



## Clinical trial results:

### A Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of Oral Azithromycin (500 Mg OD) as a Supplement to Standard Care for Adult Patients with Acute Exacerbations of Asthma

#### Summary

EudraCT number	2011-001093-26
Trial protocol	GB
Global end of trial date	30 June 2014

#### Results information

Result version number	v1 (current)
This version publication date	10 June 2016
First version publication date	10 June 2016
Summary attachment (see zip file)	AZALEA Final Report - CSR (AZALEA NIHR final report - final version 28-08-2015.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	AZALEA
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01444469
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Imperial College, London
Sponsor organisation address	Exhibition Road, London, United Kingdom, SW7 2AZ
Public contact	Professor Sebastian Johnston, Imperial College, London, 020 7 594 3764, s.johnston@imperial.ac.uk
Scientific contact	Professor Sebastian Johnston, Imperial College, London, 020 7 594 3764, s.johnston@imperial.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	24 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2014
Global end of trial reached?	Yes
Global end of trial date	30 June 2014
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 evaluate the clinical efficacy of oral Azithromycin treatment as a supplement to standard care for adult patients with acute exacerbations of asthma.

Protection of trial subjects:

- Addition of an extra exclusion criteria during the study to reflect guidelines released from the FDA on the use of azithromycin

Background therapy:

N/A

Evidence for comparator:

N/A placebo used

Actual start date of recruitment	17 October 2011
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**

Country: Number of subjects enrolled	United Kingdom: 199
Worldwide total number of subjects	199
EEA total number of subjects	199

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
Adolescents (12-17 years)	0
Adults (18-64 years)	184
From 65 to 84 years	15
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment ran from 17th October 2011 to 30th June 2014 across 31 UK sites, one of which was a primary care / GP site.

### Pre-assignment

Screening details:

4582 patients were screened for eligibility. 4383 were excluded.

### 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, Monitor

Blinding implementation details:

The identity of the study medications was blinded, packaged and supplied to the investigator by Sharp Clinical Services with code break envelopes. Over-encapsulated azithromycin capsules and placebo capsules were placed into child-resistant tamper-evident containers and a randomised label applied to each container.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Treatment Arm / Azithromycin

Arm description:

Those randomised to azithromycin received 500 mg azithromycin (two 250 mg capsules) once a day for 3 days (this is the routine dose given in clinical care).

Arm type	Experimental
Investigational medicinal product name	Azithromycin
Investigational medicinal product code	J01FA10
Other name	ZITHROMAX™ CAPSULES
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Those randomised to azithromycin received 500 mg azithromycin (two 250 mg capsules) once a day for 3 days (this is the routine dose given in clinical care). This was self administered, the first dose administered at the site in the presence of research staff and all subsequent doses taken at home.

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

Those patients randomised to the placebo received two placebo capsules once a day for 3 days.

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:

Those patients randomised to the placebo received two placebo capsules once a day for 3 days.

<b>Number of subjects in period 1</b>	Treatment Arm / Azithromycin	Placebo
Started	97	102
Completed	97	102

## Baseline characteristics

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### Reporting groups

Reporting group title	Overall trial
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Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	199	199	
Age categorical Units: Subjects			
Adults (18-64 years)	199	199	
Gender categorical Units: Subjects			
Female	139	139	
Male	60	60	

## End points

### End points reporting groups

Reporting group title	Treatment Arm / Azithromycin
Reporting group description: Those randomised to azithromycin received 500 mg azithromycin (two 250 mg capsules) once a day for 3 days (this is the routine dose given in clinical care).	
Reporting group title	Placebo
Reporting group description: Those patients randomised to the placebo received two placebo capsules once a day for 3 days.	

### Primary: Diary card summary symptom score

End point title	Diary card summary symptom score
End point description:	
End point type	Primary
End point timeframe: 10 days after randomisation	

End point values	Treatment Arm / Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	68		
Units: Symptom score	71	68		

### Statistical analyses

Statistical analysis title	Multilevel model of the primary outcome
Statistical analysis description: Multilevel modelling was used to calculate the unbiased estimates of differences in diary scores for each day between the treatment arms. Different relationships between time and diary scores were compared including linear, quadratic and square root relationships. Fixed and random effects and the use of splines were also investigated. The goodness of fit of these models were assessed by residual plots. All patients who returned at least one diary card (and received study drug) were included	
Comparison groups	Treatment Arm / Azithromycin v Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.166

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	0.337

### Secondary: Health status assessed by acute asthma QoLQ (Juniper)

End point title	Health status assessed by acute asthma QoLQ (Juniper)
End point description:	
End point type	Secondary
End point timeframe:	
Assessed at day baseline and days 5 and 10 after randomisation	

End point values	Treatment Arm / Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	83		
Units: Questionnaire score				
Baseline	96	100		
5 days post randomisation	84	87		
10 days post randomisation	80	83		

### Statistical analyses

Statistical analysis title	Multilevel model of the secondary outcomes
Statistical analysis description:	
Multilevel models, similar to those specified for the primary outcome, were used to analyse the acute asthma and mini-asthma questionnaires and also for the pulmonary function tests.	
Comparison groups	Treatment Arm / Azithromycin v Placebo
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.276
upper limit	0.539

### Secondary: Health status assessed by Mini Asthma QoLQ (Juniper)

End point title	Health status assessed by Mini Asthma QoLQ (Juniper)
End point description:	
End point type	Secondary
End point timeframe:	
Assessed at Baseline and at 5 and 10 days post randomisation	

End point values	Treatment Arm / Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	100		
Units: Questionnaire score				
Baseline	96	100		
5 days post randomisation	84	87		
10 days post randomisation	80	83		

### Statistical analyses

Statistical analysis title	Multilevel model of the secondary outcomes
Comparison groups	Treatment Arm / Azithromycin v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.409
upper limit	0.325

### Secondary: Pulmonary Function tests (FEV1, FVC, FEV1/FVC ratio, PEF, FEF25-75%, FEF50%)

End point title	Pulmonary Function tests (FEV1, FVC, FEV1/FVC ratio, PEF, FEF25-75%, FEF50%)
End point description:	
End point type	Secondary
End point timeframe:	
Assessed at Baseline and 5 and 10 days post randomisation	



<b>End point values</b>	Treatment Arm / Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	83		
Units: FEV1, FVC, FEV1/FVC ratio, PEF, FEF25-75				
Baseline	97	101		
5 days post randomisation	85	90		
10 days post randomisation	80	83		

## Statistical analyses

<b>Statistical analysis title</b>	Multilevel model of FEV1
Comparison groups	Treatment Arm / Azithromycin v Placebo
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.132
upper limit	0.231

<b>Statistical analysis title</b>	Multilevel model of FVC
Comparison groups	Treatment Arm / Azithromycin v Placebo
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.038
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.166
upper limit	0.243

<b>Statistical analysis title</b>	Multilevel model of FEV1/FVC ratio
Comparison groups	Treatment Arm / Azithromycin v Placebo

Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1.379
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.559
upper limit	4.316

<b>Statistical analysis title</b>	Multilevel model of FEF25-75%(litres/sec)
Comparison groups	Treatment Arm / Azithromycin v Placebo
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.036
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.192
upper limit	0.265

<b>Statistical analysis title</b>	Multilevel model of FEF50%(litres/sec)
Comparison groups	Treatment Arm / Azithromycin v Placebo
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.045
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.234
upper limit	0.324

<b>Statistical analysis title</b>	Multilevel model of PEF(litres/min)
Comparison groups	Treatment Arm / Azithromycin v Placebo

Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	18.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.56
upper limit	44.62

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### Secondary: Time to 50% reduction in symptom score

End point title	Time to 50% reduction in symptom score
End point description:	
End point type	Secondary
End point timeframe:	
Time from day 1 to 50% reduction in initial symptom score was calculated using the mean daytime score from the diary cards.	

End point values	Treatment Arm / Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	102		
Units: Symptom score	97	102		

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### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

For the purposes of this study, the period of observation extended from the time the subject gave informed consent until 7 days after the last dose of study medication.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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### Reporting groups

Reporting group title	Active
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Active	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 97 (1.03%)	3 / 102 (2.94%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 97 (1.03%)	2 / 102 (1.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 97 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Active	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 97 (52.58%)	52 / 102 (50.98%)	
Cardiac disorders			

Chest pain subjects affected / exposed occurrences (all)	4 / 97 (4.12%) 4	1 / 102 (0.98%) 1	
Tachycardia subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 102 (0.98%) 1	
Palpitations subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	1 / 102 (0.98%) 0	
Nervous system disorders			
Neuralgia subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 102 (0.98%) 1	
Dizziness subjects affected / exposed occurrences (all)	3 / 97 (3.09%) 3	2 / 102 (1.96%) 2	
Headache subjects affected / exposed occurrences (all)	11 / 97 (11.34%) 11	10 / 102 (9.80%) 10	
Paraesthesia subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 102 (0.98%) 1	
General disorders and administration site conditions			
Contusion subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	0 / 102 (0.00%) 0	
Blood pressure decreased subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 102 (0.98%) 1	
Dry throat subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	0 / 102 (0.00%) 0	
Ear pain subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 102 (0.98%) 1	
asthenia			

subjects affected / exposed	0 / 97 (0.00%)	1 / 102 (0.98%)
occurrences (all)	0	1
Pyrexia		
subjects affected / exposed	1 / 97 (1.03%)	0 / 102 (0.00%)
occurrences (all)	1	0
Disturbance in attention		
subjects affected / exposed	0 / 97 (0.00%)	1 / 102 (0.98%)
occurrences (all)	0	1
Arthropod bite		
subjects affected / exposed	1 / 97 (1.03%)	0 / 102 (0.00%)
occurrences (all)	1	0
Eye pruritus		
subjects affected / exposed	1 / 97 (1.03%)	0 / 102 (0.00%)
occurrences (all)	1	0
Pruritus		
subjects affected / exposed	1 / 97 (1.03%)	1 / 102 (0.98%)
occurrences (all)	1	1
Decreased appetite		
subjects affected / exposed	0 / 97 (0.00%)	1 / 102 (0.98%)
occurrences (all)	0	1
Hyperhidrosis		
subjects affected / exposed	1 / 97 (1.03%)	0 / 102 (0.00%)
occurrences (all)	1	0
Oropharyngeal pain		
subjects affected / exposed	2 / 97 (2.06%)	1 / 102 (0.98%)
occurrences (all)	2	1
Fatigue		
subjects affected / exposed	3 / 97 (3.09%)	6 / 102 (5.88%)
occurrences (all)	3	6
Muscle spasms		
subjects affected / exposed	0 / 97 (0.00%)	2 / 102 (1.96%)
occurrences (all)	0	2
Tooth fracture		
subjects affected / exposed	0 / 97 (0.00%)	1 / 102 (0.98%)
occurrences (all)	0	1
Lip dry		

subjects affected / exposed	0 / 97 (0.00%)	1 / 102 (0.98%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 97 (1.03%)	0 / 102 (0.00%)	
occurrences (all)	1	0	
Feeling of body temperature change			
subjects affected / exposed	0 / 97 (0.00%)	1 / 102 (0.98%)	
occurrences (all)	0	1	
Hot flush			
subjects affected / exposed	1 / 97 (1.03%)	0 / 102 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	2 / 97 (2.06%)	1 / 102 (0.98%)	
occurrences (all)	2	1	
Erythema			
subjects affected / exposed	0 / 97 (0.00%)	1 / 102 (0.98%)	
occurrences (all)	0	1	
Ill-defined disorder			
subjects affected / exposed	0 / 97 (0.00%)	1 / 102 (0.98%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	1 / 97 (1.03%)	0 / 102 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye pain			
subjects affected / exposed	1 / 97 (1.03%)	0 / 102 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 102 (0.98%)	
occurrences (all)	0	1	
Visual impairment			
subjects affected / exposed	1 / 97 (1.03%)	0 / 102 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	3 / 97 (3.09%)	0 / 102 (0.00%)	
occurrences (all)	3	0	
Abdominal distension			
subjects affected / exposed	3 / 97 (3.09%)	1 / 102 (0.98%)	
occurrences (all)	3	1	
constipation			
subjects affected / exposed	0 / 97 (0.00%)	1 / 102 (0.98%)	
occurrences (all)	0	1	
diarrhoea			
subjects affected / exposed	8 / 97 (8.25%)	7 / 102 (6.86%)	
occurrences (all)	8	7	
Malaise			
subjects affected / exposed	1 / 97 (1.03%)	2 / 102 (1.96%)	
occurrences (all)	1	2	
Dyspepsia			
subjects affected / exposed	4 / 97 (4.12%)	5 / 102 (4.90%)	
occurrences (all)	4	5	
Nausea			
subjects affected / exposed	6 / 97 (6.19%)	4 / 102 (3.92%)	
occurrences (all)	6	4	
Reflux gastritis			
subjects affected / exposed	2 / 97 (2.06%)	1 / 102 (0.98%)	
occurrences (all)	2	1	
Abdominal pain upper			
subjects affected / exposed	6 / 97 (6.19%)	3 / 102 (2.94%)	
occurrences (all)	6	3	
Abdominal discomfort			
subjects affected / exposed	1 / 97 (1.03%)	2 / 102 (1.96%)	
occurrences (all)	1	2	
Anal haemorrhage			
subjects affected / exposed	1 / 97 (1.03%)	0 / 102 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Dysmenorrhoea			



subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 102 (0.98%) 1	
Respiratory, thoracic and mediastinal disorders			
chronic throat clearing			
subjects affected / exposed	1 / 97 (1.03%)	0 / 102 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	6 / 97 (6.19%)	8 / 102 (7.84%)	
occurrences (all)	6	8	
Lower respiratory tract infection			
subjects affected / exposed	1 / 97 (1.03%)	2 / 102 (1.96%)	
occurrences (all)	1	2	
Chest discomfort			
subjects affected / exposed	2 / 97 (2.06%)	1 / 102 (0.98%)	
occurrences (all)	2	1	
Wheezing			
subjects affected / exposed	3 / 97 (3.09%)	1 / 102 (0.98%)	
occurrences (all)	3	1	
Cough			
subjects affected / exposed	4 / 97 (4.12%)	6 / 102 (5.88%)	
occurrences (all)	4	6	
Asthma			
subjects affected / exposed	6 / 97 (6.19%)	4 / 102 (3.92%)	
occurrences (all)	6	4	
Nasopharyngitis			
subjects affected / exposed	0 / 97 (0.00%)	2 / 102 (1.96%)	
occurrences (all)	0	2	
Productive cough			
subjects affected / exposed	1 / 97 (1.03%)	3 / 102 (2.94%)	
occurrences (all)	1	3	
Pain			
subjects affected / exposed	0 / 97 (0.00%)	1 / 102 (0.98%)	
occurrences (all)	0	1	
Musculoskeletal chest pain			

subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	2 / 102 (1.96%) 2	
Rhinorrhoea			
subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	0 / 102 (0.00%) 0	
Myalgia			
subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 102 (0.98%) 1	
Pneumonia			
subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 102 (0.98%) 1	
Sinusitis			
subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 102 (0.98%) 1	
Haemophilus infection			
subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 102 (0.98%) 1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 102 (0.98%) 1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 102 (0.98%) 1	
Emotional distress			
subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 102 (0.98%) 1	
Panic attack			
subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 102 (0.98%) 1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed occurrences (all)	2 / 97 (2.06%) 2	2 / 102 (1.96%) 2	
Foot fracture			

subjects affected / exposed	0 / 97 (0.00%)	1 / 102 (0.98%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 97 (1.03%)	2 / 102 (1.96%)	
occurrences (all)	1	2	
Mobility decreased			
subjects affected / exposed	0 / 97 (0.00%)	1 / 102 (0.98%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	1 / 97 (1.03%)	1 / 102 (0.98%)	
occurrences (all)	1	1	
Flank pain			
subjects affected / exposed	0 / 97 (0.00%)	1 / 102 (0.98%)	
occurrences (all)	0	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 97 (0.00%)	1 / 102 (0.98%)	
occurrences (all)	0	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 September 2011	<p>Protocol amended to Version 2 and included:</p> <ul style="list-style-type: none"> <li>• Addition of the name of the project manager appointed to this study</li> <li>• Addition of a throat swab in case sufficient sample is not obtained from the nasal mucus and nasal swab</li> <li>• Refinement of inclusion criteria to include FEV1 as well as PEF as a measurement of lung function</li> <li>• Refinement of exclusion criteria to clarify the type of antibiotic use that will be excluded</li> <li>• Our drug supplier (Bilcare) advised us that the placebo capsules and over-encapsulation of the Zithromax capsules will only use Lactose Powder and not Magnesium Stearate as they had originally specified. This is because they 'are producing a small amount of capsules that will be made on the hand frame so the Magnesium Stearate powder will not be required'. The protocol was changed accordingly.</li> <li>• Clarification that all standard care for asthma will be permitted</li> <li>• Addition of the option of home visits for study visits 2, 3 and 4 if requested and the patient is unable to attend hospital</li> <li>• Clarification of the leeway allowable for the day of each visit (to allow for weekends and participant unavailability)</li> <li>• Clarification as to when the patients should complete the symptom diaries</li> <li>• Inclusion of a statement that hospitalisation as a direct result of the asthma exacerbation is not an SAE as this is part of their routine clinical care and not related to their participation in the trial</li> <li>• Removal of Appendix C and D (instructions for sample collection and analysis) as this was part of the study specific SOPs that will be regularly reviewed and updated.</li> </ul>
11 April 2012	<p>Protocol amended to Version 3 and included:</p> <ul style="list-style-type: none"> <li>• Refinement of inclusion criteria to include patients aged over 65 years with less than 5 pack year smoking history</li> <li>• Addition of the telephone number of the project manager appointed to this study</li> </ul>
24 August 2012	<p>Protocol amended to Version 4 and included:</p> <ul style="list-style-type: none"> <li>• Refinement of the eligibility criteria to include patients presenting within 48 hours (of initial presentation to medical care) with an acute deterioration of asthma control (instead of 24 hours as in the previous protocol version)</li> <li>• To allow for Visit 1 to be conducted at the recruiting site or participant's home</li> <li>• Recruitment extension to April 2014</li> <li>• Minor administrative changes</li> </ul>
18 December 2012	<p>Protocol amended to Version 5 and included:</p> <ul style="list-style-type: none"> <li>• Protocol amendment to introduce participant reimbursements for completing study visits and returning all symptom diaries - participants will be eligible to receive a maximum payment of £50 at visit 4 if they have attended all study visits and completed and returned all 10 symptom diaries. The payment is equivalent to the sum of £10 for attending each study visit (1, 2, 3 and 4) plus £10 for returning all 10 symptom diaries.</li> </ul>
02 August 2013	<p>Protocol amended to Version 6 and included:</p> <ul style="list-style-type: none"> <li>• Addition of an extra exclusion criteria to reflect guidelines released from the FDA on the use of azithromycin</li> </ul>

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Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported