



Clinical trial results:

Antibiotic treatment in patients with chronic low back pain and Modic Changes: a double-blind randomized placebo-controlled trial

Summary

EudraCT number	2013-004505-14
Trial protocol	NO
Global end of trial date	16 October 2019

Results information

Result version number	v1 (current)
This version publication date	12 July 2021
First version publication date	12 July 2021
Summary attachment (see zip file)	Main results (bmj.l5654.full.pdf) Appendix (appendix.pdf)

Trial information

Trial identification

Sponsor protocol code	Modic02
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02323412
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Oslo University Hospital
Sponsor organisation address	Kirkeveien 166, Oslo, Norway, 0424
Public contact	Kjersti Storheim, Research and communication unit for musculoskeletal health, +47 22117751, kjersti.storheim@medisin.uio.no
Scientific contact	Kjersti Storheim, Research and communication unit for musculoskeletal health, +47 22117751, kjersti.storheim@medisin.uio.no

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	26 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 August 2019
Global end of trial reached?	Yes
Global end of trial date	16 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To re-examine the finding that antibiotic treatment can cure patients with chronic low back pain, earlier disc herniation, and Modic changes.

We will evaluate the effect of antibiotic treatment versus placebo on pain and disability, bothersomeness, health-related quality of life, sick leave, patients' satisfaction and side effects from inclusion to 1-year follow-up. Our trial will be the first to re-examine the Danish Modic-antibiotic study.

Protection of trial subjects:

Patients were followed up monthly during the intervention period (3 months) with blood tests (Haematological parameters (leucocytes, thrombocytes, eosinophils, haemoglobin (Hb) and hematocrit (Ht)) and measures of kidney (creatinine) and liver function (ASAT / ALAT)) together with a short clinical evaluation (blood pressure, pulse, auscultation of hearth and lungs) to monitor side effects. Adverse events (AEs) was registered at all study visits.

Background therapy:

Two former clinical studies, both conducted by the same research group, have evaluated the effect of antibiotic treatment for a selected group of patients with chronic pain and MCs in the vertebrae adjacent to a previous disc herniation. The first study was an uncontrolled pilot study reporting a clinically important and statistically significant (p 0.001) improvement in all outcome measures (LBP intensity, number of days with pain, disease-specific and patient-specific function, and global perceived effect) at the end of treatment, and at long-term follow-up. The second study was a RCT concluding that the antibiotic protocol was significantly more effective for this group of patients than placebo in all the primary and secondary outcomes.

Evidence for comparator:

Placebo

Actual start date of recruitment	01 June 2015
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	Norway: 180
Worldwide total number of subjects	180
EEA total number of subjects	180

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)	0
Adults (18-64 years)	180
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from outpatient clinics at 6 hospitals in Norway from June 2015 to September 2017.

Pre-assignment

Screening details:

Patients were recruited from outpatient clinics at 6 hospitals in Norway, should be aged 18 to 65 years, low back pain for > 6 months with intensity > 5 on a 0-10 Numerical Rating Scale, lumbar disc herniation on MRI in the preceding two years, and type I and/or type II MCs.

Pre-assignment period milestones

Number of subjects started	180
Number of subjects completed	180

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Amoxicillin

Arm description:

Amoxicillin 750 mg three times daily for 100 days

Arm type	Experimental
Investigational medicinal product name	Amoxicillin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

750 mg Three times daily

Arm title	Placebo
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Arm description:

Placebo (maiz starch) three times daily for 100 days

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

Dosage and administration details:

Encapsulated maize starch three times daily for 100 days

Number of subjects in period 1	Amoxicillin	Placebo
Started	89	91
Completed	89	91

Period 2

Period 2 title	Treatment period, 0-3 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The allocation sequence was concealed. Care providers gave each patient a prescription with a computer generated allocation number to be used at the dedicated hospital pharmacies. All care providers, research staff, statisticians, and patients were unaware of the assignment group during the data collection. Care providers, research staff and statisticians were also blinded during primary and secondary analyses and first draft of this manuscript.

Arms

Are arms mutually exclusive?	Yes
Arm title	Amoxicillin

Arm description:

Capsulated Amoxicillin 750 mg three times daily for 100 days

Arm type	Experimental
Investigational medicinal product name	Amoxicillin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

750 mg Three times daily

Arm title	Placebo
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Arm description:

Encapsulated maize starch three times daily for 100 days

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

Dosage and administration details:

Encapsulated maize starch three times daily for 100 days

Number of subjects in period 2	Amoxicillin	Placebo
Started	89	91
Completed	86	89
Not completed	3	2
Voluntarily discontinued study	2	-
Lost to follow-up	1	1
Voluntarily discontinued the study	-	1

Period 3

Period 3 title	Follow up, 3-12 months
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	Amoxicillin

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Amoxicillin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

750 mg Three times daily

Arm title	Placebo
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Arm description: -

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

Dosage and administration details:

Encapsulated maize starch three times daily for 100 days

Number of subjects in period 3	Amoxicillin	Placebo
Started	86	89
Completed	85	89
Not completed	1	0
Voluntarily discontinued the study	1	-

Baseline characteristics

Reporting groups

Reporting group title	Amoxicillin
Reporting group description:	
Amoxicillin 750 mg three times daily for 100 days	
Reporting group title	Placebo
Reporting group description:	
Placebo (maiz starch) three times daily for 100 days	

Reporting group values	Amoxicillin	Placebo	Total
Number of subjects	89	91	180
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			
Units: years			
arithmetic mean	44.7	45.2	
standard deviation	± 9.0	± 9.0	-
Gender categorical			
Units: Subjects			
Female	53	52	105
Male	36	39	75
Smoking status			
Units: Subjects			
smoker	25	21	46
non-smoker	64	68	132
Not recorded	0	2	2
Educational level			
Units: Subjects			
Primary school	10	9	19
High school	36	42	78
College or university	27	18	45
University	15	20	35
Not recorded	1	2	3
Comorbidity			
Functional Comorbidity Index – Score increased by 1 for each of 18 diagnoses associated with decreased physical function.			
Units: Subjects			
Score 1 (back pain only)	62	60	122

Score 2	21	27	48
Score >2	6	4	10
Former Disc surgery			
Units: Subjects			
yes	18	20	38
no	71	71	142
Body Mass Index			
Units: kg/m2			
arithmetic mean	26.1	25.9	
standard deviation	± 4.1	± 4.0	-

Subject analysis sets

Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized patients

Subject analysis set title	Per protocol
Subject analysis set type	Per protocol

Subject analysis set description:

All randomized patients without any major protocol deviation. Major protocol deviations were defined as (a) intake of < 80% of the pills (amoxicillin or placebo), (b) pause of the study medication for ≥ 2 weeks (in the antibiotic group: without other 'relevant' antibiotic treatment in that period), (c) 'relevant' antibiotic treatment in the placebo group for ≥ 4 continuous weeks between baseline and one-year follow-up, and (d) back surgery during the one-year follow-up. 'Relevant' antibiotic treatment was antibiotic treatment likely to affect a C. acne discitis. Further events registered as major protocol deviations were faulty inclusion (2 patients treated with antibiotics last month prior to inclusion), both amoxicillin and placebo given to patient by mistake (1 patient), and spondyloarthritis diagnosed during follow-up (1 patient).

Reporting group values	Intention to treat	Per protocol	
Number of subjects	180	155	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	
Gender categorical			
Units: Subjects			
Female	105		
Male	75		

Smoking status			
Units: Subjects			
smoker			
non-smoker			
Not recorded			
Educational level			
Units: Subjects			
Primary school			
High school			
College or university			
University			
Not recorded			
Comorbidity			
Functional Comorbidity Index – Score increased by 1 for each of 18 diagnoses associated with decreased physical function.			
Units: Subjects			
Score 1 (back pain only)			
Score 2			
Score >2			
Former Disc surgery			
Units: Subjects			
yes			
no			
Body Mass Index			
Units: kg/m2			
arithmetic mean			
standard deviation	±	±	

End points

End points reporting groups

Reporting group title	Amoxicillin
Reporting group description: Amoxicillin 750 mg three times daily for 100 days	
Reporting group title	Placebo
Reporting group description: Placebo (maiz starch) three times daily for 100 days	
Reporting group title	Amoxicillin
Reporting group description: Capsulated Amoxicillin 750 mg three times daily for 100 days	
Reporting group title	Placebo
Reporting group description: Encapsulated maize starch three times daily for 100 days	
Reporting group title	Amoxicillin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized patients	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description: All randomized patients without any major protocol deviation. Major protocol deviations were defined as (a) intake of < 80% of the pills (amoxicillin or placebo), (b) pause of the study medication for ≥ 2 weeks (in the antibiotic group: without other 'relevant' antibiotic treatment in that period), (c) 'relevant' antibiotic treatment in the placebo group for ≥ 4 continuous weeks between baseline and one-year follow-up, and (d) back surgery during the one-year follow-up. 'Relevant' antibiotic treatment was antibiotic treatment likely to affect a C. acne discitis. Further events registered as major protocol deviations were faulty inclusion (2 patients treated with antibiotics last month prior to inclusion), both amoxicillin and placebo given to patient by mistake (1 patient), and spondyloarthritis diagnosed during follow-up (1 patient).	

Primary: Roland-Morris Disability Questionnaire

End point title	Roland-Morris Disability Questionnaire
End point description:	
End point type	Primary
End point timeframe: 1 year	

End point values	Amoxicillin	Placebo	Amoxicillin	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	88	90	85	87
Units: 24				
arithmetic mean (standard deviation)	12.7 (± 4.7)	12.8 (± 3.7)	10.3 (± 5.8)	12.4 (± 4.4)

End point values	Amoxicillin	Placebo	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	85	84	178	
Units: 24				
arithmetic mean (standard deviation)	9.0 (± 6.2)	10.7 (± 5.6)	12.8 (± 4.2)	

Statistical analyses

Statistical analysis title	ANCOVA on RMDQ at 1 year
Statistical analysis description:	
Compared mean RMDQ scores between the amoxicillin group and the placebo group in the whole intention-to-treat population at 1 year using ANCOVA, adjusted for baseline RMDQ score and the stratification variables; Modic type (type 1/type 2) and former disc surgery (yes/no). Missing RMDQ values were imputed with a multiple imputation model. All 180 randomized patients were included in the analysis (imputation was performed for patients with missing values).	
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.04 ^[2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	0
Variability estimate	Standard error of the mean

Notes:

[1] - 180 subjects analysed

[2] - Significance level set to 0.05 (primary analysis)

Statistical analysis title	Linear Mixed Effects on RMDQ at 1 year
Statistical analysis description:	
A linear mixed-effects model for the ITT population with RMDQ as dependent variable, an interaction term between time and intervention group, treating time as a categorical variable, and with an unstructured covariance matrix.	
Comparison groups	Placebo v Amoxicillin

Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	-0.1
Variability estimate	Standard error of the mean

Secondary: Oswestry Disability Index

End point title	Oswestry Disability Index
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, 3 months and 1 year	

End point values	Amoxicillin	Placebo	Amoxicillin	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	88	89	86	85
Units: 100				
arithmetic mean (standard deviation)	31.9 (± 11.4)	31.8 (± 10.3)	26.6 (± 14.7)	30.4 (± 10.7)

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	84		
Units: 100				
arithmetic mean (standard deviation)	24.4 (± 10.0)	28.9 (± 14.0)		

Statistical analyses

Statistical analysis title	ANCOVA on ODI at 1 year
Statistical analysis description:	
See ANCOVA analysis of RMDQ	
Comparison groups	Amoxicillin v Placebo

Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.007 ^[4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.3
upper limit	-1.4
Variability estimate	Standard error of the mean

Notes:

[3] - 179 subjects analysed

[4] - Significance level set to 0.0167 due to multiple testing

Statistical analysis title	Linear Mixed Effects on ODI at 1 year
Statistical analysis description:	
See analysis of RMDQ	
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.004
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	-1.6
Variability estimate	Standard error of the mean

Notes:

[5] - 180 subjects analysed

Secondary: Back pain intensity

End point title	Back pain intensity
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, 3 months an 1 year	

End point values	Amoxicillin	Placebo	Amoxicillin	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	88	90	85	85
Units: 10				
arithmetic mean (standard deviation)	6.4 (± 1.2)	6.3 (± 1.5)	5.2 (± 2.3)	5.4 (± 1.9)

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	84		
Units: 10				
arithmetic mean (standard deviation)	4.7 (± 2.3)	5.2 (± 2.3)		

Statistical analyses

Statistical analysis title	ANCOVA on Back pain intensity at 1 year
Statistical analysis description: See analysis on RMDQ	
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.06 ^[7]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0
Variability estimate	Standard error of the mean

Notes:

[6] - 179 subjects included

[7] - Significance level set to 0.0167 due to multiple testing

Statistical analysis title	Linear Mixed Effects on Back pain intensity at 1 y
Statistical analysis description: A LME model for the ITT population with LBP intensity as a dependent variable (with a total of 17 time points), with an interaction term between time and intervention group, treating time as a categorical variable, and an exchangeable covariance structure.	
Comparison groups	Amoxicillin v Placebo

Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.005
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	-0.2
Variability estimate	Standard error of the mean

Notes:

[8] - 180 subjects included in analysis

Secondary: EQ5D (Quality of life score)

End point title	EQ5D (Quality of life score)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, 3 months and 1 year	

End point values	Amoxicillin	Placebo	Amoxicillin	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	89	91	85	83
Units: -0.59 til 1				
arithmetic mean (standard deviation)	0.55 (± 0.19)	0.54 (± 0.18)	0.60 (± 0.22)	0.54 (± 0.21)

End point values	Amoxicillin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	83		
Units: -0.59 til 1				
arithmetic mean (standard deviation)	0.65 (± 0.22)	0.58 (± 0.22)		

Statistical analyses

Statistical analysis title	ANCOVA on EQ5D at 1 year
Statistical analysis description:	
See analysis on RMDQ	
Comparison groups	Amoxicillin v Placebo

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.012 ^[10]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.12
Variability estimate	Standard error of the mean

Notes:

[9] - 180 subjects analysed

[10] - Significance level set to 0.0167 due to multiple testing

Statistical analysis title	Linear Mixed Effects on EQ5D at 1 year
Statistical analysis description:	
See analysis on RMDQ	
Comparison groups	Amoxicillin v Placebo
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.13
Variability estimate	Standard error of the mean

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to 1 year follow up

Adverse event reporting additional description:

Trial care providers (physicians or physiotherapists) performed active surveillance of side effects/adverse events (clinical and biochemical) from baseline to 1 year. Adverse events were monitored and cross-checked against clinical patient notes, and all are reported. Same episode of AE recorded more than once is just reported as one AE here.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	4.0

Reporting groups

Reporting group title	Amoxicillin
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Amoxicillin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 89 (6.74%)	2 / 91 (2.20%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma in situ	Additional description: Malignant cell contained in the resected area		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 89 (1.12%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture	Additional description: Not operated		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 89 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Headache	Additional description: Hospitalized due to headache		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 89 (1.12%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Hypercholesterolaemia	Additional description: Hospitalized due to suspicion of myocardial infarction		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 89 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis	Additional description: DVT in right groin after flight. Genetic predisposition.		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 89 (1.12%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc herniation	Additional description: Resulted in operative procedure		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 89 (2.25%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas	Additional description: Treated in hospital		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 89 (1.12%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Amoxicillin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 89 (76.40%)	61 / 91 (67.03%)	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 89 (3.37%)	9 / 91 (9.89%)	
occurrences (all)	5	9	
General disorders and administration site conditions			
Flu like symptoms			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 89 (8.99%)	6 / 91 (6.59%)	
occurrences (all)	10	6	
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	20 / 89 (22.47%)	17 / 91 (18.68%)	
occurrences (all)	24	20	
Abdominal pain upper			
subjects affected / exposed	7 / 89 (7.87%)	2 / 91 (2.20%)	
occurrences (all)	7	2	
Nausea			
subjects affected / exposed	9 / 89 (10.11%)	3 / 91 (3.30%)	
occurrences (all)	9	3	
Skin and subcutaneous tissue disorders			
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 89 (5.62%)	0 / 91 (0.00%)	
occurrences (all)	5	0	
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Not clearly defined term in this study population, as all had chronic low back pain. Meant to describe an episode of worsened low back pain that was more severe than what could be expected by the natural history.		
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 89 (14.61%)	18 / 91 (19.78%)	
occurrences (all)	13	21	
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 89 (3.37%) 4	6 / 91 (6.59%) 6	
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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31619437>