



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
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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, bill.deakin@manchester.ac.uk
Scientific contact	Prof Bill Deakin, The University of Manchester, 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

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
Arm title	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.

Arm title	Baseline: Placebo
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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.

Number of subjects in period 1	Baseline: 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
Arm title	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
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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.

Arm title	2 month follow-up: Placebo
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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 2	2 month follow-up: Minocycline	2 month follow-up: 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
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Arm title	6 month follow-up: Minocycline
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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
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Investigational medicinal product name	Minocycline
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Investigational medicinal product code	ATC code J01AA08 A01
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Other name	Minocycline hydrochloride
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Pharmaceutical forms	Capsule, hard
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Routes of administration	Oral use
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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.

Arm title	6 month follow-up: Placebo
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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
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Investigational medicinal product name	Placebo
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Capsule, Capsule, soft
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Routes of administration	Oral use
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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
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Arm title	9 month follow-up: Minocycline
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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.

Arm title	9 month follow-up: Placebo
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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 4	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	-
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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
Arm title	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.

Arm title	12 month follow-up: Placebo
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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 5	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
Arm title	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.

Arm title	15 month follow-up: Placebo
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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 6	15 month follow-up: Minocycline	15 month follow-up: Placebo
Started	41	48
Completed	41	48

Baseline characteristics

Reporting groups

Reporting group title	Baseline: Minocycline
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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
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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 standard deviation	67.1 ± 13.2	69.3 ± 15.4	-
CDSS score Units: CDSS score arithmetic mean standard deviation	5.2 ± 4.3	5.5 ± 5.0	-
GAF score Units: GAF score arithmetic mean standard deviation	55.5 ± 9.1	56.2 ± 11.6	-
Weight Units: Kg arithmetic mean standard deviation	82.6 ± 19.6	86.8 ± 25.3	-
BMI Units: BMI arithmetic mean standard deviation	27.1 ± 6.2	28.7 ± 7.6	-
Processing speed Units: BIP arithmetic mean standard deviation	58 ± 16.7	52.8 ± 16.8	-
Current IQ Units: IQ score arithmetic mean standard deviation	91.2 ± 14	89.2 ± 15.9	-
Pre-Morbid IQ Units: IQ score arithmetic mean standard deviation	97.7 ± 1.7	95.4 ± 19.8	-
Medial Prefrontal cortex grey-matter volume: left Units: cc arithmetic mean standard deviation	5.6 ± 0.7	5.7 ± 0.8	-
Medial Prefrontal cortex grey-matter volume: right Units: cc arithmetic mean standard deviation	4.6 ± 5.8	4.6 ± 0.7	-
N-Back BOLD activation: 1-back plus 2- back vs 0-back Units: % change arithmetic mean standard deviation	-0.02 ± 1.48	0.12 ± 1.25	-
N-Back BOLD activation: 2-back vs 1- back Units: % change arithmetic mean standard deviation	-0.04 ± 1.54	0.10 ± 1.23	-
Cytokine IL-6 Units: pg/mL 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: 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 title	2 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	2 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.	
Reporting group title	6 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	6 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.	
Reporting group title	9 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	9 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.	
Reporting group title	12 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	12 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.	

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: 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 ^[1]	0 ^[2]
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 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	0 ^[3]	0 ^[4]	0 ^[5]	0 ^[6]
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 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 ^[7]	0 ^[8]
Units: Volume (cc)				

arithmetic mean (standard deviation)	5593 (\pm 70)	5509 (\pm 787)	()	()
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Notes:

[7] - Measure not captured at this time point

[8] - 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	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 ^[9]	0 ^[10]
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 ^[11]	0 ^[12]	0 ^[13]	0 ^[14]
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

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	45	54	0 ^[15]	0 ^[16]
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

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	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: 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	101	100	0 ^[17]	0 ^[18]
Units: concentration (pg/mL)				
arithmetic mean (standard deviation)	0.690 (± 0.458)	0.840 (± 0.639)	()	()

Notes:

[17] - Measure not captured at this time point

[18] - 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	57	65	0 ^[19]	0 ^[20]
Units: concentration (pg/mL)				
arithmetic mean (standard deviation)	0.843 (± 0.926)	0.902 (± 0.753)	()	()

Notes:

[19] - Measure not captured at this time point

[20] - 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	53	56	0 ^[21]	0 ^[22]
Units: concentration (pg/mL)				
arithmetic mean (standard deviation)	0.793 (± 0.570)	0.811 (± 0.623)	()	()

Notes:

[21] - Measure not captured at this time point

[22] - 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 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:	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: 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	101	100	0 ^[23]	0 ^[24]
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 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	57	65	0 ^[25]	0 ^[26]
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 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	51	56	0 ^[27]	0 ^[28]
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

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
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.	

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	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)

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	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)

Attachments (see zip file)	Main outcome measures for minocycline and placebo
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Statistical analyses

Statistical analysis title	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)
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End point description:

End point type	Secondary
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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	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 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	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 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	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
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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
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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: 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	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 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	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 follow-up: Minocycline	12 month follow-up: Placebo	15 month follow-up: Minocycline	15 month follow-up: Placebo
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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

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	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: 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	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 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	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 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	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: 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
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End point description:

End point type	Secondary
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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	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 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	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 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	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
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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 ^[29]	0 ^[30]
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 ^[31]	0 ^[32]
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

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	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

Statistical analysis title	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: 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 ^[33]	0 ^[34]
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 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 ^[35]	0 ^[36]
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 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)	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
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End point description:

End point type	Secondary
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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 ^[37]	0 ^[38]
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 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 ^[39]	0 ^[40]
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 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)	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: 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 ^[41]	0 ^[42]
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 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 ^[43]	0 ^[44]
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 follow-up: Minocycline	12 month follow-up: Placebo	15 month follow-up: Minocycline	15 month follow-up: Placebo
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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

Statistical analysis title	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 ^[45]	0 ^[46]
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

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 ^[47]	0 ^[48]
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

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	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

Statistical analysis title	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:	
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 ^[49]	0 ^[50]
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 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 ^[51]	0 ^[52]
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 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)	34.0 (± 5.1)	34.8 (± 5.0)	34.0 (± 7.1)	35.5 (± 3.9)

Statistical analyses

Statistical analysis title	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: 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 ^[53]	0 ^[54]
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 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	64	65	0 ^[55]	0 ^[56]
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 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	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

Statistical analysis title	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	

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	95	91	0 ^[57]	0 ^[58]
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

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	0 ^[59]	0 ^[60]	0 ^[61]	0 ^[62]
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 (\pm 16.2)	58.2 (\pm 15.8)	62.6 (\pm 16.2)	61.2 (\pm 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: 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	97	101	0 ^[63]	0 ^[64]
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 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	0 ^[65]	0 ^[66]	0 ^[67]	0 ^[68]
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 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	53	58	0 ^[69]	0 ^[70]
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: 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	101	100	0 ^[71]	0 ^[72]
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 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	0 ^[73]	0 ^[74]	0 ^[75]	0 ^[76]
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 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	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

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	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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Minocycline
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Reporting group description: -

Reporting group title	Placebo
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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 %

Non-serious adverse events	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:

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:

Online references

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

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