Clinical trial results:
Understanding the molecular basis for the use of adjunctive anti-inflammatory treatment in treatment resistant depression: a stratified, randomised, placebo-controlled, experimental medicine study using minocycline.

Summary

EudraCT number	2015-003413-26
Trial protocol	GB
Global end of trial date	17 December 2019

Results information

Result version number	v1 (current)
This version publication date	30 January 2021
First version publication date	30 January 2021
Summary attachment (see zip file)	Clinical Study report (Clinical Study Report Template v1.0_MINDEP_13January2021.pdf)

Trial information

Trial identification

Sponsor protocol code	MINDEP

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Dr Valeria Mondelli, King's College London, 44 (0)207848 0353, valeria.mondelli@kcl.ac.uk
Scientific contact	Dr Valeria Mondelli, King's College London, 44 (0)207848 0353, valeria.mondelli@kcl.ac.uk
Sponsor organisation name	South London and Maudsley NHS Foundation Trust
Sponsor organisation address	Denmark Hill, London, United Kingdom, SE5 8AZ
Public contact	Dr Valeria Mondelli, South London and Maudsley NHS Foundation Trust, 44 (0)207848 0353, valeria.mondelli@kcl.ac.uk
Scientific contact	Dr Valeria Mondelli, South London and Maudsley NHS Foundation Trust, 44 (0)207848 0353, valeria.mondelli@kcl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	17 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 September 2019
Global end of trial reached?	Yes
Global end of trial date	17 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary aim is to investigate association between changes in inflammatory biomarkers and improvement in depressive symptoms following adjunctive treatment with minocycline in treatment resistant depressed patients selected for increased inflammation.

Protection of trial subjects:

Participants will have the right to withdraw from the study at any time for any reason and do not have to provide any explanation. Patients will be informed during the consent seeking process that their withdrawal at any point in the study will not affect their quality of care. The investigator also has the right to withdraw patients from the study drug event of intercurrent illness, AEs, SAE’s, protocol violations, administrative reasons or other reasons.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	44
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients were recruited from new referrals to primary (e.g., the Improving Access to Psychological Treatments, IAPT) and secondary care services linked to the South London and Maudsley NHS Foundation Trust (SLAM), in London, from primary care services referring to SLAM and other sources such as public advertisement.

Pre-assignment

Screening details:

Patients with major depressive disorder who did not respond to the current antidepressant taken at therapeutic doses for at least 6 weeks and who had increased levels of inflammation (CRP levels ≥ 1 mg/L) were recruited

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Minocycline

Arm description:

Minocycline (100 mg x 2) was taken once daily for 4 weeks in adjunct to the current antidepressant.

Arm type	Experimental
Investigational medicinal product name	minocycline
Investigational medicinal product code	
Other name	Acnamino MR 100mg capsules
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered minocycline (200 mg) (oral tablets) for the duration of 4 weeks. The dose was taken once daily.

Arm title	Placebo

Arm description:

Matching placebo tablets were taken orally once daily for 4 weeks (56 capsules) in adjunct to their current antidepressant.

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:

lactose + gelatin capsule were taken orally once daily for 4 weeks (56 capsules) in adjunct to their current antidepressant.

Number of subjects in period 1	Minocycline	Placebo
Started	22	22
Completed	18	21
Not completed	4	1
Consent withdrawn by subject	1	1
Adverse event, non-fatal	2	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Minocycline
Reporting group description:	
Minocycline (100 mg x 2) was taken once daily for 4 weeks in adjunct to the current antidepressant.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo tablets were taken orally once daily for 4 weeks (56 capsules) in adjunct to their current antidepressant.	

Reporting group values	Minocycline	Placebo	Total
Number of subjects	22	22	44
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	22	22	44
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	45.4	43.0	
standard deviation	± 9.9	± 10.9	-
Gender categorical			
Units: Subjects			
Female	14	13	27
Male	8	9	17
BMI			
Units: kg/m2			
arithmetic mean	33.5	31.6	
standard deviation	± 10.1	± 6.1	-
Depression duration from onset			
Units: years			
arithmetic mean	20.32	18.05	
standard deviation	± 10.48	± 12.39	-
HAM-D-17			
Units: score			
arithmetic mean	19.41	16.91	
standard deviation	± 3.66	± 3.21	-
hs-CRP			
Units: score			
arithmetic mean	3.96	4.37	
standard deviation	± 4.14	± 5.11	-

End points

End points reporting groups

Reporting group title	Minocycline
Reporting group description:	
Minocycline (100 mg x 2) was taken once daily for 4 weeks in adjunct to the current antidepressant.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo tablets were taken orally once daily for 4 weeks (56 capsules) in adjunct to their current antidepressant.	

Primary: HAM-D-17

End point title	HAM-D-17
End point description:	
Changes from baseline to Week 4 for Hamilton Depression Rating Scale (HAMD) total score (DELTA HAMD), including the percentage of patients who show response, defined as 50% reduction from baseline.	
End point type	Primary
End point timeframe:	
Changes from baseline to 4 weeks	

End point values	Minocycline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	21		
Units: score				
arithmetic mean (standard deviation)	5.61 (± 6.36)	2.90 (± 3.88)		

Statistical analyses

Statistical analysis title	Baseline vs Week4 Statistics
Statistical analysis description:	
Both study arms exhibited significant improvement in HAM-D-17 total score (table n 1). We did not find significant differences between the two study arms in the clinical improvement measured in terms of HAM-D-17 change (t=1.57, p=0.13)	
Comparison groups	Minocycline v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.13
Method	t-test, 2-sided

Notes:

[1] - At least 50% improvement in HAM-D-17: 3 subjects in the minocycline group and 2 subjects in the placebo group. At least 25% improvement (partial response) in HAM-D-17: 8 subjects in the minocycline group and 9 subjects in the placebo group. Chi square test was not significant. Stratification based on

CRP levels: patients with ≥3 mg/L and taking minocycline having the largest HAM-D-17 improvement and the highest proportion of partial responders. See the study report for details.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline to week 4	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23
Reporting groups	
Reporting group title	Minocycline
Reporting group description: Minocycline (100 mg x 2) was taken once daily for 4 weeks in adjunct to the current antidepressant.	
Reporting group title	Placebo
Reporting group description: Matching placebo tablets were taken orally once daily for 4 weeks (56 capsules) in adjunct to their current antidepressant.	

Serious adverse events	Minocycline	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	0 / 21 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Minocycline	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 18 (61.11%)	11 / 21 (52.38%)	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Dizziness			
subjects affected / exposed	3 / 18 (16.67%)	1 / 21 (4.76%)	
occurrences (all)	7	1	
Headache			
subjects affected / exposed	4 / 18 (22.22%)	5 / 21 (23.81%)	
occurrences (all)	5	8	
General disorders and administration site conditions			
mood flucuations			
subjects affected / exposed	1 / 18 (5.56%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 18 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Gastrointestinal disorder	Additional description: Constipation, flatulence, diarrhoea		
subjects affected / exposed	4 / 18 (22.22%)	3 / 21 (14.29%)	
occurrences (all)	4	6	
Dyspepsia			
subjects affected / exposed	1 / 18 (5.56%)	5 / 21 (23.81%)	
occurrences (all)	1	5	
bleeding			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	4 / 18 (22.22%)	1 / 21 (4.76%)	
occurrences (all)	6	1	
Decreased appetite			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
sore throat			

subjects affected / exposed	1 / 18 (5.56%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 18 (5.56%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Apathy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	3	
Insomnia			
subjects affected / exposed	0 / 18 (0.00%)	3 / 21 (14.29%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Pain	Additional description: General pain/joint pain		
subjects affected / exposed	1 / 18 (5.56%)	2 / 21 (9.52%)	
occurrences (all)	3	2	
Infections and infestations			
flu			
subjects affected / exposed	2 / 18 (11.11%)	1 / 21 (4.76%)	
occurrences (all)	2	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 April 2016	New: Protocol v2.0 22Mar16, PIS v2.0 23Mar16, ICF v2.0 23Mar16, GP letter v2.0 22Mar16 Documents amended following change in CRP level in inclusion criteria and clarification of blood sample amounts.
06 December 2016	Change in upper age limit in excl criteria from 50 to 60
25 July 2017	Eligibility updated to: - remove cap on CRP levels - remove restriction on taking other psychotrophic medications
27 November 2019	Biological outcomes updated within Protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported