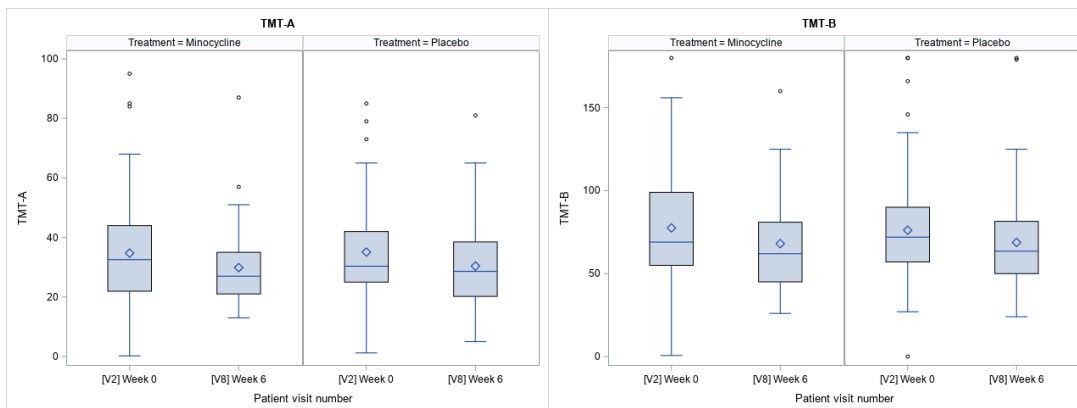
eFigure 3. BDI

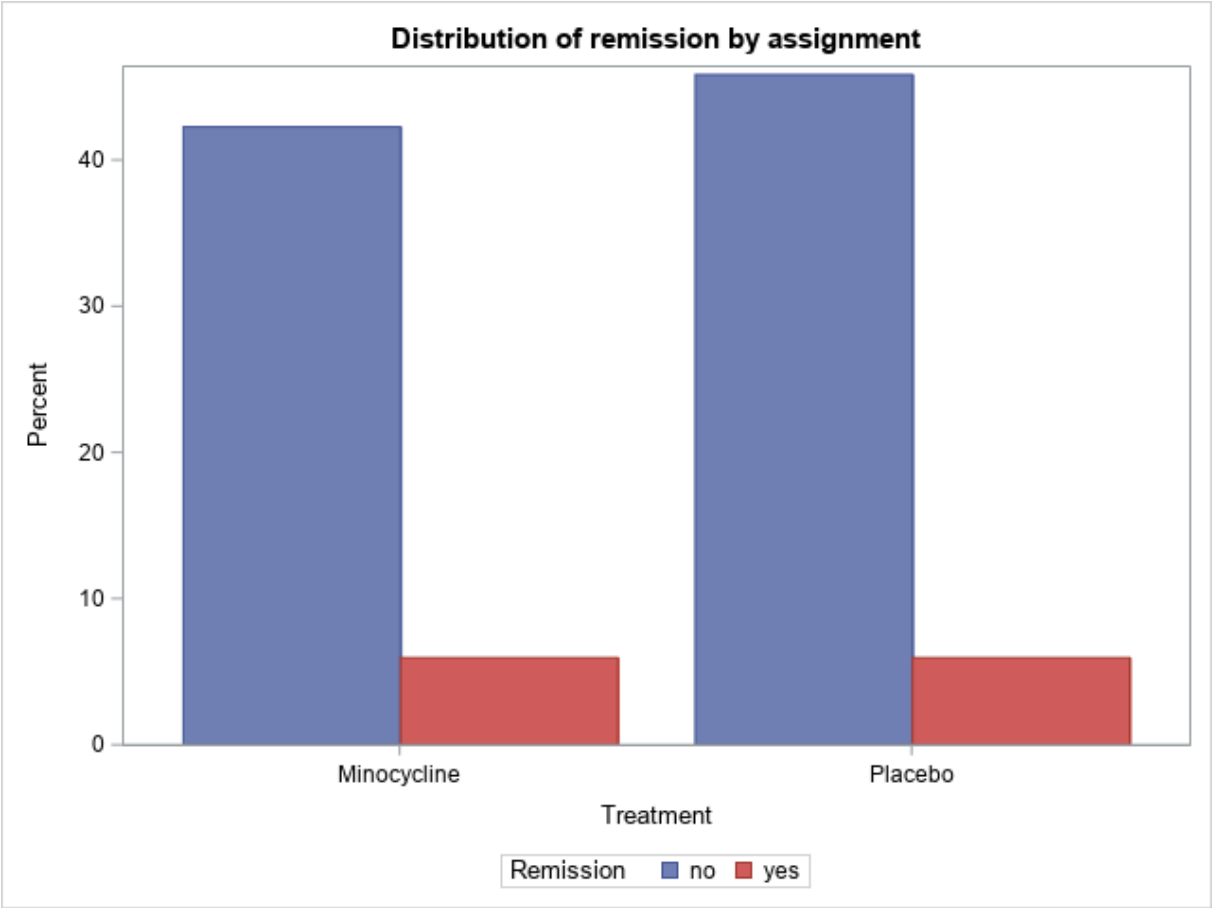


**eFigure 4. SCL-90**



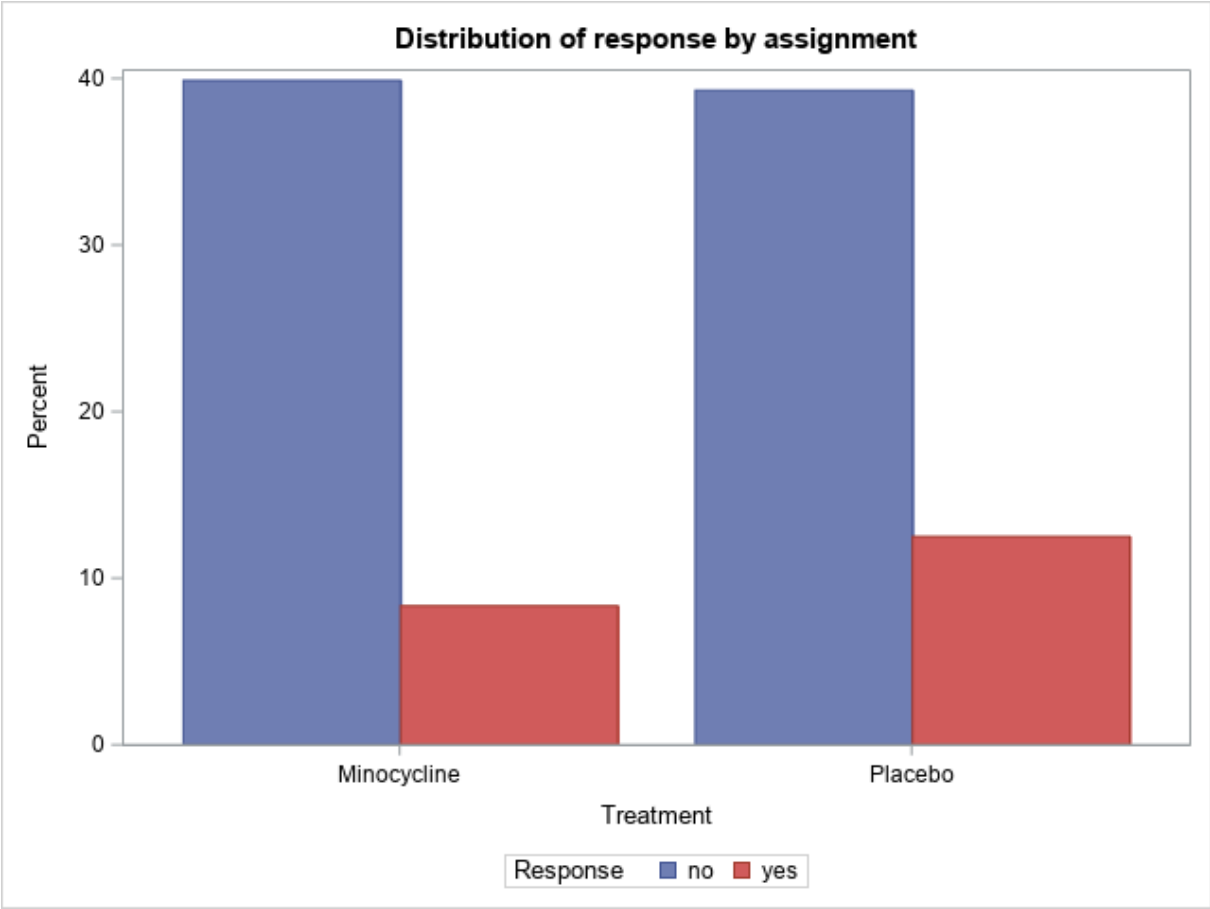
**eFigure 5. TMT-A/B**





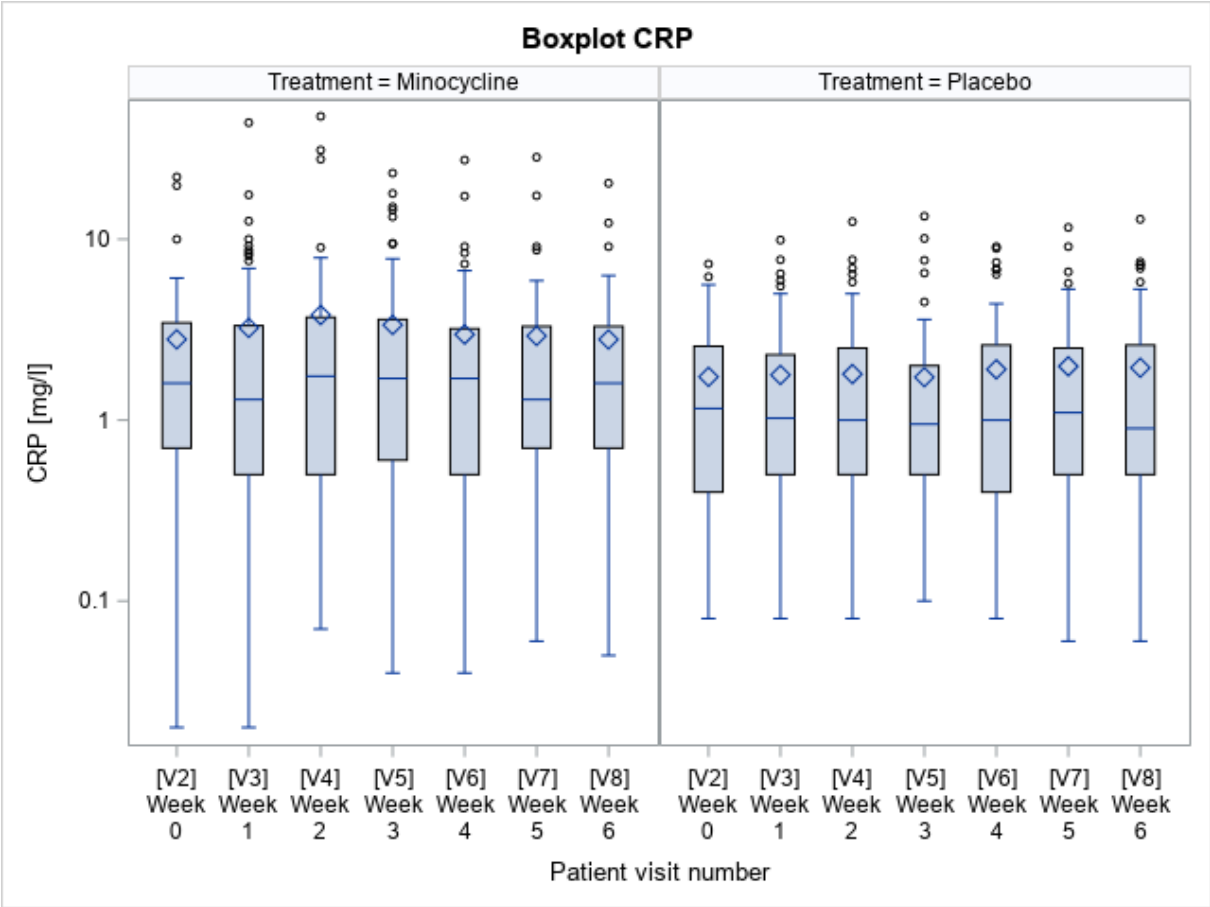
eFigure 6. Distribution of Remission by Assignment

eFigure 7. Distribution of Response by Assignment

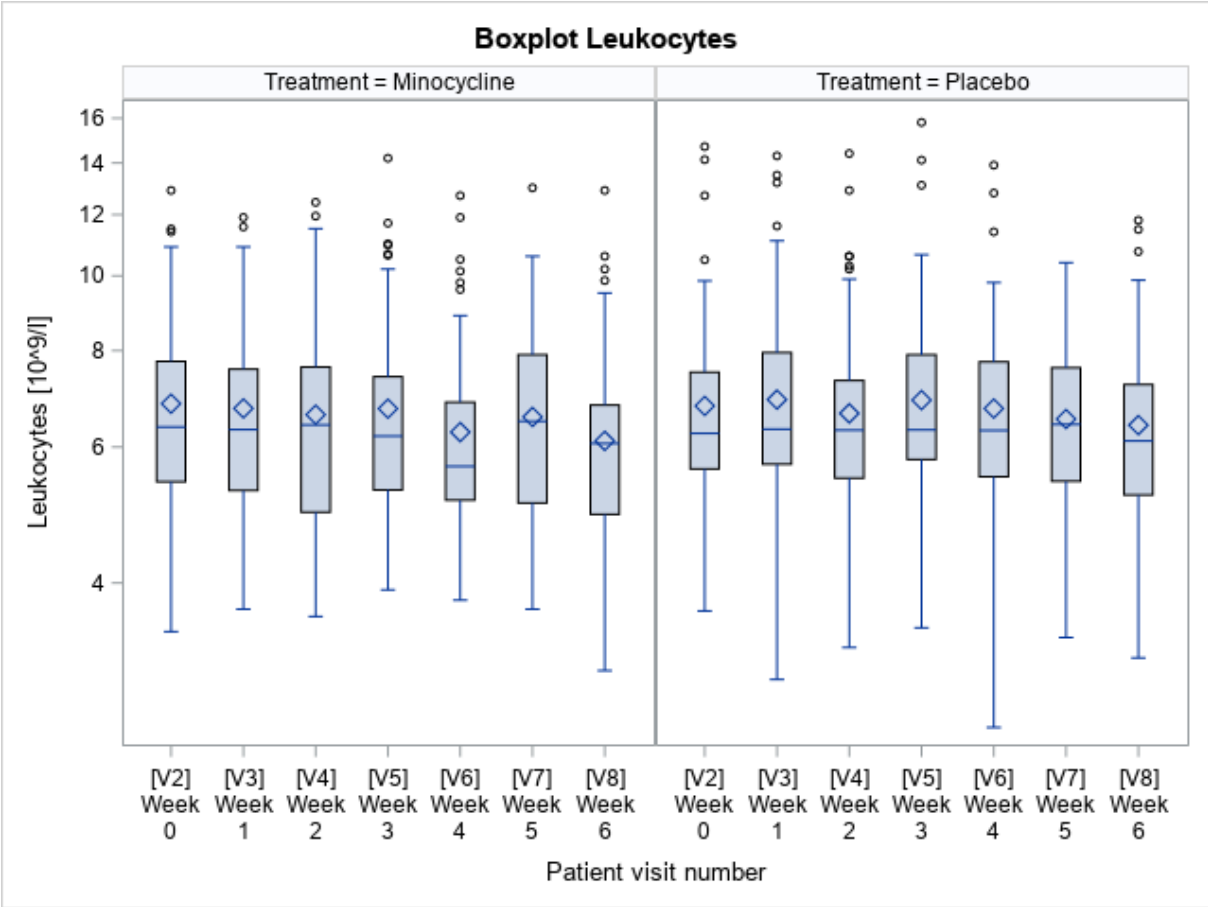


Exploratory Outcomes

eFigure 8. CRP



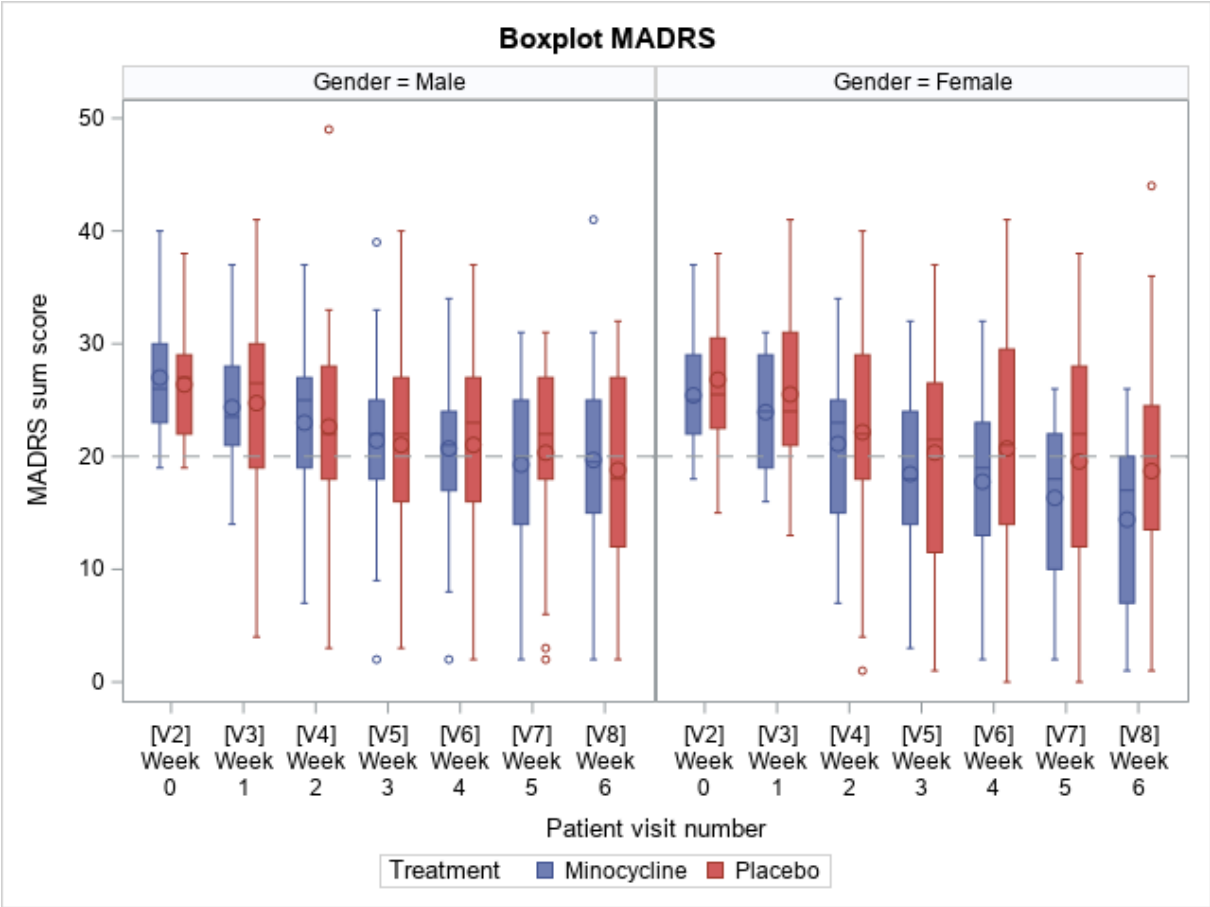
eFigure 9. Leukocytes



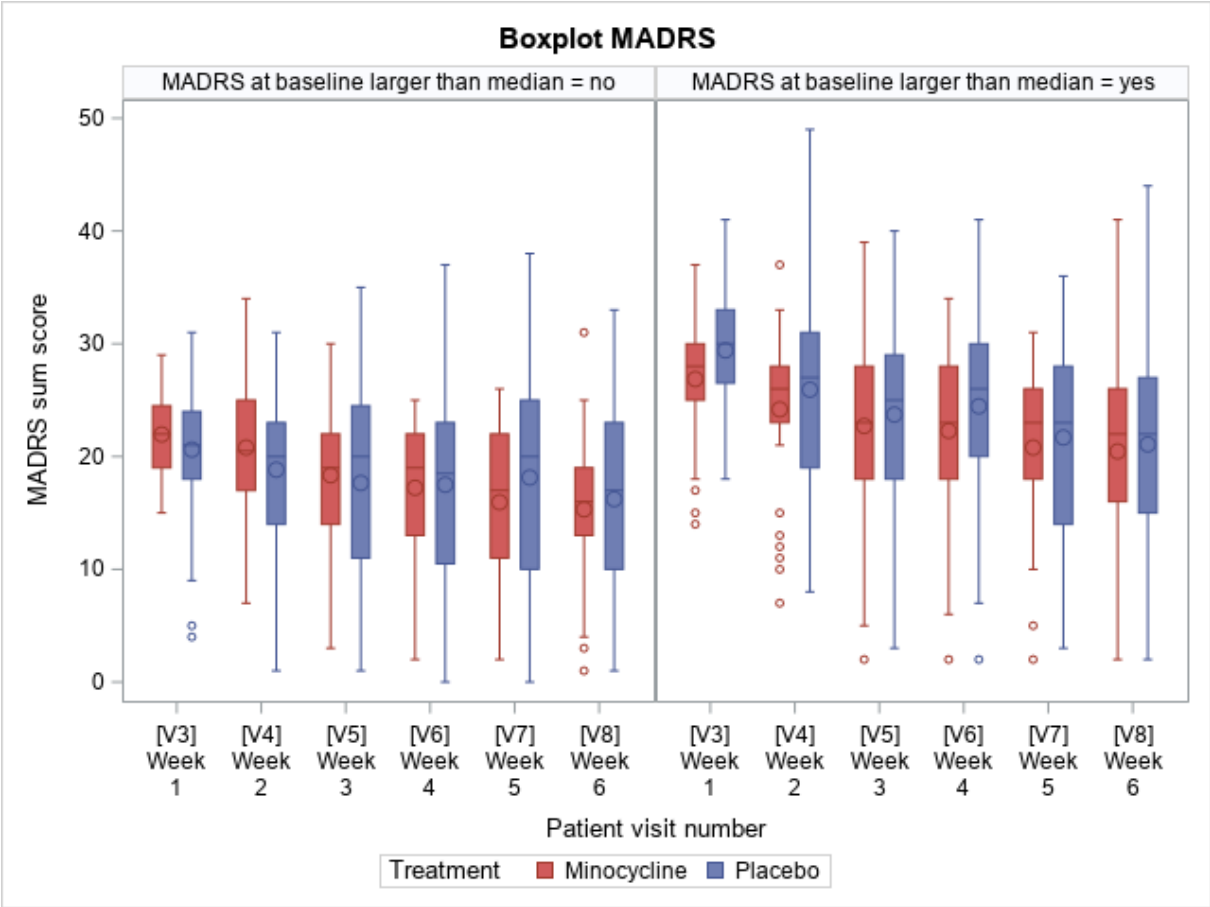


Exploratory subgroup Analyses

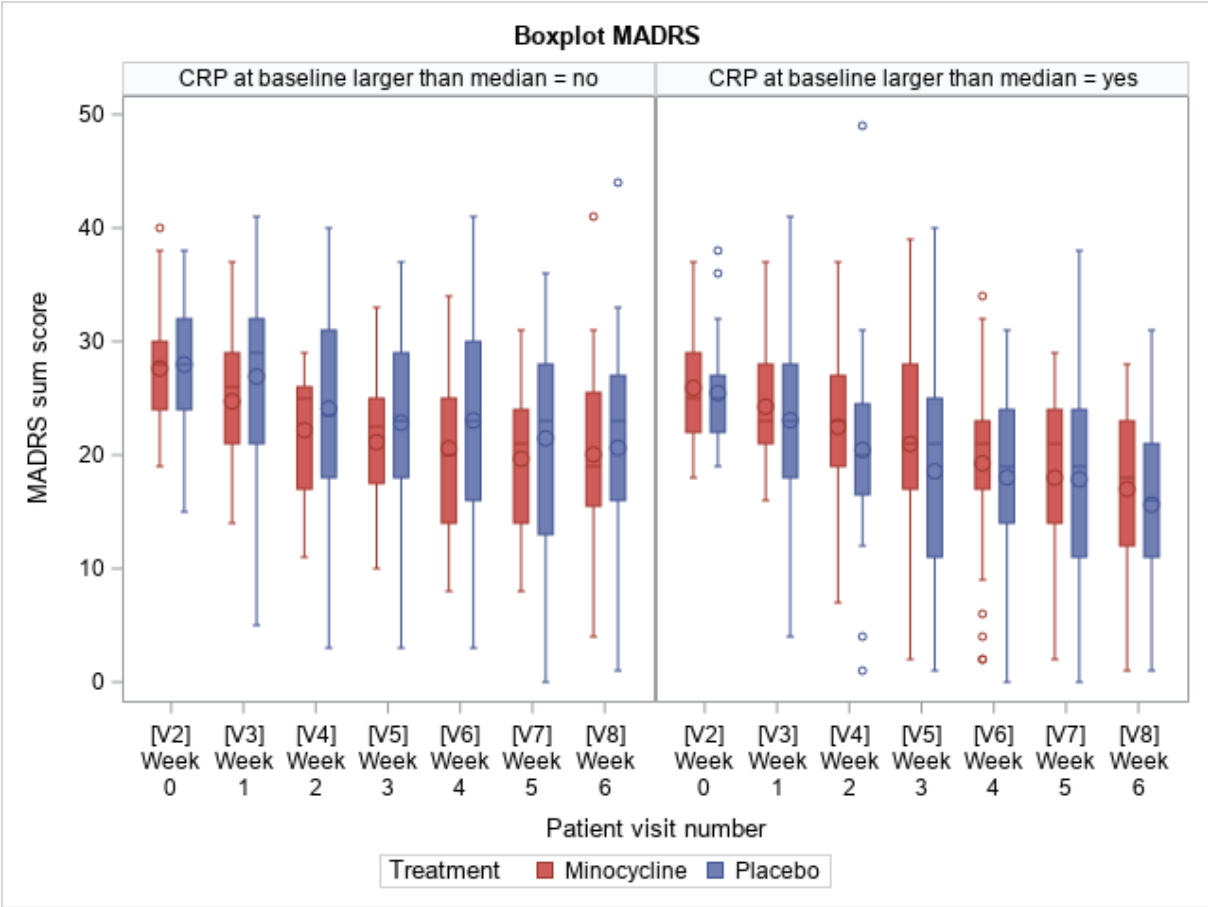
eFigure 10. Gender



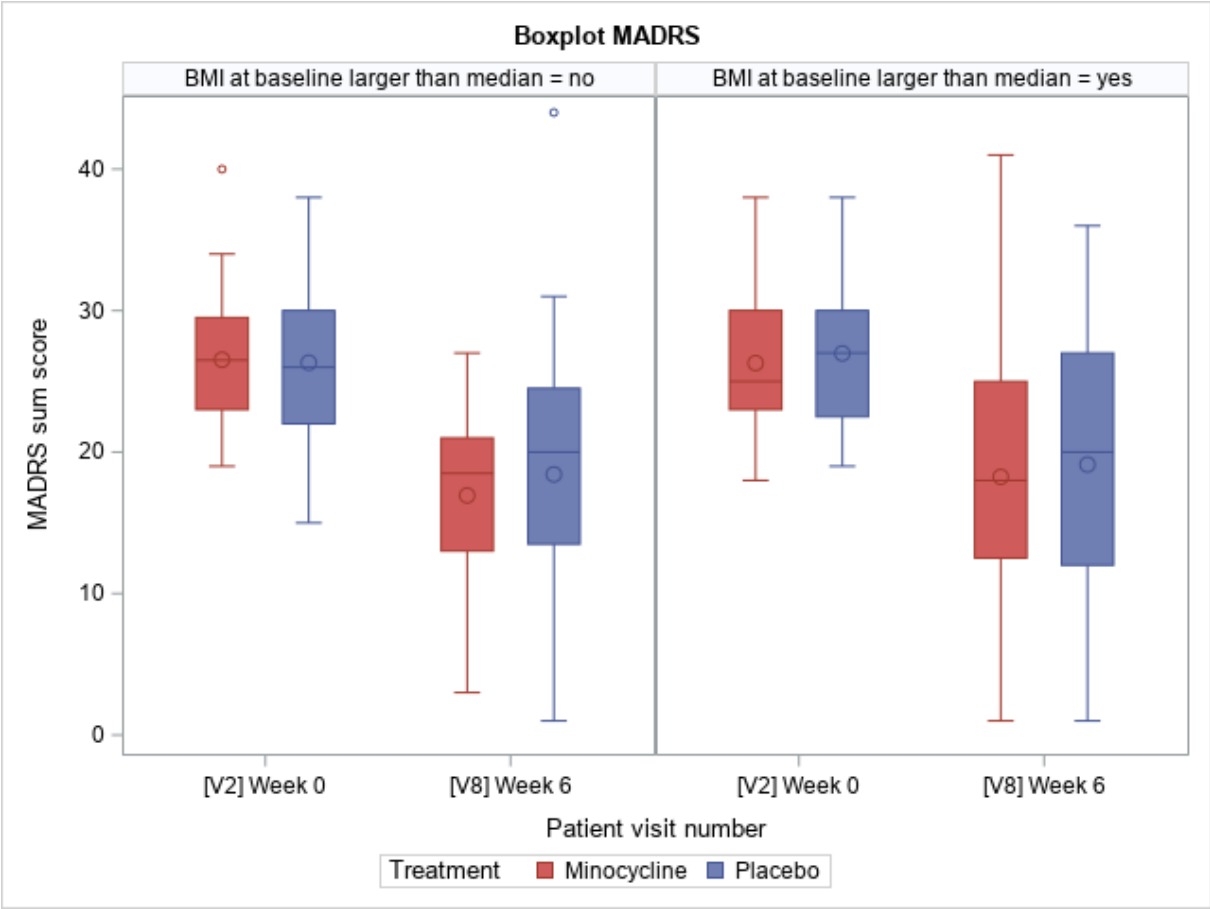
eFigure 11. MADRS at Baseline



eFigure 12. CRP



eFigure 13. BMI



eFigure 14. CTQ

