



## Clinical trial results: Minocycline in Alzheimer's disease efficacy trial:The MADE trial Summary

EudraCT number	2013-000397-30
Trial protocol	GB
Global end of trial date	16 April 2018

### Results information

Result version number	v1 (current)
This version publication date	12 October 2019
First version publication date	12 October 2019

### Trial information

#### Trial identification

Sponsor protocol code	MADE
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#### Additional study identifiers

ISRCTN number	ISRCTN16105064
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	Robert Howard, King's College London, 44 02078480545, robert.j.howard@kcl.ac.uk
Scientific contact	Robert Howard, King's College London, 44 02078480545, robert.j.howard@kcl.ac.uk
Sponsor organisation name	South London & Maudsley NHS Foundation Trust
Sponsor organisation address	Bethlem Royal Hospital, Monks Orchard Road, Beckenham, United Kingdom, BR3 3BX
Public contact	Robert Howard, South London & Maudsley NHS Foundation Trust, 44 02078480545, robert.j.howard@kcl.ac.uk
Scientific contact	Robert Howard, South London & Maudsley NHS Foundation Trust, 44 02078480545, robert.j.howard@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 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	16 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 April 2018
Global end of trial reached?	Yes
Global end of trial date	16 April 2018
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

To determine whether minocycline is superior to placebo in slowing the disease course of early AD, over a 2-year period, measured by reduced rate of decline in:

- (i) Cognition.
- (ii) Function.

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Protection of trial subjects:

Participation in MADE carries only a 1 in 3 risk of randomisation to placebo and patients will not have to forgo treatment with a cholinesterase inhibitor or memantine if their responsible clinician considers that they would benefit from such treatment.

Background therapy:

Not applicable

Evidence for comparator:

Participation in MADE carries only a 1 in 3 risk of randomisation to placebo and patients will not have to forgo treatment with a cholinesterase inhibitor or memantine if their responsible clinician considers that they would benefit from such treatment.

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Actual start date of recruitment	20 May 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	United Kingdom: 544
Worldwide total number of subjects	544
EEA total number of subjects	544

Notes:

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**Subjects enrolled per age group**

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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

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Adolescents (12-17 years)	0
Adults (18-64 years)	144
From 65 to 84 years	391
85 years and over	9

## Subject disposition

### Recruitment

Recruitment details:

Between May 23, 2014 and April 14, 2016, participants from 32 UK memory clinics were randomised

### Pre-assignment

Screening details:

Inclusion criteria:

- Diagnosis of possible or probable AD by NIA/AA criteria (McKhann et al 2011).
- sMMSE score >23 with no upper limit.
- Giving informed consent to participate
- Aged 50+
- Participants must have a potential informant who will assist in the administration of the BADLS

### 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

Blinding implementation details:

Matched placebo will be provided for the Placebo arm and Minocycline 200mg arm.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Minocycline 400mg/day

Arm description:

Minocycline (400mg) - 400mg minocycline MR administered daily for 24 months.

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

Dosage and administration details:

Minocycline (400mg) – two 100mg MR capsules of minocycline in the morning and two 100mg MR capsules in the evening.

<b>Arm title</b>	Minocycline 200mg/day
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Arm description:

Minocycline 200mg MR administered orally per day for 24 months

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

Dosage and administration details:

Minocycline (200mg) – one 100mg MR capsule of minocycline plus one minocycline placebo capsule in a morning and one 100mg MR capsule of minocycline plus one minocycline placebo capsule in an evening.

<b>Arm title</b>	Placebo
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Arm description:

Matched placebo capsules administered by mouth daily for 24 months

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

Dosage and administration details:

Placebo minocycline – two minocycline placebo capsules in a morning and two placebo minocycline capsules in the evening.

<b>Number of subjects in period 1</b>	Minocycline 400mg/day	Minocycline 200mg/day	Placebo
Started	184	181	179
Completed	53	112	114
Not completed	131	69	65
Adverse event, serious fatal	10	6	12
Consent withdrawn by Participant or Carer	23	21	18
Adverse event, non-fatal	98	42	35

## Baseline characteristics

### Reporting groups

Reporting group title	Minocycline 400mg/day
Reporting group description:	Minocycline (400mg) - 400mg minocycline MR administered daily for 24 months.
Reporting group title	Minocycline 200mg/day
Reporting group description:	Minocycline 200mg MR administered orally per day for 24 months
Reporting group title	Placebo
Reporting group description:	Matched placebo capsules administered by mouth daily for 24 months

Reporting group values	Minocycline 400mg/day	Minocycline 200mg/day	Placebo
Number of subjects	184	181	179
Age categorical			
Units: Subjects			
Adults (18-64 years)	22	22	21
From 65-74	68	66	66
75 years and over	94	93	92
Gender categorical			
Units: Subjects			
Female	80	81	80
Male	104	100	99

Reporting group values	Total		
Number of subjects	544		
Age categorical			
Units: Subjects			
Adults (18-64 years)	65		
From 65-74	200		
75 years and over	279		
Gender categorical			
Units: Subjects			
Female	241		
Male	303		

## End points

### End points reporting groups

Reporting group title	Minocycline 400mg/day
Reporting group description:	Minocycline (400mg) - 400mg minocycline MR administered daily for 24 months.
Reporting group title	Minocycline 200mg/day
Reporting group description:	Minocycline 200mg MR administered orally per day for 24 months
Reporting group title	Placebo
Reporting group description:	Matched placebo capsules administered by mouth daily for 24 months

### Primary: Primary

End point title	Primary <sup>[1]</sup>
End point description:	The primary objective is to determine whether minocycline is superior to placebo in slowing the disease course of early AD, over a 2-year period, measured by reduced rate of decline in: (i) Cognition (sMMSE) (ii) Function (BADLS)
End point type	Primary
End point timeframe:	Over a two year period

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Please see attached charts and documents.

End point values	Minocycline 400mg/day	Minocycline 200mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	112	114	
Units: Whole	53	112	114	

<b>Attachments (see zip file)</b>	RESULTS/MADE RESULTS CHARTS.pdf
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Secondary

End point title	Secondary
End point description:	The secondary objectives of MADE are: (i) To compare the safety and tolerability of minocycline at doses of 400mg/day and 200mg/day (ii) To determine whether 400mg/day offer superior neuroprotection to 200mg/day. (iii) To investigate associated risks of side-effects and serious adverse events.

(iv) To estimate the magnitude of any statistically significant positive treatment effects on cognitive and functional decline and thereby inform the design and powering of a future phase III trial of definitive clinical effectiveness within the NHS.

End point type	Secondary
End point timeframe:	
Over a two year period.	

<b>End point values</b>	Minocycline 400mg/day	Minocycline 200mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	112	114	
Units: Whole	53	112	114	

<b>Attachments (see zip file)</b>	MADE - RESULTS/NIHR REPORT_consort format_formatted
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### **Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

From consent to 24 months post randomisation

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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### Reporting groups

Reporting group title	Minocycline 400mg/day
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Reporting group description:

Minocycline (400mg) - 400mg minocycline MR administered daily for 24 months.

Reporting group title	Minocycline 200mg/day
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Reporting group description:

Minocycline 200mg MR administered orally per day for 24 months

Reporting group title	Placebo
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Reporting group description:

Matched placebo capsules administered by mouth daily for 24 months

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Data was not collected on all non-serious adverse events - only those deemed related to trial treatment; number of non-serious adverse events has therefore been reported as zero

Serious adverse events	Minocycline 400mg/day	Minocycline 200mg/day	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 184 (29.35%)	47 / 181 (25.97%)	61 / 179 (34.08%)
number of deaths (all causes)	11	6	13
number of deaths resulting from adverse events	11	6	13
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder adenocarcinoma recurrent			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal tumour			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			

subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic lymphocytic leukaemia			
subjects affected / exposed	2 / 184 (1.09%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myeloproliferative neoplasm			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowel cancer			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Oesophageal cancer			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer			
subjects affected / exposed	2 / 184 (1.09%)	0 / 181 (0.00%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's disease			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			

subjects affected / exposed	2 / 184 (1.09%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Hyperplasia</b>			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Vulval cancer</b>			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Basal cell carcinoma</b>			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Vascular disorders</b>			
<b>Stroke</b>			
subjects affected / exposed	2 / 184 (1.09%)	2 / 181 (1.10%)	5 / 179 (2.79%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
<b>Subdural haematoma</b>			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	3 / 179 (1.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cerebrovascular accident</b>			
subjects affected / exposed	2 / 184 (1.09%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
<b>Intra-cranial bleed</b>			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Transient ischaemic attack</b>			

subjects affected / exposed	0 / 184 (0.00%)	3 / 181 (1.66%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Frontal lobe cortical haemorrhage			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 184 (0.54%)	2 / 181 (1.10%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suspected thrombosis			
subjects affected / exposed	2 / 184 (1.09%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Colon operation			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillectomy	Additional description: Due to cancer		
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biopsy bladder	Additional description: No abnormality noted		
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee replacement			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernia hiatus repair			

subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Hysterectomy</b>			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Transurethral prostatectomy</b>			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Hip screw removed</b>			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cardiac stent</b>			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>General disorders and administration site conditions</b>			
<b>Collapse</b>			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Decline in health</b>			
subjects affected / exposed	1 / 184 (0.54%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
<b>Pain</b>			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Oedema genital</b>			

subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Swollen legs			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Osteoarthritis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	5 / 184 (2.72%)	5 / 181 (2.76%)	6 / 179 (3.35%)
occurrences causally related to treatment / all	1 / 6	0 / 5	0 / 6
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Shortness of breath			
subjects affected / exposed	1 / 184 (0.54%)	1 / 181 (0.55%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sepsis	Additional description: Secondary to community acquired pneumonia		
subjects affected / exposed	2 / 184 (1.09%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pulmonary fibrosis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Skull fracture			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	3 / 179 (1.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head and neck injury			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 184 (0.54%)	2 / 181 (1.10%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	3 / 179 (1.68%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubic rami fracture			
subjects affected / exposed	1 / 184 (0.54%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pelvic fracture			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shoulder operation	Additional description: Post dislocation		
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee operation			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metacarpal fracture			
subjects affected / exposed	0 / 184 (0.00%)	2 / 181 (1.10%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial injury			

subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental poisoning			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 184 (0.54%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral contusions			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Zygomatic fracture			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 184 (0.54%)	1 / 181 (0.55%)	3 / 179 (1.68%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Long QT			
Additional description: with impaired ventricular function			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac event			

subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Syncope			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart murmur	Additional description: Fluid on lungs		
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	7 / 184 (3.80%)	2 / 181 (1.10%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 8	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 0
Mitral valve regurgitation			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atherosclerosis coronary			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Aortic stenosis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Labile blood pressure			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Confusional state			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 184 (0.54%)	2 / 181 (1.10%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic behaviour			
subjects affected / exposed	1 / 184 (0.54%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia Alzheimer's type			
subjects affected / exposed	2 / 184 (1.09%)	3 / 181 (1.66%)	3 / 179 (1.68%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Loss of consciousness			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Platelets low			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 184 (0.00%)	2 / 181 (1.10%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sigmoid volvulus			

subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Diverticulitis</b>			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Ulcer haemorrhage</b>			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Abdominal pain</b>			
subjects affected / exposed	1 / 184 (0.54%)	1 / 181 (0.55%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Bleeding of stomach lining</b>			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Diarrhoea</b>			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Appendicitis</b>			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Surgery</b>			
Additional description: Complications after bowel surgery			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>Bowel obstruction</b>			

subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>Bile duct obstruction</b>			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Cyst</b>	Additional description: On small intestine		
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Severe indigestion</b>			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Bowel contusion</b>			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Reflux gastritis</b>			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Skin and subcutaneous tissue disorders</b>			
<b>Pigmentation</b>	Additional description: Minocycline type 2 pigmentation on face		
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Tenderness</b>			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Itch</b>			

subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Renal and urinary disorders</b>			
Kidney stones			
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 184 (0.54%)	1 / 181 (0.55%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Nephrectomy			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Endocrine disorders</b>			
Adenoma pituitary			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ketoacidosis			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	2 / 179 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Antidiuretic hormone abnormality			

subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthropathy			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Chest infection			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	6 / 179 (3.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary tract infection			
subjects affected / exposed	4 / 184 (2.17%)	1 / 181 (0.55%)	5 / 179 (2.79%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	3 / 179 (1.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urosepsis			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candidiasis of trachea			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Metabolism and nutrition disorders</b>			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 184 (0.54%)	0 / 181 (0.00%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Low sodium			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	1 / 179 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Potassium low	Additional description: Due to bowel preparation for CT bowel		
subjects affected / exposed	0 / 184 (0.00%)	1 / 181 (0.55%)	0 / 179 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Minocycline 400mg/day	Minocycline 200mg/day	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 184 (0.00%)	0 / 181 (0.00%)	0 / 179 (0.00%)

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2014	Amended procedure for dispatch of IMP, amended inc/exc criteria
31 March 2014	Response to REC to unfavourable opinion (modification to exclusion criteria) as well as addition of three new PIs and change of PI at Berkshire Trust.
05 September 2014	Addition of new site
16 December 2015	Increase in sample size to 560. Changes to IMP supply and management.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported