



## Clinical trial results:

## The Benefit of Minocycline on Negative Symptoms in Psychosis: Extent and Mechanisms

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2010-022463-35    |
| Trial protocol           | GB                |
| Global end of trial date | 30 September 2016 |

### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 20 August 2020 |
| First version publication date | 20 August 2020 |

### Trial information

#### Trial identification

|                       |      |
|-----------------------|------|
| Sponsor protocol code | 1007 |
|-----------------------|------|

#### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN49141214 |
| ClinicalTrials.gov id (NCT number) | NCT02928965    |
| WHO universal trial number (UTN)   | -              |

Notes:

### Sponsors

|                              |                                                                                               |
|------------------------------|-----------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Former Manchester Mental Health and Social Care Trust                                         |
| Sponsor organisation address | 1st floor Harrop House, Bury New Road, Prestwich, Greater Manchester, United Kingdom, M25 3BL |
| Public contact               | Prof Bill Deakin, The University of Manchester,<br>bill.deakin@manchester.ac.uk               |
| Scientific contact           | Prof Bill Deakin, The University of Manchester,<br>bill.deakin@manchester.ac.uk               |

Notes:

### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |                   |
|------------------------------------------------------|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 01 October 2016   |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 09 September 2016 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 30 September 2016 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To confirm that minocycline benefits the negative symptoms of schizophrenia when taken early in the course of the illness and to understand how it does so. To determine whether minocycline acts by protecting brain cells from damage, by lessening inflammation or by improving mental functions (thinking and reasoning).

Protection of trial subjects:

Protection of trial subjects managed via the IDMC.

Background therapy:

Standard antipsychotic drug treatment from CMHCT

Evidence for comparator:

Placebo, no active comparator

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 16 April 2013 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 207 |
| Worldwide total number of subjects   | 207                 |
| EEA total number of subjects         | 207                 |

Notes:

### Subjects enrolled per age group

|                                           |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 7   |
| Adults (18-64 years)                      | 200 |
| From 65 to 84 years                       | 0   |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

Recruitment between: 16/04/2013 and 30/06/2016

### Pre-assignment

Screening details:

All details present in the publication: [https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366\(18\)30345-6/fulltext](https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(18)30345-6/fulltext)

229 participants screened, of these 207 were randomised:

10 clinical exclusions

5 patients withdrawn

5 failed to consent

2 unknown reason for withdrawal

### Pre-assignment period milestones

|                                            |                 |
|--------------------------------------------|-----------------|
| Number of subjects started                 | 207             |
| Intermediate milestone: Number of subjects | Randomised: 207 |
| Number of subjects completed               | 207             |

### Period 1

|                              |                                                 |
|------------------------------|-------------------------------------------------|
| Period 1 title               | Assignment and baseline                         |
| Is this the baseline period? | Yes                                             |
| Allocation method            | Randomised - controlled                         |
| Blinding used                | Double blind                                    |
| Roles blinded                | Subject, Investigator, Monitor, Carer, Assessor |

Blinding implementation details:

Participants were randomly assigned with an automated permuted blocks algorithm and were stratified by pharmacy.openCDMS allocated the patient to a treatment group at randomisation , emailed the local pharmacy to identify the numbered treatment kit of 3 months supply to be dispensed, and recorded when kit was dispensed.

### Arms

|                              |                       |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes                   |
| <b>Arm title</b>             | Baseline: Minocycline |

Arm description:

Participants received capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                                        |                           |
|----------------------------------------|---------------------------|
| Arm type                               | Experimental              |
| Investigational medicinal product name | Minocycline               |
| Investigational medicinal product code | ATC code J01AA08 A01      |
| Other name                             | Minocycline hydrochloride |
| Pharmaceutical forms                   | Capsule, hard             |
| Routes of administration               | Oral use                  |

Dosage and administration details:

Participants received capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Baseline: Placebo |
|------------------|-------------------|

Arm description:

Participants received placebo capsules entirely matching minocycline, two per day for the first two

weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                                        |               |
|----------------------------------------|---------------|
| Arm type                               | Placebo       |
| Investigational medicinal product name | Placebo       |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

Participants received placebo capsules entirely match minocycline capsules, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

| <b>Number of subjects in period 1</b> | Baseline:<br>Minocycline | Baseline: Placebo |
|---------------------------------------|--------------------------|-------------------|
| Started                               | 103                      | 104               |
| Completed                             | 88                       | 88                |
| Not completed                         | 15                       | 16                |
| Consent withdrawn by subject          | 4                        | 5                 |
| LTFU                                  | 6                        | 9                 |
| Skin                                  | 1                        | -                 |
| Dysphagia                             | 2                        | -                 |
| Moved                                 | 1                        | 1                 |
| Abdominal pain                        | -                        | 1                 |
| Malaise                               | 1                        | -                 |

## Period 2

|                              |                                                 |
|------------------------------|-------------------------------------------------|
| Period 2 title               | 2 month follow up                               |
| Is this the baseline period? | No                                              |
| Allocation method            | Randomised - controlled                         |
| Blinding used                | Double blind                                    |
| Roles blinded                | Subject, Investigator, Monitor, Carer, Assessor |

## Arms

|                              |                                |
|------------------------------|--------------------------------|
| Are arms mutually exclusive? | Yes                            |
| <b>Arm title</b>             | 2 month follow-up: Minocycline |

Arm description:

Participants will receive capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|                                        |                           |
|----------------------------------------|---------------------------|
| Investigational medicinal product name | Minocycline               |
| Investigational medicinal product code | ATC code J01AA08 A01      |
| Other name                             | Minocycline hydrochloride |
| Pharmaceutical forms                   | Capsule, hard             |
| Routes of administration               | Oral use                  |

**Dosage and administration details:**

Participants will receive capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                  |                            |
|------------------|----------------------------|
| <b>Arm title</b> | 2 month follow-up: Placebo |
|------------------|----------------------------|

**Arm description:**

Participants will receive placebo capsules entirely matching minocycline, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Placebo                |
| Investigational medicinal product name | Placebo                |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Capsule, Capsule, soft |
| Routes of administration               | Oral use               |

**Dosage and administration details:**

Participants will receive placebo capsules entirely match minocycline capsules, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

| <b>Number of subjects in period 2</b> | 2 month follow-up:<br>Minocycline | 2 month follow-up:<br>Placebo |
|---------------------------------------|-----------------------------------|-------------------------------|
| Started                               | 88                                | 88                            |
| Completed                             | 77                                | 74                            |
| Not completed                         | 11                                | 14                            |
| Consent withdrawn by subject          | 3                                 | 3                             |
| LTFU                                  | 7                                 | 7                             |
| Vomit                                 | -                                 | 1                             |
| Abdominal pain                        | 1                                 | -                             |
| Mole                                  | -                                 | 1                             |
| Malaise                               | -                                 | 2                             |

**Period 3**

|                              |                                                               |
|------------------------------|---------------------------------------------------------------|
| Period 3 title               | 6 month follow-up                                             |
| Is this the baseline period? | No                                                            |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind                                                  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

**Arms**

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | 6 month follow-up: Minocycline |
|------------------|--------------------------------|

**Arm description:**

Participants will receive capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                                        |                           |
|----------------------------------------|---------------------------|
| Arm type                               | Experimental              |
| Investigational medicinal product name | Minocycline               |
| Investigational medicinal product code | ATC code J01AA08 A01      |
| Other name                             | Minocycline hydrochloride |
| Pharmaceutical forms                   | Capsule, hard             |
| Routes of administration               | Oral use                  |

**Dosage and administration details:**

Participants will receive capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                  |                            |
|------------------|----------------------------|
| <b>Arm title</b> | 6 month follow-up: Placebo |
|------------------|----------------------------|

**Arm description:**

Participants will receive placebo capsules entirely matching minocycline, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Placebo                |
| Investigational medicinal product name | Placebo                |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Capsule, Capsule, soft |
| Routes of administration               | Oral use               |

**Dosage and administration details:**

Participants will receive placebo capsules entirely match minocycline capsules, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

| Number of subjects in period 3 | 6 month follow-up: Minocycline | 6 month follow-up: Placebo |
|--------------------------------|--------------------------------|----------------------------|
| Started                        | 77                             | 74                         |
| Completed                      | 71                             | 70                         |
| Not completed                  | 6                              | 4                          |
| Consent withdrawn by subject   | 2                              | -                          |
| Relapse                        | 1                              | -                          |
| LTFU                           | 3                              | 4                          |

**Period 4**

|                              |                                                               |
|------------------------------|---------------------------------------------------------------|
| Period 4 title               | 9 month follow-up                                             |
| Is this the baseline period? | No                                                            |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind                                                  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

**Arms**

|                              |                                |
|------------------------------|--------------------------------|
| Are arms mutually exclusive? | Yes                            |
| <b>Arm title</b>             | 9 month follow-up: Minocycline |

## Arm description:

Participants will receive capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                                        |                           |
|----------------------------------------|---------------------------|
| Arm type                               | Experimental              |
| Investigational medicinal product name | Minocycline               |
| Investigational medicinal product code | ATC code J01AA08 A01      |
| Other name                             | Minocycline hydrochloride |
| Pharmaceutical forms                   | Capsule, hard             |
| Routes of administration               | Oral use                  |

## Dosage and administration details:

Participants will receive capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                  |                            |
|------------------|----------------------------|
| <b>Arm title</b> | 9 month follow-up: Placebo |
|------------------|----------------------------|

## Arm description:

Participants will receive placebo capsules entirely matching minocycline, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Placebo                |
| Investigational medicinal product name | Placebo                |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Capsule, Capsule, soft |
| Routes of administration               | Oral use               |

## Dosage and administration details:

Participants will receive placebo capsules entirely match minocycline capsules, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

| <b>Number of subjects in period 4</b> | 9 month follow-up: Minocycline | 9 month follow-up: Placebo |
|---------------------------------------|--------------------------------|----------------------------|
| Started                               | 71                             | 70                         |
| Completed                             | 64                             | 65                         |
| Not completed                         | 7                              | 5                          |
| Consent withdrawn by subject          | 2                              | 1                          |
| Visual dist                           | 1                              | -                          |
| LTFU                                  | 3                              | 4                          |



|          |   |   |
|----------|---|---|
| Epilepsy | 1 | - |
|----------|---|---|

## Period 5

|                              |                                                               |
|------------------------------|---------------------------------------------------------------|
| Period 5 title               | 12 month follow-up                                            |
| Is this the baseline period? | No                                                            |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind                                                  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

## Arms

|                              |                                 |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | Yes                             |
| <b>Arm title</b>             | 12 month follow-up: Minocycline |

### Arm description:

Participants will receive capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                                        |                           |
|----------------------------------------|---------------------------|
| Arm type                               | Experimental              |
| Investigational medicinal product name | Minocycline               |
| Investigational medicinal product code | ATC code J01AA08 A01      |
| Other name                             | Minocycline hydrochloride |
| Pharmaceutical forms                   | Capsule, hard             |
| Routes of administration               | Oral use                  |

### Dosage and administration details:

Participants will receive capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | 12 month follow-up: Placebo |
|------------------|-----------------------------|

### Arm description:

Participants will receive placebo capsules entirely matching minocycline, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Placebo                |
| Investigational medicinal product name | Placebo                |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Capsule, Capsule, soft |
| Routes of administration               | Oral use               |

### Dosage and administration details:

Participants will receive placebo capsules entirely match minocycline capsules, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

| <b>Number of subjects in period 5</b> | 12 month follow-up: Minocycline | 12 month follow-up: Placebo |
|---------------------------------------|---------------------------------|-----------------------------|
| Started                               | 64                              | 65                          |
| Completed                             | 41                              | 48                          |
| Not completed                         | 23                              | 17                          |
| Consent withdrawn by subject          | 5                               | 2                           |
| LTFU                                  | 18                              | 15                          |

## Period 6

|                              |                                                 |
|------------------------------|-------------------------------------------------|
| Period 6 title               | 15 month follow-up                              |
| Is this the baseline period? | No                                              |
| Allocation method            | Randomised - controlled                         |
| Blinding used                | Double blind                                    |
| Roles blinded                | Subject, Investigator, Monitor, Carer, Assessor |

## Arms

|                              |                                 |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | Yes                             |
| <b>Arm title</b>             | 15 month follow-up: Minocycline |

### Arm description:

Participants will receive capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                                        |                           |
|----------------------------------------|---------------------------|
| Arm type                               | Experimental              |
| Investigational medicinal product name | Minocycline               |
| Investigational medicinal product code | ATC code J01AA08 A01      |
| Other name                             | Minocycline hydrochloride |
| Pharmaceutical forms                   | Capsule, hard             |
| Routes of administration               | Oral use                  |

### Dosage and administration details:

Participants will receive capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | 15 month follow-up: Placebo |
|------------------|-----------------------------|

### Arm description:

Participants will receive placebo capsules entirely matching minocycline, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Placebo                |
| Investigational medicinal product name | Placebo                |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Capsule, Capsule, soft |
| Routes of administration               | Oral use               |

### Dosage and administration details:

Participants will receive placebo capsules entirely match minocycline capsules, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

| <b>Number of subjects in period 6</b> | 15 month follow-up:<br>Minocycline | 15 month follow-up:<br>Placebo |
|---------------------------------------|------------------------------------|--------------------------------|
| Started                               | 41                                 | 48                             |
| Completed                             | 41                                 | 48                             |

## Baseline characteristics

### Reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Baseline: Minocycline |
|-----------------------|-----------------------|

Reporting group description:

Participants received capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Baseline: Placebo |
|-----------------------|-------------------|

Reporting group description:

Participants received placebo capsules entirely matching minocycline, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.

| Reporting group values                             | Baseline: Minocycline | Baseline: Placebo | Total |
|----------------------------------------------------|-----------------------|-------------------|-------|
| Number of subjects                                 | 103                   | 104               | 207   |
| Age categorical                                    |                       |                   |       |
| Units: Subjects                                    |                       |                   |       |
| In utero                                           |                       |                   | 0     |
| Preterm newborn infants (gestational age < 37 wks) |                       |                   | 0     |
| Newborns (0-27 days)                               |                       |                   | 0     |
| Infants and toddlers (28 days-23 months)           |                       |                   | 0     |
| Children (2-11 years)                              |                       |                   | 0     |
| Adolescents (12-17 years)                          |                       |                   | 0     |
| Adults (18-64 years)                               |                       |                   | 0     |
| From 65-84 years                                   |                       |                   | 0     |
| 85 years and over                                  |                       |                   | 0     |
| Age continuous                                     |                       |                   |       |
| none                                               |                       |                   |       |
| Units: years                                       |                       |                   |       |
| arithmetic mean                                    | 25.7                  | 25.5              |       |
| standard deviation                                 | ± 5.1                 | ± 5.2             | -     |
| Gender categorical                                 |                       |                   |       |
| none                                               |                       |                   |       |
| Units: Subjects                                    |                       |                   |       |
| Female                                             | 30                    | 27                | 57    |
| Male                                               | 73                    | 77                | 150   |
| PANSS score: Negative symptoms subscale            |                       |                   |       |
| Units: PANSS score                                 |                       |                   |       |
| arithmetic mean                                    | 17.7                  | 16.8              |       |
| standard deviation                                 | ± 5.9                 | ± 5.5             | -     |
| PANSS score: Positive symptom subscale             |                       |                   |       |
| Units: PANSS score                                 |                       |                   |       |
| arithmetic mean                                    | 16.3                  | 17.3              |       |
| standard deviation                                 | ± 4.1                 | ± 5.3             | -     |
| Total PANSS score                                  |                       |                   |       |
| Units: PANSS score                                 |                       |                   |       |

|                                                                                                                      |                 |                |   |
|----------------------------------------------------------------------------------------------------------------------|-----------------|----------------|---|
| arithmetic mean<br>standard deviation                                                                                | 67.1<br>± 13.2  | 69.3<br>± 15.4 | - |
| CDSS score<br>Units: CDSS score<br>arithmetic mean<br>standard deviation                                             | 5.2<br>± 4.3    | 5.5<br>± 5.0   | - |
| GAF score<br>Units: GAF score<br>arithmetic mean<br>standard deviation                                               | 55.5<br>± 9.1   | 56.2<br>± 11.6 | - |
| Weight<br>Units: Kg<br>arithmetic mean<br>standard deviation                                                         | 82.6<br>± 19.6  | 86.8<br>± 25.3 | - |
| BMI<br>Units: BMI<br>arithmetic mean<br>standard deviation                                                           | 27.1<br>± 6.2   | 28.7<br>± 7.6  | - |
| Processing speed<br>Units: BIP<br>arithmetic mean<br>standard deviation                                              | 58<br>± 16.7    | 52.8<br>± 16.8 | - |
| Current IQ<br>Units: IQ score<br>arithmetic mean<br>standard deviation                                               | 91.2<br>± 14    | 89.2<br>± 15.9 | - |
| Pre-Morbid IQ<br>Units: IQ score<br>arithmetic mean<br>standard deviation                                            | 97.7<br>± 1.7   | 95.4<br>± 19.8 | - |
| Medial Prefrontal cortex grey-matter<br>volume: left<br>Units: cc<br>arithmetic mean<br>standard deviation           | 5.6<br>± 0.7    | 5.7<br>± 0.8   | - |
| Medial Prefrontal cortex grey-matter<br>volume: right<br>Units: cc<br>arithmetic mean<br>standard deviation          | 4.6<br>± 5.8    | 4.6<br>± 0.7   | - |
| N-Back BOLD activation: 1-back plus 2-<br>back vs 0-back<br>Units: % change<br>arithmetic mean<br>standard deviation | -0.02<br>± 1.48 | 0.12<br>± 1.25 | - |
| N-Back BOLD activation: 2-back vs 1-<br>back<br>Units: % change<br>arithmetic mean<br>standard deviation             | -0.04<br>± 1.54 | 0.10<br>± 1.23 | - |
| Cytokine IL-6<br>Units: pg/mL<br>arithmetic mean                                                                     | 0.69            | 0.84           |   |

|                    |        |        |   |
|--------------------|--------|--------|---|
| standard deviation | ± 0.46 | ± 0.64 | - |
| hs-CRP             |        |        |   |
| Units: mg/L        |        |        |   |
| arithmetic mean    | 3.08   | 3.83   |   |
| standard deviation | ± 3.82 | ± 5.45 | - |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                           |                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | Baseline: Minocycline           |
| Reporting group description:<br>Participants received capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.     |                                 |
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | Baseline: Placebo               |
| Reporting group description:<br>Participants received placebo capsules entirely matching minocycline, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.                  |                                 |
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | 2 month follow-up: Minocycline  |
| Reporting group description:<br>Participants will receive capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer. |                                 |
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | 2 month follow-up: Placebo      |
| Reporting group description:<br>Participants will receive placebo capsules entirely matching minocycline, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.              |                                 |
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | 6 month follow-up: Minocycline  |
| Reporting group description:<br>Participants will receive capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer. |                                 |
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | 6 month follow-up: Placebo      |
| Reporting group description:<br>Participants will receive placebo capsules entirely matching minocycline, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.              |                                 |
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | 9 month follow-up: Minocycline  |
| Reporting group description:<br>Participants will receive capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer. |                                 |
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | 9 month follow-up: Placebo      |
| Reporting group description:<br>Participants will receive placebo capsules entirely matching minocycline, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.              |                                 |
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | 12 month follow-up: Minocycline |
| Reporting group description:<br>Participants will receive capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer. |                                 |
| Reporting group title                                                                                                                                                                                                                                                                                                                                     | 12 month follow-up: Placebo     |
| Reporting group description:<br>Participants will receive placebo capsules entirely matching minocycline, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.              |                                 |

|                                                                                                                                                                                                                                                                                                                           |                                 |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                     | 15 month follow-up: Minocycline |
| Reporting group description:                                                                                                                                                                                                                                                                                              |                                 |
| Participants will receive capsules containing 100mg of minocycline (modified release), two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer. |                                 |
| Reporting group title                                                                                                                                                                                                                                                                                                     | 15 month follow-up: Placebo     |
| Reporting group description:                                                                                                                                                                                                                                                                                              |                                 |
| Participants will receive placebo capsules entirely matching minocycline, two per day for the first two weeks of the trial and then three per day for the remainder of the 12 month treatment period in addition to antipsychotic drug treatment and other interventions by the responsible medical officer.              |                                 |

### Primary: Left grey-matter volume

|                                               |                         |
|-----------------------------------------------|-------------------------|
| End point title                               | Left grey-matter volume |
| End point description:                        |                         |
| Note: measures in mm(squared) for mean and SD |                         |
| End point type                                | Primary                 |
| End point timeframe:                          |                         |
| across follow-up timepoints                   |                         |

| End point values                     | Baseline:<br>Minocycline | Baseline:<br>Placebo | 2 month<br>follow-up:<br>Minocycline | 2 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------|----------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group          | Reporting group      | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 94                       | 88                   | 0 <sup>[1]</sup>                     | 0 <sup>[2]</sup>                 |
| Units: Volume (cc)                   |                          |                      |                                      |                                  |
| arithmetic mean (standard deviation) | 5644 (± 723)             | 5669 (± 786)         | ()                                   | ()                               |

Notes:

[1] - Measure not captured at this time point

[2] - Measure not captured at this time point

| End point values                     | 6 month<br>follow-up:<br>Minocycline | 6 month<br>follow-up:<br>Placebo | 9 month<br>follow-up:<br>Minocycline | 9 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------------------|----------------------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group                      | Reporting group                  | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 0 <sup>[3]</sup>                     | 0 <sup>[4]</sup>                 | 0 <sup>[5]</sup>                     | 0 <sup>[6]</sup>                 |
| Units: Volume (cc)                   |                                      |                                  |                                      |                                  |
| arithmetic mean (standard deviation) | ()                                   | ()                               | ()                                   | ()                               |

Notes:

[3] - Measure not captured at this time point

[4] - Measure not captured at this time point

[5] - Measure not captured at this time point

[6] - Measure not captured at this time point

| End point values            | 12 month<br>follow-up:<br>Minocycline | 12 month<br>follow-up:<br>Placebo | 15 month<br>follow-up:<br>Minocycline | 15 month<br>follow-up:<br>Placebo |
|-----------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
| Subject group type          | Reporting group                       | Reporting group                   | Reporting group                       | Reporting group                   |
| Number of subjects analysed | 45                                    | 54                                | 0 <sup>[7]</sup>                      | 0 <sup>[8]</sup>                  |
| Units: Volume (cc)          |                                       |                                   |                                       |                                   |



|                                      |                  |                   |    |    |
|--------------------------------------|------------------|-------------------|----|----|
| arithmetic mean (standard deviation) | 5593 ( $\pm$ 70) | 5509 ( $\pm$ 787) | () | () |
|--------------------------------------|------------------|-------------------|----|----|

Notes:

[7] - Measure not captured at this time point

[8] - Measure not captured at this time point

## Statistical analyses

|                                         |                                                                                                           |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | best estimates of treatment effects                                                                       |
| Comparison groups                       | Baseline: Minocycline v Baseline: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo |
| Number of subjects included in analysis | 281                                                                                                       |
| Analysis specification                  | Pre-specified                                                                                             |
| Analysis type                           | superiority                                                                                               |
| P-value                                 | = 0.4                                                                                                     |
| Method                                  | t-test, 2-sided                                                                                           |
| Parameter estimate                      | Mean difference (final values)                                                                            |
| Point estimate                          | -0.09                                                                                                     |
| Confidence interval                     |                                                                                                           |
| level                                   | 95 %                                                                                                      |
| sides                                   | 2-sided                                                                                                   |
| lower limit                             | -0.3                                                                                                      |
| upper limit                             | 0.12                                                                                                      |
| Variability estimate                    | Standard error of the mean                                                                                |
| Dispersion value                        | 0.11                                                                                                      |

## Primary: Right grey-matter volume

|                                               |                          |
|-----------------------------------------------|--------------------------|
| End point title                               | Right grey-matter volume |
| End point description:                        |                          |
| Note: measures in mm(squared) for mean and SD |                          |
| End point type                                | Primary                  |
| End point timeframe:                          |                          |
| across follow-up timepoints                   |                          |

| End point values                     | Baseline: Minocycline | Baseline: Placebo | 2 month follow-up: Minocycline | 2 month follow-up: Placebo |
|--------------------------------------|-----------------------|-------------------|--------------------------------|----------------------------|
| Subject group type                   | Reporting group       | Reporting group   | Reporting group                | Reporting group            |
| Number of subjects analysed          | 94                    | 88                | 0 <sup>[9]</sup>               | 0 <sup>[10]</sup>          |
| Units: Volume (cc)                   |                       |                   |                                |                            |
| arithmetic mean (standard deviation) | 4574 ( $\pm$ 551)     | 4581 ( $\pm$ 658) | ()                             | ()                         |

Notes:

[9] - Measure not captured at this time point

[10] - Measure not captured at this time point

| End point values | 6 month follow-up: | 6 month follow-up: | 9 month follow-up: | 9 month follow-up: |
|------------------|--------------------|--------------------|--------------------|--------------------|
|------------------|--------------------|--------------------|--------------------|--------------------|

|                                      | Minocycline       | Placebo           | Minocycline       | Placebo           |
|--------------------------------------|-------------------|-------------------|-------------------|-------------------|
| Subject group type                   | Reporting group   | Reporting group   | Reporting group   | Reporting group   |
| Number of subjects analysed          | 0 <sup>[11]</sup> | 0 <sup>[12]</sup> | 0 <sup>[13]</sup> | 0 <sup>[14]</sup> |
| Units: Volume (cc)                   |                   |                   |                   |                   |
| arithmetic mean (standard deviation) | ()                | ()                | ()                | ()                |

Notes:

[11] - Measure not captured at this time point

[12] - Measure not captured at this time point

[13] - Measure not captured at this time point

[14] - Measure not captured at this time point

| <b>End point values</b>              | 12 month follow-up: Minocycline | 12 month follow-up: Placebo | 15 month follow-up: Minocycline | 15 month follow-up: Placebo |
|--------------------------------------|---------------------------------|-----------------------------|---------------------------------|-----------------------------|
| Subject group type                   | Reporting group                 | Reporting group             | Reporting group                 | Reporting group             |
| Number of subjects analysed          | 45                              | 54                          | 0 <sup>[15]</sup>               | 0 <sup>[16]</sup>           |
| Units: Volume (cc)                   |                                 |                             |                                 |                             |
| arithmetic mean (standard deviation) | 4543 (± 551)                    | 4425 (± 680)                | ()                              | ()                          |

Notes:

[15] - Measure not captured at this time point

[16] - Measure not captured at this time point

## Statistical analyses

|                                         |                                                                                                           |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | best estimates of treatment effects                                                                       |
| Comparison groups                       | Baseline: Minocycline v Baseline: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo |
| Number of subjects included in analysis | 281                                                                                                       |
| Analysis specification                  | Pre-specified                                                                                             |
| Analysis type                           | superiority                                                                                               |
| P-value                                 | = 0.34                                                                                                    |
| Method                                  | t-test, 2-sided                                                                                           |
| Parameter estimate                      | Mean difference (final values)                                                                            |
| Point estimate                          | -0.07                                                                                                     |
| Confidence interval                     |                                                                                                           |
| level                                   | 95 %                                                                                                      |
| sides                                   | 2-sided                                                                                                   |
| lower limit                             | -0.21                                                                                                     |
| upper limit                             | 0.08                                                                                                      |
| Variability estimate                    | Standard error of the mean                                                                                |
| Dispersion value                        | 0.07                                                                                                      |

## Primary: Interleukin 6

|                                                                                               |               |
|-----------------------------------------------------------------------------------------------|---------------|
| End point title                                                                               | Interleukin 6 |
| End point description:                                                                        |               |
| There were no systematic trends in cytokine concentrations over time and no treatment effects |               |
| End point type                                                                                | Primary       |
| End point timeframe:                                                                          |               |
| across all follow-up timepoints                                                               |               |

| End point values                     | Baseline:<br>Minocycline | Baseline:<br>Placebo    | 2 month<br>follow-up:<br>Minocycline | 2 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------|-------------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group          | Reporting group         | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 101                      | 100                     | 0 <sup>[17]</sup>                    | 0 <sup>[18]</sup>                |
| Units: concentration (pg/mL)         |                          |                         |                                      |                                  |
| arithmetic mean (standard deviation) | 0.690 ( $\pm$<br>0.458)  | 0.840 ( $\pm$<br>0.639) | ()                                   | ()                               |

Notes:

[17] - Measure not captured at this time point

[18] - Measure not captured at this time point

| End point values                     | 6 month<br>follow-up:<br>Minocycline | 6 month<br>follow-up:<br>Placebo | 9 month<br>follow-up:<br>Minocycline | 9 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------------------|----------------------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group                      | Reporting group                  | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 57                                   | 65                               | 0 <sup>[19]</sup>                    | 0 <sup>[20]</sup>                |
| Units: concentration (pg/mL)         |                                      |                                  |                                      |                                  |
| arithmetic mean (standard deviation) | 0.843 ( $\pm$<br>0.926)              | 0.902 ( $\pm$<br>0.753)          | ()                                   | ()                               |

Notes:

[19] - Measure not captured at this time point

[20] - Measure not captured at this time point

| End point values                     | 12 month<br>follow-up:<br>Minocycline | 12 month<br>follow-up:<br>Placebo | 15 month<br>follow-up:<br>Minocycline | 15 month<br>follow-up:<br>Placebo |
|--------------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
| Subject group type                   | Reporting group                       | Reporting group                   | Reporting group                       | Reporting group                   |
| Number of subjects analysed          | 53                                    | 56                                | 0 <sup>[21]</sup>                     | 0 <sup>[22]</sup>                 |
| Units: concentration (pg/mL)         |                                       |                                   |                                       |                                   |
| arithmetic mean (standard deviation) | 0.793 ( $\pm$<br>0.570)               | 0.811 ( $\pm$<br>0.623)           | ()                                    | ()                                |

Notes:

[21] - Measure not captured at this time point

[22] - Measure not captured at this time point

## Statistical analyses

|                                         |                                                                                                                                                                         |
|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | best estimates of treatment effects                                                                                                                                     |
| Comparison groups                       | Baseline: Minocycline v Baseline: Placebo v 6 month follow-up: Minocycline v 6 month follow-up: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo |
| Number of subjects included in analysis | 432                                                                                                                                                                     |
| Analysis specification                  | Pre-specified                                                                                                                                                           |
| Analysis type                           | superiority                                                                                                                                                             |
| P-value                                 | = 0.46                                                                                                                                                                  |
| Method                                  | t-test, 2-sided                                                                                                                                                         |
| Parameter estimate                      | Mean difference (final values)                                                                                                                                          |
| Point estimate                          | 0.07                                                                                                                                                                    |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -0.12                      |
| upper limit          | 0.26                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.41                       |

### Primary: High-sensitivity C-reactive protein

|                                                                                                                         |                                     |
|-------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| End point title                                                                                                         | High-sensitivity C-reactive protein |
| End point description:<br>There were no systematic trends in cytokine concentrations over time and no treatment effects |                                     |
| End point type                                                                                                          | Primary                             |
| End point timeframe:<br>across all follow-up timepoints                                                                 |                                     |

| End point values                     | Baseline:<br>Minocycline | Baseline:<br>Placebo | 2 month<br>follow-up:<br>Minocycline | 2 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------|----------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group          | Reporting group      | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 101                      | 100                  | 0 <sup>[23]</sup>                    | 0 <sup>[24]</sup>                |
| Units: find out                      |                          |                      |                                      |                                  |
| arithmetic mean (standard deviation) | 3.08 (± 3.82)            | 3.83 (± 5.45)        | ()                                   | ()                               |

Notes:

[23] - Measure not captured at this time point

[24] - Measure not captured at this time point

| End point values                     | 6 month<br>follow-up:<br>Minocycline | 6 month<br>follow-up:<br>Placebo | 9 month<br>follow-up:<br>Minocycline | 9 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------------------|----------------------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group                      | Reporting group                  | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 57                                   | 65                               | 0 <sup>[25]</sup>                    | 0 <sup>[26]</sup>                |
| Units: find out                      |                                      |                                  |                                      |                                  |
| arithmetic mean (standard deviation) | 4.56 (± 11.23)                       | 5.33 (± 9.54)                    | ()                                   | ()                               |

Notes:

[25] - Measure not captured at this time point

[26] - Measure not captured at this time point

| End point values                     | 12 month<br>follow-up:<br>Minocycline | 12 month<br>follow-up:<br>Placebo | 15 month<br>follow-up:<br>Minocycline | 15 month<br>follow-up:<br>Placebo |
|--------------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
| Subject group type                   | Reporting group                       | Reporting group                   | Reporting group                       | Reporting group                   |
| Number of subjects analysed          | 51                                    | 56                                | 0 <sup>[27]</sup>                     | 0 <sup>[28]</sup>                 |
| Units: find out                      |                                       |                                   |                                       |                                   |
| arithmetic mean (standard deviation) | 6.01 (± 18.91)                        | 4.40 (± 5.30)                     | ()                                    | ()                                |

Notes:

[27] - Measure not captured at this time point

**Statistical analyses**

|                                         |                                                                                                                                                                         |
|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | best estimates of treatment effects                                                                                                                                     |
| Comparison groups                       | Baseline: Minocycline v Baseline: Placebo v 6 month follow-up: Minocycline v 6 month follow-up: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo |
| Number of subjects included in analysis | 430                                                                                                                                                                     |
| Analysis specification                  | Pre-specified                                                                                                                                                           |
| Analysis type                           | superiority                                                                                                                                                             |
| P-value                                 | = 0.28                                                                                                                                                                  |
| Method                                  | t-test, 2-sided                                                                                                                                                         |
| Parameter estimate                      | Mean difference (final values)                                                                                                                                          |
| Point estimate                          | 1.72                                                                                                                                                                    |
| Confidence interval                     |                                                                                                                                                                         |
| level                                   | 95 %                                                                                                                                                                    |
| sides                                   | 2-sided                                                                                                                                                                 |
| lower limit                             | -1.42                                                                                                                                                                   |
| upper limit                             | 4.85                                                                                                                                                                    |
| Variability estimate                    | Standard error of the mean                                                                                                                                              |
| Dispersion value                        | 1.6                                                                                                                                                                     |

**Secondary: PANSS Negative symptoms**

|                                                                           |                         |
|---------------------------------------------------------------------------|-------------------------|
| End point title                                                           | PANSS Negative symptoms |
| End point description:                                                    |                         |
| Measure = Estimate of treatment effects across all follow up time points. |                         |
| End point type                                                            | Secondary               |
| End point timeframe:                                                      |                         |
| Across all follow up time points.                                         |                         |

| <b>End point values</b>              | Baseline:<br>Minocycline | Baseline:<br>Placebo | 2 month<br>follow-up:<br>Minocycline | 2 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------|----------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group          | Reporting group      | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 103                      | 104                  | 83                                   | 85                               |
| Units: PANSS score                   |                          |                      |                                      |                                  |
| arithmetic mean (standard deviation) | 17.7 (± 5.9)             | 16.8 (± 5.5)         | 16.4 (± 5.9)                         | 15.1 (± 5.8)                     |

| <b>End point values</b> | 6 month<br>follow-up: | 6 month<br>follow-up: | 9 month<br>follow-up: | 9 month<br>follow-up: |
|-------------------------|-----------------------|-----------------------|-----------------------|-----------------------|
|-------------------------|-----------------------|-----------------------|-----------------------|-----------------------|

|                                      | Minocycline     | Placebo         | Minocycline     | Placebo         |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed          | 69              | 67              | 68              | 62              |
| Units: PANSS score                   |                 |                 |                 |                 |
| arithmetic mean (standard deviation) | 15.8 (± 6.5)    | 15.7 (± 5.8)    | 15.9 (± 6.3)    | 14.5 (± 4.9)    |

| End point values                     | 12 month follow-up: Minocycline | 12 month follow-up: Placebo | 15 month follow-up: Minocycline | 15 month follow-up: Placebo |
|--------------------------------------|---------------------------------|-----------------------------|---------------------------------|-----------------------------|
| Subject group type                   | Reporting group                 | Reporting group             | Reporting group                 | Reporting group             |
| Number of subjects analysed          | 62                              | 65                          | 41                              | 48                          |
| Units: PANSS score                   |                                 |                             |                                 |                             |
| arithmetic mean (standard deviation) | 16.4 (± 6.2)                    | 14.2 (± 5.2)                | 15.6 (± 6.6)                    | 14.0 (± 4.9)                |

|                                   |                                                   |
|-----------------------------------|---------------------------------------------------|
| <b>Attachments (see zip file)</b> | Main outcome measures for minocycline and placebo |
|-----------------------------------|---------------------------------------------------|

## Statistical analyses

|                                                                |                                                                                                                                                                                                                                                                                                                                                                     |
|----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                              | best estimates of treatment effects                                                                                                                                                                                                                                                                                                                                 |
| Statistical analysis description:                              |                                                                                                                                                                                                                                                                                                                                                                     |
| Best estimate of treatment effects across all follow-up points |                                                                                                                                                                                                                                                                                                                                                                     |
| Comparison groups                                              | Baseline: Minocycline v Baseline: Placebo v 2 month follow-up: Minocycline v 2 month follow-up: Placebo v 6 month follow-up: Minocycline v 6 month follow-up: Placebo v 9 month follow-up: Minocycline v 9 month follow-up: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo v 15 month follow-up: Minocycline v 15 month follow-up: Placebo |
| Number of subjects included in analysis                        | 857                                                                                                                                                                                                                                                                                                                                                                 |
| Analysis specification                                         | Pre-specified                                                                                                                                                                                                                                                                                                                                                       |
| Analysis type                                                  | superiority                                                                                                                                                                                                                                                                                                                                                         |
| P-value                                                        | = 0.73                                                                                                                                                                                                                                                                                                                                                              |
| Method                                                         | t-test, 2-sided                                                                                                                                                                                                                                                                                                                                                     |
| Parameter estimate                                             | Mean difference (final values)                                                                                                                                                                                                                                                                                                                                      |
| Point estimate                                                 | -0.19                                                                                                                                                                                                                                                                                                                                                               |
| Confidence interval                                            |                                                                                                                                                                                                                                                                                                                                                                     |
| level                                                          | 95 %                                                                                                                                                                                                                                                                                                                                                                |
| sides                                                          | 2-sided                                                                                                                                                                                                                                                                                                                                                             |
| lower limit                                                    | -1.23                                                                                                                                                                                                                                                                                                                                                               |
| upper limit                                                    | 0.85                                                                                                                                                                                                                                                                                                                                                                |
| Variability estimate                                           | Standard error of the mean                                                                                                                                                                                                                                                                                                                                          |
| Dispersion value                                               | 0.53                                                                                                                                                                                                                                                                                                                                                                |

## Secondary: Positive symptoms (PANSS)

|                 |                           |
|-----------------|---------------------------|
| End point title | Positive symptoms (PANSS) |
|-----------------|---------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

across all follow-up timepoints

| End point values                 | Baseline:<br>Minocycline | Baseline:<br>Placebo | 2 month<br>follow-up:<br>Minocycline | 2 month<br>follow-up:<br>Placebo |
|----------------------------------|--------------------------|----------------------|--------------------------------------|----------------------------------|
| Subject group type               | Reporting group          | Reporting group      | Reporting group                      | Reporting group                  |
| Number of subjects analysed      | 103                      | 104                  | 83                                   | 86                               |
| Units: PANSS score               |                          |                      |                                      |                                  |
| arithmetic mean (standard error) | 16.3 (± 4.1)             | 17.3 (± 5.3)         | 13.8 (± 4.5)                         | 14.5 (± 4.8)                     |

| End point values                 | 6 month<br>follow-up:<br>Minocycline | 6 month<br>follow-up:<br>Placebo | 9 month<br>follow-up:<br>Minocycline | 9 month<br>follow-up:<br>Placebo |
|----------------------------------|--------------------------------------|----------------------------------|--------------------------------------|----------------------------------|
| Subject group type               | Reporting group                      | Reporting group                  | Reporting group                      | Reporting group                  |
| Number of subjects analysed      | 69                                   | 67                               | 68                                   | 63                               |
| Units: PANSS score               |                                      |                                  |                                      |                                  |
| arithmetic mean (standard error) | 13.4 (± 5.0)                         | 14.4 (± 5.2)                     | 12.8 (± 4.6)                         | 13.6 (± 5.0)                     |

| End point values                 | 12 month<br>follow-up:<br>Minocycline | 12 month<br>follow-up:<br>Placebo | 15 month<br>follow-up:<br>Minocycline | 15 month<br>follow-up:<br>Placebo |
|----------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
| Subject group type               | Reporting group                       | Reporting group                   | Reporting group                       | Reporting group                   |
| Number of subjects analysed      | 63                                    | 65                                | 41                                    | 48                                |
| Units: PANSS score               |                                       |                                   |                                       |                                   |
| arithmetic mean (standard error) | 13.4 (± 6.1)                          | 14.0 (± 4.8)                      | 13.2 (± 5.3)                          | 13.8 (± 5.2)                      |

## Statistical analyses

|                            |                                                |
|----------------------------|------------------------------------------------|
| Statistical analysis title | Summary of best estimates of treatment effects |
|----------------------------|------------------------------------------------|

Statistical analysis description:

Across all follow-up time points

|                   |                                                                                                                                                                                                                                                                                                                                                                     |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Comparison groups | Baseline: Placebo v Baseline: Minocycline v 2 month follow-up: Minocycline v 2 month follow-up: Placebo v 6 month follow-up: Minocycline v 6 month follow-up: Placebo v 9 month follow-up: Minocycline v 9 month follow-up: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo v 15 month follow-up: Minocycline v 15 month follow-up: Placebo |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 860                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.68                         |
| Method                                  | t-test, 2-sided                |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.19                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -1.12                          |
| upper limit                             | 0.73                           |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.47                           |

### Secondary: Total Symptoms PANSS

|                                 |                      |
|---------------------------------|----------------------|
| End point title                 | Total Symptoms PANSS |
| End point description:          |                      |
| End point type                  | Secondary            |
| End point timeframe:            |                      |
| across all follow-up timepoints |                      |

| End point values                     | Baseline:<br>Minocycline | Baseline:<br>Placebo | 2 month<br>follow-up:<br>Minocycline | 2 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------|----------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group          | Reporting group      | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 103                      | 103                  | 83                                   | 85                               |
| Units: PANSS score                   |                          |                      |                                      |                                  |
| arithmetic mean (standard deviation) | 67.1 (± 13.2)            | 69.3 (± 15.4)        | 59.6 (± 14.9)                        | 60.1 (± 15.7)                    |

| End point values                     | 6 month<br>follow-up:<br>Minocycline | 6 month<br>follow-up:<br>Placebo | 9 month<br>follow-up:<br>Minocycline | 9 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------------------|----------------------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group                      | Reporting group                  | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 69                                   | 66                               | 68                                   | 62                               |
| Units: PANSS score                   |                                      |                                  |                                      |                                  |
| arithmetic mean (standard deviation) | 57.5 (± 15.7)                        | 59.4 (± 16.8)                    | 57.0 (± 14.7)                        | 56.8 (± 14.7)                    |

| End point values | 12 month<br>follow-up:<br>Minocycline | 12 month<br>follow-up:<br>Placebo | 15 month<br>follow-up:<br>Minocycline | 15 month<br>follow-up:<br>Placebo |
|------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
|------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|



|                                      |                    |                    |                    |                    |
|--------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type                   | Reporting group    | Reporting group    | Reporting group    | Reporting group    |
| Number of subjects analysed          | 62                 | 65                 | 41                 | 48                 |
| Units: PANSS score                   |                    |                    |                    |                    |
| arithmetic mean (standard deviation) | 59.0 ( $\pm$ 17.3) | 57.1 ( $\pm$ 17.3) | 57.7 ( $\pm$ 16.5) | 55.8 ( $\pm$ 15.4) |

## Statistical analyses

|                                                                      |                                                                                                                                                                                                                                                                                                                                                                     |
|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                    | Summary of best estimates of treatment effects                                                                                                                                                                                                                                                                                                                      |
| Statistical analysis description:<br>Across all follow-up timepoints |                                                                                                                                                                                                                                                                                                                                                                     |
| Comparison groups                                                    | Baseline: Minocycline v Baseline: Placebo v 2 month follow-up: Minocycline v 2 month follow-up: Placebo v 6 month follow-up: Minocycline v 6 month follow-up: Placebo v 9 month follow-up: Minocycline v 9 month follow-up: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo v 15 month follow-up: Minocycline v 15 month follow-up: Placebo |
| Number of subjects included in analysis                              | 855                                                                                                                                                                                                                                                                                                                                                                 |
| Analysis specification                                               | Pre-specified                                                                                                                                                                                                                                                                                                                                                       |
| Analysis type                                                        | superiority                                                                                                                                                                                                                                                                                                                                                         |
| P-value                                                              | = 0.72                                                                                                                                                                                                                                                                                                                                                              |
| Method                                                               | t-test, 2-sided                                                                                                                                                                                                                                                                                                                                                     |
| Parameter estimate                                                   | Mean difference (final values)                                                                                                                                                                                                                                                                                                                                      |
| Point estimate                                                       | -0.58                                                                                                                                                                                                                                                                                                                                                               |
| Confidence interval                                                  |                                                                                                                                                                                                                                                                                                                                                                     |
| level                                                                | 95 %                                                                                                                                                                                                                                                                                                                                                                |
| sides                                                                | 2-sided                                                                                                                                                                                                                                                                                                                                                             |
| lower limit                                                          | -3.75                                                                                                                                                                                                                                                                                                                                                               |
| upper limit                                                          | 2.53                                                                                                                                                                                                                                                                                                                                                                |
| Variability estimate                                                 | Standard error of the mean                                                                                                                                                                                                                                                                                                                                          |
| Dispersion value                                                     | 1.62                                                                                                                                                                                                                                                                                                                                                                |

## Secondary: CDSS score

|                                                         |            |
|---------------------------------------------------------|------------|
| End point title                                         | CDSS score |
| End point description:                                  |            |
| End point type                                          | Secondary  |
| End point timeframe:<br>Across all follow-up timepoints |            |

| End point values                 | Baseline:<br>Minocycline | Baseline:<br>Placebo | 2 month<br>follow-up:<br>Minocycline | 2 month<br>follow-up:<br>Placebo |
|----------------------------------|--------------------------|----------------------|--------------------------------------|----------------------------------|
| Subject group type               | Reporting group          | Reporting group      | Reporting group                      | Reporting group                  |
| Number of subjects analysed      | 102                      | 100                  | 84                                   | 85                               |
| Units: CDSS score                |                          |                      |                                      |                                  |
| arithmetic mean (standard error) | 5.17 (± 4.27)            | 5.5 (± 4.96)         | 3.31 (± 3.85)                        | 3.40 (± 3.99)                    |

| End point values                 | 6 month<br>follow-up:<br>Minocycline | 6 month<br>follow-up:<br>Placebo | 9 month<br>follow-up:<br>Minocycline | 9 month<br>follow-up:<br>Placebo |
|----------------------------------|--------------------------------------|----------------------------------|--------------------------------------|----------------------------------|
| Subject group type               | Reporting group                      | Reporting group                  | Reporting group                      | Reporting group                  |
| Number of subjects analysed      | 68                                   | 67                               | 68                                   | 63                               |
| Units: CDSS score                |                                      |                                  |                                      |                                  |
| arithmetic mean (standard error) | 2.6 (± 3.59)                         | 3.05 (± 4.17)                    | 3.25 (± 3.78)                        | 2.73 (± 3.77)                    |

| End point values                 | 12 month<br>follow-up:<br>Minocycline | 12 month<br>follow-up:<br>Placebo | 15 month<br>follow-up:<br>Minocycline | 15 month<br>follow-up:<br>Placebo |
|----------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
| Subject group type               | Reporting group                       | Reporting group                   | Reporting group                       | Reporting group                   |
| Number of subjects analysed      | 62                                    | 63                                | 41                                    | 48                                |
| Units: CDSS score                |                                       |                                   |                                       |                                   |
| arithmetic mean (standard error) | 3.09 (± 3.98)                         | 3.12 (± 4.28)                     | 2.49 (± 3.53)                         | 2.88 (± 4.43)                     |

## Statistical analyses

| Statistical analysis title                                           | Summary of best estimates of treatment effects                                                                                                                                                                                                                                                                                                                      |
|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Statistical analysis description:<br>Across all follow-up timepoints |                                                                                                                                                                                                                                                                                                                                                                     |
| Comparison groups                                                    | Baseline: Minocycline v Baseline: Placebo v 2 month follow-up: Minocycline v 2 month follow-up: Placebo v 6 month follow-up: Minocycline v 6 month follow-up: Placebo v 9 month follow-up: Minocycline v 9 month follow-up: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo v 15 month follow-up: Minocycline v 15 month follow-up: Placebo |
| Number of subjects included in analysis                              | 851                                                                                                                                                                                                                                                                                                                                                                 |
| Analysis specification                                               | Pre-specified                                                                                                                                                                                                                                                                                                                                                       |
| Analysis type                                                        | superiority                                                                                                                                                                                                                                                                                                                                                         |
| P-value                                                              | = 0.88                                                                                                                                                                                                                                                                                                                                                              |
| Method                                                               | t-test, 2-sided                                                                                                                                                                                                                                                                                                                                                     |
| Parameter estimate                                                   | Mean difference (final values)                                                                                                                                                                                                                                                                                                                                      |
| Point estimate                                                       | -0.06                                                                                                                                                                                                                                                                                                                                                               |
| Confidence interval                                                  |                                                                                                                                                                                                                                                                                                                                                                     |
| level                                                                | 95 %                                                                                                                                                                                                                                                                                                                                                                |
| sides                                                                | 2-sided                                                                                                                                                                                                                                                                                                                                                             |
| lower limit                                                          | -0.84                                                                                                                                                                                                                                                                                                                                                               |
| upper limit                                                          | 0.72                                                                                                                                                                                                                                                                                                                                                                |

|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.4                        |

### Secondary: GAF score

|                                 |           |
|---------------------------------|-----------|
| End point title                 | GAF score |
| End point description:          |           |
| End point type                  | Secondary |
| End point timeframe:            |           |
| across all follow-up timepoints |           |

| End point values                 | Baseline:<br>Minocycline | Baseline:<br>Placebo | 2 month<br>follow-up:<br>Minocycline | 2 month<br>follow-up:<br>Placebo |
|----------------------------------|--------------------------|----------------------|--------------------------------------|----------------------------------|
| Subject group type               | Reporting group          | Reporting group      | Reporting group                      | Reporting group                  |
| Number of subjects analysed      | 102                      | 103                  | 83                                   | 85                               |
| Units: GAF score                 |                          |                      |                                      |                                  |
| arithmetic mean (standard error) | 55.5 (± 9.1)             | 56.2 (± 11.6)        | 58.1 (± 11.6)                        | 59.5 (± 11.4)                    |

| End point values                 | 6 month<br>follow-up:<br>Minocycline | 6 month<br>follow-up:<br>Placebo | 9 month<br>follow-up:<br>Minocycline | 9 month<br>follow-up:<br>Placebo |
|----------------------------------|--------------------------------------|----------------------------------|--------------------------------------|----------------------------------|
| Subject group type               | Reporting group                      | Reporting group                  | Reporting group                      | Reporting group                  |
| Number of subjects analysed      | 68                                   | 65                               | 67                                   | 63                               |
| Units: GAF score                 |                                      |                                  |                                      |                                  |
| arithmetic mean (standard error) | 60.2 (± 13.2)                        | 59.6 (± 12.1)                    | 58.5 (± 12.7)                        | 60.8 (± 12.0)                    |

| End point values                 | 12 month<br>follow-up:<br>Minocycline | 12 month<br>follow-up:<br>Placebo | 15 month<br>follow-up:<br>Minocycline | 15 month<br>follow-up:<br>Placebo |
|----------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
| Subject group type               | Reporting group                       | Reporting group                   | Reporting group                       | Reporting group                   |
| Number of subjects analysed      | 60                                    | 64                                | 41                                    | 47                                |
| Units: GAF score                 |                                       |                                   |                                       |                                   |
| arithmetic mean (standard error) | 56.3 (± 14.1)                         | 60.4 (± 13.4)                     | 56.5 (± 13.6)                         | 61.7 (± 13.0)                     |

### Statistical analyses

|                                   |                                                |
|-----------------------------------|------------------------------------------------|
| Statistical analysis title        | Summary of best estimates of treatment effects |
| Statistical analysis description: |                                                |
| Across all follow-up timepoints   |                                                |

|                                         |                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Comparison groups                       | Baseline: Minocycline v Baseline: Placebo v 2 month follow-up: Minocycline v 2 month follow-up: Placebo v 6 month follow-up: Minocycline v 6 month follow-up: Placebo v 9 month follow-up: Minocycline v 9 month follow-up: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo v 15 month follow-up: Minocycline v 15 month follow-up: Placebo |
| Number of subjects included in analysis | 848                                                                                                                                                                                                                                                                                                                                                                 |
| Analysis specification                  | Pre-specified                                                                                                                                                                                                                                                                                                                                                       |
| Analysis type                           | superiority                                                                                                                                                                                                                                                                                                                                                         |
| P-value                                 | = 0.21                                                                                                                                                                                                                                                                                                                                                              |
| Method                                  | t-test, 2-sided                                                                                                                                                                                                                                                                                                                                                     |
| Parameter estimate                      | Mean difference (final values)                                                                                                                                                                                                                                                                                                                                      |
| Point estimate                          | 2.71                                                                                                                                                                                                                                                                                                                                                                |
| Confidence interval                     |                                                                                                                                                                                                                                                                                                                                                                     |
| level                                   | 95 %                                                                                                                                                                                                                                                                                                                                                                |
| sides                                   | 2-sided                                                                                                                                                                                                                                                                                                                                                             |
| lower limit                             | -1.57                                                                                                                                                                                                                                                                                                                                                               |
| upper limit                             | 6.98                                                                                                                                                                                                                                                                                                                                                                |
| Variability estimate                    | Standard error of the mean                                                                                                                                                                                                                                                                                                                                          |
| Dispersion value                        | 2.15                                                                                                                                                                                                                                                                                                                                                                |

## Secondary: SFS withdrawal

|                                 |                |
|---------------------------------|----------------|
| End point title                 | SFS withdrawal |
| End point description:          |                |
| End point type                  | Secondary      |
| End point timeframe:            |                |
| across all follow-up timepoints |                |

| End point values                     | Baseline: Minocycline | Baseline: Placebo | 2 month follow-up: Minocycline | 2 month follow-up: Placebo |
|--------------------------------------|-----------------------|-------------------|--------------------------------|----------------------------|
| Subject group type                   | Reporting group       | Reporting group   | Reporting group                | Reporting group            |
| Number of subjects analysed          | 103                   | 101               | 0 <sup>[29]</sup>              | 0 <sup>[30]</sup>          |
| Units: Find out                      |                       |                   |                                |                            |
| arithmetic mean (standard deviation) | 10.5 (± 3.1)          | 10.2 (± 2.9)      | ()                             | ()                         |

Notes:

[29] - Measure not captured at this time point

[30] - Measure not captured at this time point

| End point values                     | 6 month follow-up: Minocycline | 6 month follow-up: Placebo | 9 month follow-up: Minocycline | 9 month follow-up: Placebo |
|--------------------------------------|--------------------------------|----------------------------|--------------------------------|----------------------------|
| Subject group type                   | Reporting group                | Reporting group            | Reporting group                | Reporting group            |
| Number of subjects analysed          | 65                             | 65                         | 0 <sup>[31]</sup>              | 0 <sup>[32]</sup>          |
| Units: Find out                      |                                |                            |                                |                            |
| arithmetic mean (standard deviation) | 11.0 (± 3.2)                   | 11.0 (± 3.2)               | ()                             | ()                         |

Notes:

[31] - Measure not captured at this time point

[32] - Measure not captured at this time point

| <b>End point values</b>              | 12 month follow-up: Minocycline | 12 month follow-up: Placebo | 15 month follow-up: Minocycline | 15 month follow-up: Placebo |
|--------------------------------------|---------------------------------|-----------------------------|---------------------------------|-----------------------------|
| Subject group type                   | Reporting group                 | Reporting group             | Reporting group                 | Reporting group             |
| Number of subjects analysed          | 61                              | 63                          | 41                              | 48                          |
| Units: Find out                      |                                 |                             |                                 |                             |
| arithmetic mean (standard deviation) | 10.7 (± 3.7)                    | 10.9 (± 3.4)                | 10.6 (± 3.2)                    | 11.5 (± 3.5)                |

## Statistical analyses

|                                         |                                                                                                           |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | best estimates of treatment effects                                                                       |
| Comparison groups                       | Baseline: Placebo v 15 month follow-up: Minocycline v 15 month follow-up: Placebo v Baseline: Minocycline |
| Number of subjects included in analysis | 293                                                                                                       |
| Analysis specification                  | Pre-specified                                                                                             |
| Analysis type                           | superiority                                                                                               |
| P-value                                 | = 0.55                                                                                                    |
| Method                                  | t-test, 2-sided                                                                                           |
| Parameter estimate                      | Mean difference (final values)                                                                            |
| Point estimate                          | -0.24                                                                                                     |
| Confidence interval                     |                                                                                                           |
| level                                   | 95 %                                                                                                      |
| sides                                   | 2-sided                                                                                                   |
| lower limit                             | -1.57                                                                                                     |
| upper limit                             | 6.98                                                                                                      |
| Variability estimate                    | Standard error of the mean                                                                                |
| Dispersion value                        | 2.15                                                                                                      |

## Secondary: SFS relations

|                                 |               |
|---------------------------------|---------------|
| End point title                 | SFS relations |
| End point description:          |               |
| End point type                  | Secondary     |
| End point timeframe:            |               |
| across all follow-up timepoints |               |

| End point values                     | Baseline:<br>Minocycline | Baseline:<br>Placebo | 2 month<br>follow-up:<br>Minocycline | 2 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------|----------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group          | Reporting group      | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 103                      | 102                  | 0 <sup>[33]</sup>                    | 0 <sup>[34]</sup>                |
| Units: Find out                      |                          |                      |                                      |                                  |
| arithmetic mean (standard deviation) | 6.4 (± 8.1)              | 6.6 (± 1.9)          | ()                                   | ()                               |

Notes:

[33] - Measure not captured at this time point

[34] - Measure not captured at this time point

| End point values                     | 6 month<br>follow-up:<br>Minocycline | 6 month<br>follow-up:<br>Placebo | 9 month<br>follow-up:<br>Minocycline | 9 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------------------|----------------------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group                      | Reporting group                  | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 65                                   | 65                               | 0 <sup>[35]</sup>                    | 0 <sup>[36]</sup>                |
| Units: Find out                      |                                      |                                  |                                      |                                  |
| arithmetic mean (standard deviation) | 6.8 (± 2.0)                          | 7.2 (± 2.0)                      | ()                                   | ()                               |

Notes:

[35] - Measure not captured at this time point

[36] - Measure not captured at this time point

| End point values                     | 12 month<br>follow-up:<br>Minocycline | 12 month<br>follow-up:<br>Placebo | 15 month<br>follow-up:<br>Minocycline | 15 month<br>follow-up:<br>Placebo |
|--------------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
| Subject group type                   | Reporting group                       | Reporting group                   | Reporting group                       | Reporting group                   |
| Number of subjects analysed          | 61                                    | 63                                | 41                                    | 48                                |
| Units: Find out                      |                                       |                                   |                                       |                                   |
| arithmetic mean (standard deviation) | 6.6 (± 2.2)                           | 7.1 (± 2.0)                       | 6.9 (± 2.1)                           | 7.1 (± 2.0)                       |

## Statistical analyses

|                                         |                                                                                                                                                                                                                                         |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Statistical analysis title              | best estimates of treatment effects                                                                                                                                                                                                     |
| Comparison groups                       | Baseline: Minocycline v Baseline: Placebo v 6 month follow-up: Minocycline v 6 month follow-up: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo v 15 month follow-up: Minocycline v 15 month follow-up: Placebo |
| Number of subjects included in analysis | 548                                                                                                                                                                                                                                     |
| Analysis specification                  | Pre-specified                                                                                                                                                                                                                           |
| Analysis type                           | superiority                                                                                                                                                                                                                             |
| P-value                                 | = 0.94                                                                                                                                                                                                                                  |
| Method                                  | t-test, 2-sided                                                                                                                                                                                                                         |
| Parameter estimate                      | Mean difference (final values)                                                                                                                                                                                                          |
| Point estimate                          | -0.02                                                                                                                                                                                                                                   |
| Confidence interval                     |                                                                                                                                                                                                                                         |
| level                                   | 95 %                                                                                                                                                                                                                                    |
| sides                                   | 2-sided                                                                                                                                                                                                                                 |
| lower limit                             | -0.55                                                                                                                                                                                                                                   |
| upper limit                             | 0.51                                                                                                                                                                                                                                    |
| Variability estimate                    | Standard error of the mean                                                                                                                                                                                                              |
| Dispersion value                        | 0.27                                                                                                                                                                                                                                    |

## Secondary: SFS independence-performance

|                 |                              |
|-----------------|------------------------------|
| End point title | SFS independence-performance |
|-----------------|------------------------------|

|                        |
|------------------------|
| End point description: |
|------------------------|

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

|                      |
|----------------------|
| End point timeframe: |
|----------------------|

|                                 |
|---------------------------------|
| across all follow-up timepoints |
|---------------------------------|

| End point values                     | Baseline:<br>Minocycline | Baseline:<br>Placebo | 2 month<br>follow-up:<br>Minocycline | 2 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------|----------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group          | Reporting group      | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 103                      | 101                  | 0 <sup>[37]</sup>                    | 0 <sup>[38]</sup>                |
| Units: find out                      |                          |                      |                                      |                                  |
| arithmetic mean (standard deviation) | 26.3 (± 7.5)             | 26.1 (± 6.4)         | ()                                   | ()                               |

Notes:

[37] - Measure not captured at this time point

[38] - Measure not captured at this time point

| End point values                     | 6 month<br>follow-up:<br>Minocycline | 6 month<br>follow-up:<br>Placebo | 9 month<br>follow-up:<br>Minocycline | 9 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------------------|----------------------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group                      | Reporting group                  | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 65                                   | 65                               | 0 <sup>[39]</sup>                    | 0 <sup>[40]</sup>                |
| Units: find out                      |                                      |                                  |                                      |                                  |
| arithmetic mean (standard deviation) | 26.7 (± 8.2)                         | 27.4 (± 7.2)                     | ()                                   | ()                               |

Notes:

[39] - Measure not captured at this time point

[40] - Measure not captured at this time point

| End point values                     | 12 month<br>follow-up:<br>Minocycline | 12 month<br>follow-up:<br>Placebo | 15 month<br>follow-up:<br>Minocycline | 15 month<br>follow-up:<br>Placebo |
|--------------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
| Subject group type                   | Reporting group                       | Reporting group                   | Reporting group                       | Reporting group                   |
| Number of subjects analysed          | 61                                    | 63                                | 41                                    | 48                                |
| Units: find out                      |                                       |                                   |                                       |                                   |
| arithmetic mean (standard deviation) | 26.3 (± 6.8)                          | 27.4 (± 7.0)                      | 26.0 (± 7.4)                          | 26.6 (± 6.8)                      |

## Statistical analyses

|                            |                                     |
|----------------------------|-------------------------------------|
| Statistical analysis title | best estimates of treatment effects |
|----------------------------|-------------------------------------|

|                   |                                                                                                                                                                                                                                         |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Comparison groups | Baseline: Minocycline v Baseline: Placebo v 6 month follow-up: Minocycline v 6 month follow-up: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo v 15 month follow-up: Minocycline v 15 month follow-up: Placebo |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 547                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.38                         |
| Method                                  | t-test, 2-sided                |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -0.78                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -2.53                          |
| upper limit                             | 0.97                           |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.89                           |

### Secondary: SFS Recreation

|                                 |                |
|---------------------------------|----------------|
| End point title                 | SFS Recreation |
| End point description:          |                |
| End point type                  | Secondary      |
| End point timeframe:            |                |
| across all follow-up timepoints |                |

| End point values                     | Baseline:<br>Minocycline | Baseline:<br>Placebo | 2 month<br>follow-up:<br>Minocycline | 2 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------|----------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group          | Reporting group      | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 103                      | 102                  | 0 <sup>[41]</sup>                    | 0 <sup>[42]</sup>                |
| Units: find out                      |                          |                      |                                      |                                  |
| arithmetic mean (standard deviation) | 18.2 (± 7.8)             | 17.7 (± 6.02)        | ()                                   | ()                               |

Notes:

[41] - Measure not captured at this time point

[42] - Measure not captured at this time point

| End point values                     | 6 month<br>follow-up:<br>Minocycline | 6 month<br>follow-up:<br>Placebo | 9 month<br>follow-up:<br>Minocycline | 9 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------------------|----------------------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group                      | Reporting group                  | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 65                                   | 65                               | 0 <sup>[43]</sup>                    | 0 <sup>[44]</sup>                |
| Units: find out                      |                                      |                                  |                                      |                                  |
| arithmetic mean (standard deviation) | 17.6 (± 7.3)                         | 18.4 (± 7.8)                     | ()                                   | ()                               |

Notes:

[43] - Measure not captured at this time point

[44] - Measure not captured at this time point

| End point values | 12 month<br>follow-up:<br>Minocycline | 12 month<br>follow-up:<br>Placebo | 15 month<br>follow-up:<br>Minocycline | 15 month<br>follow-up:<br>Placebo |
|------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
|------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|



|                                      |                 |                 |                 |                 |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed          | 61              | 63              | 41              | 48              |
| Units: find out                      |                 |                 |                 |                 |
| arithmetic mean (standard deviation) | 17.4 (± 7.1)    | 18.4 (± 7.0)    | 17.4 (± 7.6)    | 17.1 (± 6.8)    |

## Statistical analyses

|                                         |                                                                                                                                                                                                                                         |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | best estimates of treatment effects                                                                                                                                                                                                     |
| Comparison groups                       | 15 month follow-up: Minocycline v 15 month follow-up: Placebo v Baseline: Minocycline v Baseline: Placebo v 6 month follow-up: Minocycline v 6 month follow-up: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo |
| Number of subjects included in analysis | 548                                                                                                                                                                                                                                     |
| Analysis specification                  | Pre-specified                                                                                                                                                                                                                           |
| Analysis type                           | superiority                                                                                                                                                                                                                             |
| P-value                                 | = 0.3                                                                                                                                                                                                                                   |
| Method                                  | t-test, 2-sided                                                                                                                                                                                                                         |
| Parameter estimate                      | Mean difference (final values)                                                                                                                                                                                                          |
| Point estimate                          | -0.91                                                                                                                                                                                                                                   |
| Confidence interval                     |                                                                                                                                                                                                                                         |
| level                                   | 95 %                                                                                                                                                                                                                                    |
| sides                                   | 2-sided                                                                                                                                                                                                                                 |
| lower limit                             | -2.65                                                                                                                                                                                                                                   |
| upper limit                             | 0.82                                                                                                                                                                                                                                    |
| Variability estimate                    | Standard error of the mean                                                                                                                                                                                                              |
| Dispersion value                        | 0.89                                                                                                                                                                                                                                    |

## Secondary: SFS Prosocial-activities

|                                 |                          |
|---------------------------------|--------------------------|
| End point title                 | SFS Prosocial-activities |
| End point description:          |                          |
| End point type                  | Secondary                |
| End point timeframe:            |                          |
| across all follow-up timepoints |                          |

| End point values                     | Baseline: Minocycline | Baseline: Placebo | 2 month follow-up: Minocycline | 2 month follow-up: Placebo |
|--------------------------------------|-----------------------|-------------------|--------------------------------|----------------------------|
| Subject group type                   | Reporting group       | Reporting group   | Reporting group                | Reporting group            |
| Number of subjects analysed          | 103                   | 102               | 0 <sup>[45]</sup>              | 0 <sup>[46]</sup>          |
| Units: find out                      |                       |                   |                                |                            |
| arithmetic mean (standard deviation) | 16.6 (± 10.3)         | 16.7 (± 10.5)     | ()                             | ()                         |

Notes:

[45] - Measure not captured at this time point

[46] - Measure not captured at this time point

| <b>End point values</b>              | 6 month follow-up: Minocycline | 6 month follow-up: Placebo | 9 month follow-up: Minocycline | 9 month follow-up: Placebo |
|--------------------------------------|--------------------------------|----------------------------|--------------------------------|----------------------------|
| Subject group type                   | Reporting group                | Reporting group            | Reporting group                | Reporting group            |
| Number of subjects analysed          | 65                             | 65                         | 0 <sup>[47]</sup>              | 0 <sup>[48]</sup>          |
| Units: find out                      |                                |                            |                                |                            |
| arithmetic mean (standard deviation) | 16.3 (± 9.6)                   | 17.3 (± 11.6)              | ()                             | ()                         |

Notes:

[47] - Measure not captured at this time point

[48] - Measure not captured at this time point

| <b>End point values</b>              | 12 month follow-up: Minocycline | 12 month follow-up: Placebo | 15 month follow-up: Minocycline | 15 month follow-up: Placebo |
|--------------------------------------|---------------------------------|-----------------------------|---------------------------------|-----------------------------|
| Subject group type                   | Reporting group                 | Reporting group             | Reporting group                 | Reporting group             |
| Number of subjects analysed          | 61                              | 63                          | 41                              | 48                          |
| Units: find out                      |                                 |                             |                                 |                             |
| arithmetic mean (standard deviation) | 16.5 (± 10.1)                   | 17.2 (± 10.8)               | 15.9 (± 10.0)                   | 18.9 (± 11.5)               |

## Statistical analyses

|                                         |                                                                                                                                                                                                                                         |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | best estimates of treatment effects                                                                                                                                                                                                     |
| Comparison groups                       | Baseline: Minocycline v 15 month follow-up: Minocycline v 15 month follow-up: Placebo v Baseline: Placebo v 6 month follow-up: Minocycline v 6 month follow-up: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo |
| Number of subjects included in analysis | 548                                                                                                                                                                                                                                     |
| Analysis specification                  | Pre-specified                                                                                                                                                                                                                           |
| Analysis type                           | superiority                                                                                                                                                                                                                             |
| P-value                                 | = 0.88                                                                                                                                                                                                                                  |
| Method                                  | t-test, 2-sided                                                                                                                                                                                                                         |
| Parameter estimate                      | Mean difference (final values)                                                                                                                                                                                                          |
| Point estimate                          | 0.19                                                                                                                                                                                                                                    |
| Confidence interval                     |                                                                                                                                                                                                                                         |
| level                                   | 95 %                                                                                                                                                                                                                                    |
| sides                                   | 2-sided                                                                                                                                                                                                                                 |
| lower limit                             | -2.25                                                                                                                                                                                                                                   |
| upper limit                             | 2.62                                                                                                                                                                                                                                    |
| Variability estimate                    | Standard error of the mean                                                                                                                                                                                                              |
| Dispersion value                        | 1.24                                                                                                                                                                                                                                    |

## Secondary: SFS independence-competence

|                        |                             |
|------------------------|-----------------------------|
| End point title        | SFS independence-competence |
| End point description: |                             |

|                                                         |           |
|---------------------------------------------------------|-----------|
| End point type                                          | Secondary |
| End point timeframe:<br>across all follow-up timepoints |           |

| End point values                     | Baseline:<br>Minocycline | Baseline:<br>Placebo | 2 month<br>follow-up:<br>Minocycline | 2 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------|----------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group          | Reporting group      | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 103                      | 102                  | 0 <sup>[49]</sup>                    | 0 <sup>[50]</sup>                |
| Units: find out                      |                          |                      |                                      |                                  |
| arithmetic mean (standard deviation) | 34.8 (± 4.9)             | 34.0 (± 6.2)         | ()                                   | ()                               |

Notes:

[49] - Measure not captured at this time point

[50] - Measure not captured at this time point

| End point values                     | 6 month<br>follow-up:<br>Minocycline | 6 month<br>follow-up:<br>Placebo | 9 month<br>follow-up:<br>Minocycline | 9 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------------------|----------------------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group                      | Reporting group                  | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 65                                   | 65                               | 0 <sup>[51]</sup>                    | 0 <sup>[52]</sup>                |
| Units: find out                      |                                      |                                  |                                      |                                  |
| arithmetic mean (standard deviation) | 34.7 (± 5.4)                         | 35.0 (± 4.8)                     | ()                                   | ()                               |

Notes:

[51] - Measure not captured at this time point

[52] - Measure not captured at this time point

| End point values                     | 12 month<br>follow-up:<br>Minocycline | 12 month<br>follow-up:<br>Placebo | 15 month<br>follow-up:<br>Minocycline | 15 month<br>follow-up:<br>Placebo |
|--------------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
| Subject group type                   | Reporting group                       | Reporting group                   | Reporting group                       | Reporting group                   |
| Number of subjects analysed          | 61                                    | 63                                | 41                                    | 48                                |
| Units: find out                      |                                       |                                   |                                       |                                   |
| arithmetic mean (standard deviation) | 34.0 (± 5.1)                          | 34.8 (± 5.0)                      | 34.0 (± 7.1)                          | 35.5 (± 3.9)                      |

## Statistical analyses

|                                         |                                                                                                                                                                                                                                         |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | best estimates of treatment effects                                                                                                                                                                                                     |
| Comparison groups                       | Baseline: Minocycline v Baseline: Placebo v 15 month follow-up: Minocycline v 15 month follow-up: Placebo v 6 month follow-up: Minocycline v 6 month follow-up: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo |
| Number of subjects included in analysis | 548                                                                                                                                                                                                                                     |
| Analysis specification                  | Pre-specified                                                                                                                                                                                                                           |
| Analysis type                           | superiority                                                                                                                                                                                                                             |
| P-value                                 | = 0.46                                                                                                                                                                                                                                  |
| Method                                  | t-test, 2-sided                                                                                                                                                                                                                         |
| Parameter estimate                      | Mean difference (final values)                                                                                                                                                                                                          |
| Point estimate                          | -0.49                                                                                                                                                                                                                                   |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -1.79                      |
| upper limit          | 0.81                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.67                       |

## Secondary: SFS employment

|                                 |                |
|---------------------------------|----------------|
| End point title                 | SFS employment |
| End point description:          |                |
|                                 |                |
| End point type                  | Secondary      |
| End point timeframe:            |                |
| across all follow-up timepoints |                |

| End point values                     | Baseline:<br>Minocycline | Baseline:<br>Placebo | 2 month<br>follow-up:<br>Minocycline | 2 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------|----------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group          | Reporting group      | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 103                      | 102                  | 0 <sup>[53]</sup>                    | 0 <sup>[54]</sup>                |
| Units: find out                      |                          |                      |                                      |                                  |
| arithmetic mean (standard deviation) | 4.7 (± 3.1)              | 4.9 (± 3.0)          | ()                                   | ()                               |

Notes:

[53] - Measure not captured at this time point

[54] - Measure not captured at this time point

| End point values                     | 6 month<br>follow-up:<br>Minocycline | 6 month<br>follow-up:<br>Placebo | 9 month<br>follow-up:<br>Minocycline | 9 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------------------|----------------------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group                      | Reporting group                  | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 64                                   | 65                               | 0 <sup>[55]</sup>                    | 0 <sup>[56]</sup>                |
| Units: find out                      |                                      |                                  |                                      |                                  |
| arithmetic mean (standard deviation) | 4.9 (± 3.3)                          | 5.6 (± 3.4)                      | ()                                   | ()                               |

Notes:

[55] - Measure not captured at this time point

[56] - Measure not captured at this time point

| End point values                     | 12 month<br>follow-up:<br>Minocycline | 12 month<br>follow-up:<br>Placebo | 15 month<br>follow-up:<br>Minocycline | 15 month<br>follow-up:<br>Placebo |
|--------------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
| Subject group type                   | Reporting group                       | Reporting group                   | Reporting group                       | Reporting group                   |
| Number of subjects analysed          | 61                                    | 63                                | 41                                    | 47                                |
| Units: find out                      |                                       |                                   |                                       |                                   |
| arithmetic mean (standard deviation) | 5.3 (± 3.3)                           | 5.9 (± 3.1)                       | 5.4 (± 3.7)                           | 5.3 (± 3.3)                       |

## Statistical analyses

|                                         |                                                                                                                                                                                                                                         |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | best estimates of treatment effects                                                                                                                                                                                                     |
| Comparison groups                       | Baseline: Minocycline v Baseline: Placebo v 15 month follow-up: Minocycline v 15 month follow-up: Placebo v 6 month follow-up: Minocycline v 6 month follow-up: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo |
| Number of subjects included in analysis | 546                                                                                                                                                                                                                                     |
| Analysis specification                  | Pre-specified                                                                                                                                                                                                                           |
| Analysis type                           | superiority                                                                                                                                                                                                                             |
| P-value                                 | = 0.78                                                                                                                                                                                                                                  |
| Method                                  | t-test, 2-sided                                                                                                                                                                                                                         |
| Parameter estimate                      | Mean difference (final values)                                                                                                                                                                                                          |
| Point estimate                          | -0.12                                                                                                                                                                                                                                   |
| Confidence interval                     |                                                                                                                                                                                                                                         |
| level                                   | 95 %                                                                                                                                                                                                                                    |
| sides                                   | 2-sided                                                                                                                                                                                                                                 |
| lower limit                             | -0.95                                                                                                                                                                                                                                   |
| upper limit                             | 0.71                                                                                                                                                                                                                                    |
| Variability estimate                    | Standard error of the mean                                                                                                                                                                                                              |
| Dispersion value                        | 0.43                                                                                                                                                                                                                                    |

## Secondary: Processing speed

|                                 |                  |
|---------------------------------|------------------|
| End point title                 | Processing speed |
| End point description:          |                  |
| End point type                  | Secondary        |
| End point timeframe:            |                  |
| across all follow-up timepoints |                  |

| <b>End point values</b>              | Baseline:<br>Minocycline | Baseline:<br>Placebo | 2 month<br>follow-up:<br>Minocycline | 2 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------|----------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group          | Reporting group      | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 95                       | 91                   | 0 <sup>[57]</sup>                    | 0 <sup>[58]</sup>                |
| Units: find out                      |                          |                      |                                      |                                  |
| arithmetic mean (standard deviation) | 58.0 (± 16.7)            | 52.8 (± 16.8)        | ()                                   | ()                               |

Notes:

[57] - Measure not captured at this time point

[58] - Measure not captured at this time point

| <b>End point values</b>              | 6 month<br>follow-up:<br>Minocycline | 6 month<br>follow-up:<br>Placebo | 9 month<br>follow-up:<br>Minocycline | 9 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------------------|----------------------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group                      | Reporting group                  | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 0 <sup>[59]</sup>                    | 0 <sup>[60]</sup>                | 0 <sup>[61]</sup>                    | 0 <sup>[62]</sup>                |
| Units: find out                      |                                      |                                  |                                      |                                  |
| arithmetic mean (standard deviation) | ()                                   | ()                               | ()                                   | ()                               |

Notes:

[59] - Measure not captured at this time point

[60] - Measure not captured at this time point

[61] - Measure not captured at this time point

[62] - Measure not captured at this time point

| End point values                     | 12 month follow-up: Minocycline | 12 month follow-up: Placebo | 15 month follow-up: Minocycline | 15 month follow-up: Placebo |
|--------------------------------------|---------------------------------|-----------------------------|---------------------------------|-----------------------------|
| Subject group type                   | Reporting group                 | Reporting group             | Reporting group                 | Reporting group             |
| Number of subjects analysed          | 58                              | 59                          | 36                              | 47                          |
| Units: find out                      |                                 |                             |                                 |                             |
| arithmetic mean (standard deviation) | 56.1 (± 16.2)                   | 58.2 (± 15.8)               | 62.6 (± 16.2)                   | 61.2 (± 15.9)               |

## Statistical analyses

|                                         |                                                                                                                                                                           |
|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Statistical analysis title              | best estimates of treatment effects                                                                                                                                       |
| Comparison groups                       | Baseline: Minocycline v Baseline: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo v 15 month follow-up: Minocycline v 15 month follow-up: Placebo |
| Number of subjects included in analysis | 386                                                                                                                                                                       |
| Analysis specification                  | Pre-specified                                                                                                                                                             |
| Analysis type                           | superiority                                                                                                                                                               |
| P-value                                 | = 0.35                                                                                                                                                                    |
| Method                                  | t-test, 2-sided                                                                                                                                                           |
| Parameter estimate                      | Mean difference (final values)                                                                                                                                            |
| Point estimate                          | -2.14                                                                                                                                                                     |
| Confidence interval                     |                                                                                                                                                                           |
| level                                   | 95 %                                                                                                                                                                      |
| sides                                   | 2-sided                                                                                                                                                                   |
| lower limit                             | -6.63                                                                                                                                                                     |
| upper limit                             | 2.35                                                                                                                                                                      |
| Variability estimate                    | Standard error of the mean                                                                                                                                                |
| Dispersion value                        | 2.26                                                                                                                                                                      |

## Secondary: Weight

|                                 |           |
|---------------------------------|-----------|
| End point title                 | Weight    |
| End point description:          |           |
| End point type                  | Secondary |
| End point timeframe:            |           |
| across all follow-up timepoints |           |

| End point values                     | Baseline:<br>Minocycline | Baseline:<br>Placebo | 2 month<br>follow-up:<br>Minocycline | 2 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------|----------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group          | Reporting group      | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 97                       | 101                  | 0 <sup>[63]</sup>                    | 0 <sup>[64]</sup>                |
| Units: Kg                            |                          |                      |                                      |                                  |
| arithmetic mean (standard deviation) | 82.6 (± 19.6)            | 86.8 (± 25.3)        | ()                                   | ()                               |

Notes:

[63] - Measure not captured at this time point

[64] - Measure not captured at this time point

| End point values                     | 6 month<br>follow-up:<br>Minocycline | 6 month<br>follow-up:<br>Placebo | 9 month<br>follow-up:<br>Minocycline | 9 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------------------|----------------------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group                      | Reporting group                  | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 0 <sup>[65]</sup>                    | 0 <sup>[66]</sup>                | 0 <sup>[67]</sup>                    | 0 <sup>[68]</sup>                |
| Units: Kg                            |                                      |                                  |                                      |                                  |
| arithmetic mean (standard deviation) | ()                                   | ()                               | ()                                   | ()                               |

Notes:

[65] - Measure not captured at this time point

[66] - Measure not captured at this time point

[67] - Measure not captured at this time point

[68] - Measure not captured at this time point

| End point values                     | 12 month<br>follow-up:<br>Minocycline | 12 month<br>follow-up:<br>Placebo | 15 month<br>follow-up:<br>Minocycline | 15 month<br>follow-up:<br>Placebo |
|--------------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
| Subject group type                   | Reporting group                       | Reporting group                   | Reporting group                       | Reporting group                   |
| Number of subjects analysed          | 53                                    | 58                                | 0 <sup>[69]</sup>                     | 0 <sup>[70]</sup>                 |
| Units: Kg                            |                                       |                                   |                                       |                                   |
| arithmetic mean (standard deviation) | 88 (± 18.2)                           | 91.8 (± 28.5)                     | ()                                    | ()                                |

Notes:

[69] - Measure not captured at this time point

[70] - Measure not captured at this time point

## Statistical analyses

| Statistical analysis title              | best estimates of treatment effects                                                                       |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Comparison groups                       | Baseline: Minocycline v Baseline: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo |
| Number of subjects included in analysis | 309                                                                                                       |
| Analysis specification                  | Pre-specified                                                                                             |
| Analysis type                           | superiority                                                                                               |
| P-value                                 | = 0.21                                                                                                    |
| Method                                  | t-test, 2-sided                                                                                           |
| Parameter estimate                      | Mean difference (final values)                                                                            |
| Point estimate                          | 2.71                                                                                                      |
| Confidence interval                     |                                                                                                           |
| level                                   | 95 %                                                                                                      |
| sides                                   | 2-sided                                                                                                   |
| lower limit                             | -1.57                                                                                                     |
| upper limit                             | 6.98                                                                                                      |
| Variability estimate                    | Standard error of the mean                                                                                |
| Dispersion value                        | 2.15                                                                                                      |

**Other pre-specified: Current IQ**

|                 |            |
|-----------------|------------|
| End point title | Current IQ |
|-----------------|------------|

|                        |  |
|------------------------|--|
| End point description: |  |
|------------------------|--|

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

|                                 |  |
|---------------------------------|--|
| End point timeframe:            |  |
| across all follow-up timepoints |  |

| End point values                     | Baseline:<br>Minocycline | Baseline:<br>Placebo | 2 month<br>follow-up:<br>Minocycline | 2 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------|----------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group          | Reporting group      | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 101                      | 100                  | 0 <sup>[71]</sup>                    | 0 <sup>[72]</sup>                |
| Units: Score                         |                          |                      |                                      |                                  |
| arithmetic mean (standard deviation) | 91.2 (± 14.0)            | 89.2 (± 15.9)        | ()                                   | ()                               |

Notes:

[71] - Measure not captured at this time point

[72] - Measure not captured at this time point

| End point values                     | 6 month<br>follow-up:<br>Minocycline | 6 month<br>follow-up:<br>Placebo | 9 month<br>follow-up:<br>Minocycline | 9 month<br>follow-up:<br>Placebo |
|--------------------------------------|--------------------------------------|----------------------------------|--------------------------------------|----------------------------------|
| Subject group type                   | Reporting group                      | Reporting group                  | Reporting group                      | Reporting group                  |
| Number of subjects analysed          | 0 <sup>[73]</sup>                    | 0 <sup>[74]</sup>                | 0 <sup>[75]</sup>                    | 0 <sup>[76]</sup>                |
| Units: Score                         |                                      |                                  |                                      |                                  |
| arithmetic mean (standard deviation) | ()                                   | ()                               | ()                                   | ()                               |

Notes:

[73] - Measure not captured at this time point

[74] - Measure not captured at this time point

[75] - Measure not captured at this time point

[76] - Measure not captured at this time point

| End point values                     | 12 month<br>follow-up:<br>Minocycline | 12 month<br>follow-up:<br>Placebo | 15 month<br>follow-up:<br>Minocycline | 15 month<br>follow-up:<br>Placebo |
|--------------------------------------|---------------------------------------|-----------------------------------|---------------------------------------|-----------------------------------|
| Subject group type                   | Reporting group                       | Reporting group                   | Reporting group                       | Reporting group                   |
| Number of subjects analysed          | 59                                    | 61                                | 38                                    | 48                                |
| Units: Score                         |                                       |                                   |                                       |                                   |
| arithmetic mean (standard deviation) | 93.7 (± 14.2)                         | 94.6 (± 16.6)                     | 98.2 (± 16.1)                         | 97.0 (± 17.5)                     |

**Statistical analyses**

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| <b>Statistical analysis title</b> | best estimates of treatment effects |
|-----------------------------------|-------------------------------------|

|                   |                                                                                                                      |
|-------------------|----------------------------------------------------------------------------------------------------------------------|
| Comparison groups | Baseline: Minocycline v Baseline: Placebo v 12 month follow-up: Minocycline v 12 month follow-up: Placebo v 15 month |
|-------------------|----------------------------------------------------------------------------------------------------------------------|



|                                         |                                                      |
|-----------------------------------------|------------------------------------------------------|
|                                         | follow-up: Minocycline v 15 month follow-up: Placebo |
| Number of subjects included in analysis | 407                                                  |
| Analysis specification                  | Pre-specified                                        |
| Analysis type                           | superiority                                          |
| P-value                                 | = 0.72                                               |
| Method                                  | t-test, 2-sided                                      |
| Parameter estimate                      | Mean difference (final values)                       |
| Point estimate                          | -0.56                                                |
| Confidence interval                     |                                                      |
| level                                   | 95 %                                                 |
| sides                                   | 2-sided                                              |
| lower limit                             | -3.59                                                |
| upper limit                             | 2.47                                                 |
| Variability estimate                    | Standard error of the mean                           |
| Dispersion value                        | 1.53                                                 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Recorded from the randomisation visit to the month 3 non interventional post trial follow up visit.

Adverse event reporting additional description:

Standard variables collected: verbatim, start and end time/date, seriousness, causality, action regarding IMP, outcome.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Minocycline |
|-----------------------|-------------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events                            | Minocycline                                                                                                                                                                                                                                                                        | Placebo         |  |
|---------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|--|
| Total subjects affected by serious adverse events |                                                                                                                                                                                                                                                                                    |                 |  |
| subjects affected / exposed                       | 12 / 103 (11.65%)                                                                                                                                                                                                                                                                  | 7 / 104 (6.73%) |  |
| number of deaths (all causes)                     | 0                                                                                                                                                                                                                                                                                  | 0               |  |
| number of deaths resulting from adverse events    | 0                                                                                                                                                                                                                                                                                  | 0               |  |
| Blood and lymphatic system disorders              |                                                                                                                                                                                                                                                                                    |                 |  |
| DVT                                               |                                                                                                                                                                                                                                                                                    |                 |  |
| subjects affected / exposed                       | 0 / 103 (0.00%)                                                                                                                                                                                                                                                                    | 1 / 104 (0.96%) |  |
| occurrences causally related to treatment / all   | 0 / 0                                                                                                                                                                                                                                                                              | 0 / 1           |  |
| deaths causally related to treatment / all        | 0 / 0                                                                                                                                                                                                                                                                              | 0 / 0           |  |
| Gastrointestinal disorders                        |                                                                                                                                                                                                                                                                                    |                 |  |
| Abdominal pain                                    |                                                                                                                                                                                                                                                                                    |                 |  |
| subjects affected / exposed                       | 2 / 103 (1.94%)                                                                                                                                                                                                                                                                    | 0 / 104 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 3                                                                                                                                                                                                                                                                              | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0                                                                                                                                                                                                                                                                              | 0 / 0           |  |
| Psychiatric disorders                             |                                                                                                                                                                                                                                                                                    |                 |  |
| Hospitalisation                                   | Additional description: Psychiatric hospitalisations- admissions due to worsening of psychiatric illness, with a combination of intensification of psychosis, dysphoria, suicidal ideation and intent. Other factors contributing: poor meds adherence & substance/alcohol misuse. |                 |  |
| subjects affected / exposed                       | 10 / 103 (9.71%)                                                                                                                                                                                                                                                                   | 6 / 104 (5.77%) |  |
| occurrences causally related to treatment / all   | 0 / 15                                                                                                                                                                                                                                                                             | 0 / 10          |  |
| deaths causally related to treatment / all        | 0 / 0                                                                                                                                                                                                                                                                              | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | Minocycline                                                             | Placebo           |  |
|-------------------------------------------------------|-------------------------------------------------------------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                                                                         |                   |  |
| subjects affected / exposed                           | 60 / 103 (58.25%)                                                       | 67 / 104 (64.42%) |  |
| Immune system disorders                               |                                                                         |                   |  |
| Immune system disorder                                | Additional description: Immune system disorder                          |                   |  |
| subjects affected / exposed                           | 1 / 103 (0.97%)                                                         | 0 / 104 (0.00%)   |  |
| occurrences (all)                                     | 1                                                                       | 0                 |  |
| Respiratory, thoracic and mediastinal disorders       |                                                                         |                   |  |
| Respiratory disorders                                 | Additional description: Respiratory, thoracic and mediastinal disorders |                   |  |
| subjects affected / exposed                           | 1 / 103 (0.97%)                                                         | 1 / 104 (0.96%)   |  |
| occurrences (all)                                     | 1                                                                       | 1                 |  |
| Psychiatric disorders                                 |                                                                         |                   |  |
| Psychiatric disorders                                 | Additional description: Psychiatric disorders                           |                   |  |
| subjects affected / exposed                           | 8 / 103 (7.77%)                                                         | 16 / 104 (15.38%) |  |
| occurrences (all)                                     | 8                                                                       | 16                |  |
| Congenital, familial and genetic disorders            |                                                                         |                   |  |
| Congenital, familial and genetic disorder             | Additional description: Congenital, familial and genetic disorder       |                   |  |
| subjects affected / exposed                           | 1 / 103 (0.97%)                                                         | 0 / 104 (0.00%)   |  |
| occurrences (all)                                     | 1                                                                       | 0                 |  |
| Cardiac disorders                                     |                                                                         |                   |  |
| Cardiac disorders                                     | Additional description: Cardiac disorders                               |                   |  |
| subjects affected / exposed                           | 1 / 103 (0.97%)                                                         | 5 / 104 (4.81%)   |  |
| occurrences (all)                                     | 1                                                                       | 5                 |  |
| Nervous system disorders                              |                                                                         |                   |  |
| Nervous system disorders                              | Additional description: Nervous system disorders                        |                   |  |
| subjects affected / exposed                           | 12 / 103 (11.65%)                                                       | 8 / 104 (7.69%)   |  |
| occurrences (all)                                     | 12                                                                      | 8                 |  |
| Ear and labyrinth disorders                           |                                                                         |                   |  |
| Ear disorder                                          | Additional description: Ear and labyrinth disorders                     |                   |  |
| subjects affected / exposed                           | 0 / 103 (0.00%)                                                         | 1 / 104 (0.96%)   |  |
| occurrences (all)                                     | 0                                                                       | 1                 |  |

|                                                 |                                                                               |                   |  |
|-------------------------------------------------|-------------------------------------------------------------------------------|-------------------|--|
| Gastrointestinal disorders                      |                                                                               |                   |  |
| Gastrointestinal disorders                      | Additional description: Gastrointestinal disorders including GI upset         |                   |  |
| subjects affected / exposed                     | 19 / 103 (18.45%)                                                             | 12 / 104 (11.54%) |  |
| occurrences (all)                               | 19                                                                            | 12                |  |
| Skin and subcutaneous tissue disorders          |                                                                               |                   |  |
| Skin disorder                                   | Additional description: Skin and subcutaneous tissue disorder including rash. |                   |  |
| subjects affected / exposed                     | 8 / 103 (7.77%)                                                               | 10 / 104 (9.62%)  |  |
| occurrences (all)                               | 8                                                                             | 10                |  |
| Renal and urinary disorders                     |                                                                               |                   |  |
| Renal and urinary disorders                     | Additional description: Renal and urinary disorders                           |                   |  |
| subjects affected / exposed                     | 1 / 103 (0.97%)                                                               | 1 / 104 (0.96%)   |  |
| occurrences (all)                               | 1                                                                             | 1                 |  |
| Endocrine disorders                             |                                                                               |                   |  |
| Endocrine disorder                              | Additional description: Endocrine disorder                                    |                   |  |
| subjects affected / exposed                     | 2 / 103 (1.94%)                                                               | 1 / 104 (0.96%)   |  |
| occurrences (all)                               | 2                                                                             | 1                 |  |
| Musculoskeletal and connective tissue disorders |                                                                               |                   |  |
| Musculoskeletal disorder                        | Additional description: Musculoskeletal and connective tissue disorders       |                   |  |
| subjects affected / exposed                     | 3 / 103 (2.91%)                                                               | 3 / 104 (2.88%)   |  |
| occurrences (all)                               | 3                                                                             | 3                 |  |
| Infections and infestations                     |                                                                               |                   |  |
| Infections and infestations                     | Additional description: Infections and infestations                           |                   |  |
| subjects affected / exposed                     | 2 / 103 (1.94%)                                                               | 9 / 104 (8.65%)   |  |
| occurrences (all)                               | 2                                                                             | 9                 |  |
| Metabolism and nutrition disorders              |                                                                               |                   |  |
| Metabolism and nutrition disorders              | Additional description: Metabolism and nutrition disorders                    |                   |  |
| subjects affected / exposed                     | 1 / 103 (0.97%)                                                               | 0 / 104 (0.00%)   |  |
| occurrences (all)                               | 1                                                                             | 0                 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                              |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 19 June 2012      | Included a Data Monitoring Committee, added the Mini International Neuropsychiatric Interview to screening procedures, added the Auditory Verbal Learning Task to the cognitive tasks. |
| 25 March 2013     | Removal of ANF- anitnuclear anitbody ANA- from the screening as test was deemed obsolete.                                                                                              |
| 03 June 2013      | Inclusion of hallucinations to the PANNS criteria for inclusion into the study.                                                                                                        |
| 26 September 2013 | Changed inclusion criterion 6 'within 3 years of onset of symptoms' to 'within 5 years of onset of symptoms'.                                                                          |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

High drop out rate but does not differ between the 2 treatment arms.

Full information available at <https://doi.org/10.3310/eme06070>

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30322824>

<http://www.ncbi.nlm.nih.gov/pubmed/31465163>