



Clinical trial results:

Do oral corticosteroids provide clinical and cost-effective symptom relief for sore throat? A multi-centre, double blind, randomized, placebo-controlled trial.

Summary

EudraCT number	2012-004330-41
Trial protocol	GB
Global end of trial date	16 April 2015

Results information

Result version number	v1 (current)
This version publication date	01 May 2016
First version publication date	01 May 2016

Trial information

Trial identification

Sponsor protocol code	CH-GH/TOAST/0006
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Additional study identifiers

ISRCTN number	ISRCTN17435450
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Block 60, Churchill Hospital, Oxford, United Kingdom, OX3 7LJ
Public contact	Professor Carl Heneghan, Nuffield Department of Primary Care Health Sciences, University of Oxford, carl.heneghan@phc.ox.ac.uk
Scientific contact	Professor Carl Heneghan, Nuffield Department of Primary Care Health Sciences, University of Oxford, carl.heneghan@phc.ox.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 April 2015
Global end of trial reached?	Yes
Global end of trial date	16 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate in adults 18 years and over presenting to their GP with acute sore throat, if the use of a single dose of an oral steroid, dexamethasone, compared with no steroid treatment leads to increased resolution or improvement in symptoms.

Protection of trial subjects:

The DSMC were conducted to review of all SAEs for the study reported during the quarter and cumulatively.

No formal interim analysis is planned to stop the trial early.

Dexamethasone is already licenced and used at this dosage in a wide variety of disorders as well as in the control of cerebral oedema. Previous trials have not reported any serious adverse events nor differences in all adverse events, relapse or recurrence rates between participants receiving corticosteroids and those receiving placebo, hence it is anticipated that the likelihood of serious adverse events (SAEs) associated with a single dose of dexamethasone 10mg taken orally will be extremely low. There is therefore no defined criteria for termination of the trial due to safety however serious adverse events and events leading to withdrawal will be reviewed in order to monitor anything unexpected.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 576
Worldwide total number of subjects	576
EEA total number of subjects	576

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)	546
From 65 to 84 years	26
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

The first participant was recruited on 12th April 2013 and the final participant on 27th February 2015. Participants were recruited from general practices in Oxford, Bristol, and Southampton in England, UK. The site gives adults presenting with sore throat a participant information sheet which details what is involved in trial participation.

Pre-assignment

Screening details:

During the initial consultation the primary care clinician (referred to from now onwards as the responsible clinician) discusses trial participation and screens the participant using the inclusion and exclusion criteria.

Period 1

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

Blinding implementation details:

Matching placebo and use of pack numbers. The pack numbers are produced by an independent statistician who was not involved in any other aspect of the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Dexamethasone

Arm description:

10mg oral dexamethasone

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

Dosage and administration details:

5 x 2mg tablets were over-encapsulated into one capsule and was administered orally as single dose.

Arm title	Placebo
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Arm description:

Placebo - Single capsule using lactose

Arm type	Placebo
Investigational medicinal product name	PR1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matching size 1 capsule using lactose. Administered orally as the IMP

Number of subjects in period 1	Dexamethasone	Placebo
Started	293	283
Completed	293	283

Period 2

Period 2 title	Subgroup - No antibiotic prescription
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Dexamethasone
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

5 x 2mg tablets were over-encapsulated into one capsule and was administered orally as single dose.

Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	PR1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matching size 1 capsule using lactose. Administered orally as the IMP

Number of subjects in period 2 ^[1]	Dexamethasone	Placebo
Started	175	174
Completed	175	174

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Data provided in Period 2 relates to the subgroup receiving a delayed antibiotic prescription, as specified in the protocol as a secondary objective.

Baseline characteristics

Reporting groups

Reporting group title	Dexamethasone
Reporting group description: 10mg oral dexamethasone	
Reporting group title	Placebo
Reporting group description: Placebo - Single capsule using lactose	

Reporting group values	Dexamethasone	Placebo	Total
Number of subjects	293	283	576
Age categorical			
Age at randomisation			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	3	3
Adults (18-64 years)	276	267	543
From 65-84 years	16	10	26
85 years and over	1	3	4
Age continuous			
Age at randomisation			
Units: years			
arithmetic mean	33.7	34.2	
inter-quartile range (Q1-Q3)	26.2 to 45.7	25.6 to 45	-
Gender categorical			
Units: Subjects			
Female	226	210	436
Male	67	73	140
Smoking status			
Units: Subjects			
Non-smoker	197	177	374
Smoker	53	52	105
Ex-smoker	43	54	97
In paid work or education			
Units: Subjects			
No	71	62	133
Full-Time	175	175	350
Part-Time	47	46	93
Study centre			
Units: Subjects			
Bristol	79	73	152
Oxford	144	141	285

Southampton	70	69	139
Symptoms - sore throat			
Units: Subjects			
None	0	0	0
Slight	11	9	20
Moderate	187	179	366
Severe	95	95	190
Symptom - runny nose in last 24 hours			
Units: Subjects			
None	165	144	309
Slight	75	80	155
Moderate	47	53	100
Severe	6	6	12
Symptom - runny nose during illness			
Units: Subjects			
None	163	150	313
Slight	81	84	165
Moderate	44	42	86
Severe	5	7	12
Symptom - cough in last 24 hours			
Units: Subjects			
None	131	117	248
Slight	84	89	173
Moderate	61	64	125
Severe	17	13	30
Symptom - cough during illness			
Units: Subjects			
None	128	113	241
Slight	88	90	178
Moderate	65	68	133
Severe	12	12	24
Symptom - hoarse in last 24 hours			
Units: Subjects			
None	114	99	213
Slight	93	97	190
Moderate	59	61	120
Severe	27	26	53
Symptom - hoarse voice during illness			
Units: Subjects			
None	112	90	202
Slight	99	108	207
Moderate	63	67	130
Severe	19	18	37
Symptom - disturbed sleep			
Units: Subjects			
None	68	60	128
Slight	70	68	138
Moderate	91	97	188
Severe	64	58	122
Symptom - difficulty swallowing			
Units: Subjects			

None	17	15	32
Slight	74	68	142
Moderate	133	139	272
Severe	69	61	130
Symptom - generally unwell Units: Subjects			
None	46	45	91
Slight	97	73	170
Moderate	129	140	269
Severe	21	25	46
Symptom - fever in last 24 hours Units: Subjects			
None	131	137	268
Slight	82	73	155
Moderate	70	59	129
Severe	10	14	24
Symptom - fever during illness Units: Subjects			
None	127	130	257
Slight	81	71	152
Moderate	74	68	142
Severe	11	14	25
Symptom - headache Units: Subjects			
None	135	113	248
Slight	76	74	150
Moderate	65	75	140
Severe	17	21	38
Symptom -muscle ache Units: Subjects			
None	150	132	282
Slight	66	69	135
Moderate	58	64	122
Severe	19	18	37
Symptom - abdominal pain Units: Subjects			
None	255	245	500
Slight	27	25	52
Moderate	10	9	19
Severe	1	4	5
Symptom - diarrhoea Units: Subjects			
None	271	262	533
Slight	18	14	32
Moderate	4	4	8
Severe	0	3	3
Symptom - vomiting Units: Subjects			
None	279	268	547
Slight	8	10	18
Moderate	6	4	10

Severe	0	1	1
Symptom - earache			
Units: Subjects			
None	161	176	337
Slight	83	61	144
Moderate	40	36	76
Severe	9	10	19
Physical examination			
Units: Subjects			
None	34	29	63
Slight	74	65	139
Moderate	163	170	333
Severe	22	19	41
Presence of tonsils			
Units: Subjects			
No	89	88	177
Yes	204	195	399
Cervical lymphadenopathy			
Units: Subjects			
No	158	158	316
Yes	135	125	260
Delayed antibiotic prescription			
Units: Subjects			
No	175	174	349
Yes	118	109	227
Fever PAIN score			
Units: Subjects			
Low (0-1)	147	146	293
Intermediate (2-3)	140	132	272
High (4-5)	6	5	11
Centor Score			
Units: Subjects			
Not severe (≤ 2)	252	242	494
Severe (> 2)	41	41	82
Throat swab completed			
Units: Subjects			
No	28	35	63
Yes	265	248	513
Inflamed Tonsils			
Only those who have presence of tonsils			
Units: Subjects			
None	68	71	139
Slight	52	36	88
Moderate	75	83	158
Severe	9	5	14
N/A	89	88	177
Purulent tonsils			
Only those who had presence of tonsils			
Units: Subjects			
No	173	164	337
Yes	31	31	62

N/A	89	88	177
Tender cervical lymphadenopathy			
If cervical lymphadenopathy = yes			
Units: Subjects			
No	37	31	68
Yes	98	94	192
N/A	158	158	316
Delayed antibiotic prescription			
Units: Subjects			
No	175	174	349
Yes	118	109	227
Delayed Antibiotic prescription medication			
If delayed antibiotic prescription = yes			
Units: Subjects			
Penicillin PV	93	75	168
Erythromycin	1	6	7
Clarithromycin	8	6	14
Doxycycline	2	1	3
Co-amoxiclav (augmentin)	0	3	3
Amoxicillin	13	17	30
Other	1	1	2
N/A	175	174	349
Streptococcal Group A			
If throat swab completed = yes			
Units: Subjects			
No significant growth	234	214	448
Organism isolated	31	34	65
N/A	28	35	63
Streptococcal group C			
If throat swab completed = yes			
Units: Subjects			
No significant growth	258	238	496
Organism isolated	7	10	17
N/A	28	35	63
Streptococcal group G			
If throat swab completed = yes			
Units: Subjects			
No significant growth	264	245	509
Organism isolated	1	3	4
N/A	28	35	63
Duration of pain			
Units: Days			
arithmetic mean	3.9	3.9	
standard deviation	± 2	± 1.8	-
Duration of sore throat			
Units: Days			
arithmetic mean	3.9	3.9	
standard deviation	± 2	± 1.8	-
Patient temperature			
Units: degree celcius			
arithmetic mean	36.8	36.8	

standard deviation	± 0.5	± 0.6	-
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Subject analysis sets

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

Subject analysis set description:

The primary analysis were intention to treat (ITT). All eligible randomised patients were included in the analysis of the primary outcome, assuming no complete resolution for any missing data. Ineligible participants (i.e. not in the target population) who were randomised in error were detailed in the CONSORT flow chart and were excluded from all analyses. Therefore, all endpoints analyses will be identical for ITT and reporting groups.

Reporting group values	ITT		
Number of subjects	565		
Age categorical			
Age at randomisation			
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)	536		
From 65-84 years	25		
85 years and over	4		
Age continuous			
Age at randomisation			
Units: years			
arithmetic mean	37.2		
inter-quartile range (Q1-Q3)	26 to 45.5		
Gender categorical			
Units: Subjects			
Female	425		
Male	140		
Smoking status			
Units: Subjects			
Non-smoker	368		
Smoker	103		
Ex-smoker	94		
In paid work or education			
Units: Subjects			
No	131		
Full-Time	341		
Part-Time	93		
Study centre			
Units: Subjects			
Bristol	151		

Oxford	282		
Southampton	132		
Symptoms - sore throat Units: Subjects			
None	0		
Slight	20		
Moderate	362		
Severe	183		
Symptom - runny nose in last 24 hours Units: Subjects			
None	301		
Slight	152		
Moderate	100		
Severe	12		
Symptom - runny nose during illness Units: Subjects			
None	306		
Slight	162		
Moderate	85		
Severe	12		
Symptom - cough in last 24 hours Units: Subjects			
None	242		
Slight	171		
Moderate	123		
Severe	29		
Symptom - cough during illness Units: Subjects			
None	236		
Slight	175		
Moderate	130		
Severe	24		
Symptom - hoarse in last 24 hours Units: Subjects			
None	208		
Slight	189		
Moderate	115		
Severe	53		
Symptom - hoarse voice during illness Units: Subjects			
None	197		
Slight	206		
Moderate	125		
Severe	37		
Symptom - disturbed sleep Units: Subjects			
None	123		
Slight	137		
Moderate	186		
Severe	119		
Symptom - difficulty swallowing			

Units: Subjects			
None	31		
Slight	140		
Moderate	186		
Severe	119		
Symptom - generally unwell			
Units: Subjects			
None	88		
Slight	165		
Moderate	267		
Severe	45		
Symptom - fever in last 24 hours			
Units: Subjects			
None	262		
Slight	152		
Moderate	127		
Severe	23		
Symptom - fever during illness			
Units: Subjects			
None	252		
Slight	150		
Moderate	139		
Severe	24		
Symptom - headache			
Units: Subjects			
None	244		
Slight	147		
Moderate	137		
Severe	37		
Symptom - muscle ache			
Units: Subjects			
None	275		
Slight	133		
Moderate	120		
Severe	37		
Symptom - abdominal pain			
Units: Subjects			
None	490		
Slight	51		
Moderate	19		
Severe	5		
Symptom - diarrhoea			
Units: Subjects			
None	522		
Slight	32		
Moderate	8		
Severe	3		
Symptom - vomiting			
Units: Subjects			
None	437		
Slight	17		

Moderate	10		
Severe	1		
Symptom - earache			
Units: Subjects			
None	230		
Slight	141		
Moderate	76		
Severe	18		
Physical examination			
Units: Subjects			
None	63		
Slight	135		
Moderate	329		
Severe	38		
Presence of tonsils			
Units: Subjects			
No	174		
Yes	391		
Cervical lymphadenopathy			
Units: Subjects			
No	311		
Yes	254		
Delayed antibiotic prescription			
Units: Subjects			
No	342		
Yes	223		
Fever PAIN score			
Units: Subjects			
Low (0-1)	288		
Intermediate (2-3)	266		
High (4-5)	11		
Centor Score			
Units: Subjects			
Not severe (<=2)	284		
Severe (>2)	81		
Throat swab completed			
Units: Subjects			
No	63		
Yes	502		
Inflamed Tonsils			
Only those who have presence of tonsils			
Units: Subjects			
None	138		
Slight	86		
Moderate	156		
Severe	11		
N/A	174		
Purulent tonsils			
Only those who had presence of tonsils			
Units: Subjects			
No	330		

Yes	61		
N/A	174		
Tender cervical lymphadenopathy			
If cervical lymphadenopathy = yes			
Units: Subjects			
No	65		
Yes	189		
N/A	311		
Delayed antibiotic prescription			
Units: Subjects			
No	343		
Yes	223		
Delayed Antibiotic prescription medication			
If delayed antibiotic prescription = yes			
Units: Subjects			
Penicillin PV	165		
Erythromycin	7		
Clarithromycin	14		
Doxycycline	3		
Co-amoxiclav (augmentin)	3		
Amoxicillin	29		
Other	2		
N/A	343		
Streptococcal Group A			
If throat swab completed = yes			
Units: Subjects			
No significant growth	439		
Organism isolated	63		
N/A	63		
Streptococcal group C			
If throat swab completed = yes			
Units: Subjects			
No significant growth	485		
Organism isolated	17		
N/A	63		
Streptococcal group G			
If throat swab completed = yes			
Units: Subjects			
No significant growth	498		
Organism isolated	4		
N/A	63		
Duration of pain			
Units: Days			
arithmetic mean	3.9		
standard deviation	± 1.7		
Duration of sore throat			
Units: Days			
arithmetic mean	3.9		
standard deviation	± 1.7		
Patient temperature			
Units: degree celcius			

arithmetic mean	36.8		
standard deviation	± 0.6		

End points

End points reporting groups

Reporting group title	Dexamethasone
Reporting group description:	
10mg oral dexamethasone	
Reporting group title	Placebo
Reporting group description:	
Placebo - Single capsule using lactose	
Reporting group title	Dexamethasone
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The primary analysis were intention to treat (ITT). All eligible randomised patients were included in the analysis of the primary outcome, assuming no complete resolution for any missing data. Ineligible participants (i.e. not in the target population) who were randomised in error were detailed in the CONSORT flow chart and were excluded from all analyses. Therefore, all endpoints analyses will be identical for ITT and reporting groups.	

Primary: Resolution of sore throat 24 hours

End point title	Resolution of sore throat 24 hours
End point description:	
Had your sore throat completely resolved 24 hours after taking the medication?	
End point type	Primary
End point timeframe:	
24 hours	

End point values	Dexamethason e	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	288	277	565	
Units: subjects				
No	223	228	451	
Yes	65	49	114	

Statistical analyses

Statistical analysis title	Primary Analysis
Statistical analysis description:	
The primary outcome of resolution of sore throat 24 hours after randomisation was analysed using a log-binomial regression model adjusted for centre and whether or not the patient received a delayed prescription for antibiotics.	
Comparison groups	Dexamethasone v Placebo

Number of subjects included in analysis	565
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.144
Method	Log-binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.78

Secondary: Complete resolution of sore throat at 48 hours

End point title	Complete resolution of sore throat at 48 hours
End point description:	
End point type	Secondary
End point timeframe:	
48 hours	

End point values	Dexamethason e	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	288	277	565	
Units: Subjects				
No	186	202	388	
Yes	102	75	177	

Statistical analyses

Statistical analysis title	Primary Analysis
Statistical analysis description:	
Adjusted for centre and whether or not the patient received a delayed prescription for antibiotics	
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	565
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031
Method	Log-binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	1.31

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.68

Secondary: Resolution at 24 hours (delayed antibiotic prescription)

End point title	Resolution at 24 hours (delayed antibiotic prescription)
End point description:	
End point type	Secondary
End point timeframe:	
24 hours	

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	169		
Units: Subjects				
No	130	137		
Yes	43	32		

Statistical analyses

Statistical analysis title	Secondary analysis
Statistical analysis description:	
Model adjusted for centre	
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Log-binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.96

Secondary: Time to onset of pain relief

End point title	Time to onset of pain relief
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End point description:

End point type	Secondary
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End point timeframe:

within 7 days

End point values	Dexamethason e	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	102		
Units: hours				
median (inter-quartile range (Q1-Q3))	27.5 (21 to 44.5)	27 (21.4 to 45.8)		

Statistical analyses

Statistical analysis title	Secondary analysis
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Statistical analysis description:

Adjusted for delayed antibiotic prescription and centre.

Comparison groups	Dexamethasone v Placebo
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Number of subjects included in analysis	231
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.452
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Method	Regression, Cox
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Parameter estimate	Hazard ratio (HR)
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Point estimate	1.106
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0.85
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upper limit	1.44
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Secondary: Time completed symptom resolution

End point title	Time completed symptom resolution
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End point description:

End point type	Secondary
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End point timeframe:

within 7 days

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	94		
Units: hours				
median (inter-quartile range (Q1-Q3))	65.8 (41 to 105.9)	60 (39.8 to 92.3)		

Statistical analyses

Statistical analysis title	Secondary analysis
Statistical analysis description: Adjusted for delayed antibiotic prescription and centre.	
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.776
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.781
upper limit	1.393

Secondary: Pain on swallowing

End point title	Pain on swallowing
End point description: Days reporting moderately bad (or worse) symptom over 7 days from treatment onset	
End point type	Secondary
End point timeframe: 7 days	

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	197		
Units: days				
0 days	73	72		
1 day	41	54		
2 days	27	27		
3 days	27	19		
4 days	12	11		
5 days	6	6		
6 days	5	1		
7 days	3	7		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
Adjusted for delayed prescriptions at baseline and centre, and including the number of completed diary as an offset.	
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.569
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	1.075
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.837
upper limit	1.381

Secondary: Sore throat

End point title	Sore throat
End point description:	
Days reporting moderately bad (or worse) symptom over 7 days from treatment onset	
End point type	Secondary
End point timeframe:	
7 days	

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	197		
Units: Subjects				
0 days	58	54		
1 day	44	55		
2 days	27	30		
3 days	26	22		
4 days	18	18		
5 days	8	5		
6 days	7	3		
7 days	6	10		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
The total number of days reporting at least moderately bad symptoms were analysed using a negative binomial model adjusting for centre, delayed prescriptions at baseline and including the number of completed diary days as an offset.	
Comparison groups	Placebo v Dexamethasone
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.563
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	1.068
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.854
upper limit	1.336

Secondary: Difficulty swallowing

End point title	Difficulty swallowing
End point description:	
Days reporting moderately bad (or worse) symptom over 7 days from treatment onset	
End point type	Secondary
End point timeframe:	
7 days	

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	197		
Units: Subjects				
0 days	100	97		
1 day	33	41		
2 days	22	22		
3 days	23	17		
4 days	7	9		
5 days	5	5		
6 days	2	2		
7 days	2	4		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
The total number of days reporting at least moderately bad symptoms were analysed using a negative binomial model adjusting for centre, delayed prescriptions at baseline and including the number of completed diary days as an offset.	
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.947
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	1.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.738
upper limit	1.385

Secondary: Feeling unwell

End point title	Feeling unwell
End point description:	
Days reporting moderately bad (or worse) symptom over 7 days from treatment onset	
End point type	Secondary
End point timeframe:	
7 days	

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	197		
Units: Subjects				
0 days	85	80		
1 day	30	43		
2 days	23	25		
3 days	19	13		
4 days	13	16		
5 days	9	8		
6 days	8	5		
7 days	7	7		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
The total number of days reporting at least moderately bad symptoms were analysed using a negative binomial model adjusting for centre, delayed prescriptions at baseline and including the number of completed diary days as an offset.	
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.672
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	1.064
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.799
upper limit	1.416

Secondary: Cough

End point title	Cough
End point description:	
Days reporting moderately bad (or worse) symptom over 7 days from treatment onset	
End point type	Secondary
End point timeframe:	
7 days	

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	197		
Units: Subjects				
0 days	111	118		
1 day	14	25		
2 days	14	8		
3 days	8	12		
4 days	7	6		
5 days	15	9		
6 days	9	7		
7 days	16	12		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
The total number of days reporting at least moderately bad symptoms were analysed using a negative binomial model adjusting for centre, delayed prescriptions at baseline and including the number of completed diary days as an offset.	
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.329
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.819
upper limit	1.818

Secondary: Fever

End point title	Fever
End point description:	
Days reporting moderately bad (or worse) symptom over 7 days from treatment onset	
End point type	Secondary
End point timeframe:	
7 days	

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	197		
Units: Subjects				
0 days	157	148		
1 day	19	29		
2 days	10	7		
3 days	6	6		
4 days	0	5		
5 days	1	1		
6 days	0	1		
7 days	1	0		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
The total number of days reporting at least moderately bad symptoms were analysed using a negative binomial model adjusting for centre, delayed prescriptions at baseline and including the number of completed diary days as an offset.	
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.173
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	0.684
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.396
upper limit	1.181

Secondary: Sleep disturbance

End point title	Sleep disturbance
End point description:	
Days reporting moderately bad (or worse) symptom over 7 days from treatment onset	
End point type	Secondary
End point timeframe:	
7 days	

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	197		
Units: Subjects				
0 days	99	98		
1 day	32	40		
2 days	20	19		
3 days	16	12		
4 days	10	9		
5 days	4	7		
6 days	1	3		
7 days	12	9		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
The total number of days reporting at least moderately bad symptoms were analysed using a negative binomial model adjusting for centre, delayed prescriptions at baseline and including the number of completed diary days as an offset.	
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.595
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	1.095
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.783
upper limit	1.533

Secondary: Tender glands in neck

End point title	Tender glands in neck
End point description:	
Days reporting moderately bad (or worse) symptom over 7 days from treatment onset	
End point type	Secondary
End point timeframe:	
7 days	

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	197		
Units: Subjects				
0 days	149	146		
1 day	14	29		
2 days	15	5		
3 days	4	5		
4 days	3	6		
5 days	3	2		
6 days	3	2		
7 days	3	2		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
The total number of days reporting at least moderately bad symptoms were analysed using a negative binomial model adjusting for centre, delayed prescriptions at baseline and including the number of completed diary days as an offset.	
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.89
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	0.974
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.674
upper limit	1.408

Secondary: Change in mood

End point title	Change in mood
End point description:	
Days reporting moderately bad (or worse) symptom over 7 days from treatment onset	
End point type	Secondary
End point timeframe:	
7 days	

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	197		
Units: Subjects				
0 days	149	146		
1 day	14	29		
2 days	15	5		
3 days	4	5		
4 days	3	6		
5 days	3	2		
6 days	3	2		
7 days	3	2		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
The total number of days reporting at least moderately bad symptoms were analysed using a negative binomial model adjusting for centre, delayed prescriptions at baseline and including the number of completed diary days as an offset.	
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	1.283
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.745
upper limit	2.21

Secondary: Vomiting

End point title	Vomiting
End point description:	
Days reporting moderately bad (or worse) symptom over 7 days from treatment onset	
End point type	Secondary
End point timeframe:	
7 days	

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194	197		
Units: Subjects				
0 days	186	189		
1 day	5	4		
2 days	1	3		
3 days	0	1		
4 days	0	0		
5 days	0	0		
6 days	0	0		
7 days	2	0		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
The total number of days reporting at least moderately bad symptoms were analysed using a negative binomial model adjusting for centre, delayed prescriptions at baseline and including the number of completed diary days as an offset.	
Comparison groups	Placebo v Dexamethasone
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.815
Method	Negative binomial model
Parameter estimate	Incidence rate ratio
Point estimate	1.174
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.305
upper limit	4.514

Secondary: Uptake of delayed antibiotic prescription

End point title	Uptake of delayed antibiotic prescription
End point description:	
End point type	Secondary
End point timeframe:	
7 days	

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	108		
Units: Subjects				
No	36	30		
Yes	79	78		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
Adjusted for centre	
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.233
Method	Log-binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.831
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.613
upper limit	1.126

Secondary: Sore throat pain

End point title	Sore throat pain
End point description:	
Summarised as area under the curve over 7 days using trapezoidal rule with estimates from mixed effects repeated measures model adjusting for symptom at baseline, centre, and delayed antibiotic prescription.	
End point type	Secondary
End point timeframe:	
7 days	

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	195		
Units: points				
arithmetic mean (confidence interval 95%)	181.8 (173.5 to 190)	179.7 (171.9 to 187.5)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	388
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.723
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	2.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.282
upper limit	13.377

Notes:

[1] - Linear Regression model adjusting for symptom at baseline, centre and delayed antibiotic prescription

Secondary: Pain on swallowing VAS scores

End point title	Pain on swallowing VAS scores
End point description:	
Summarised as area under the curve over 7 days using trapezoidal rule with estimates from mixed effects repeated measures model adjusting for symptom at baseline, centre, and delayed antibiotic prescription.	
End point type	Secondary
End point timeframe:	
7 days	

End point values	Dexamethason e	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	194		
Units: points				
arithmetic mean (confidence interval 95%)	163.3 (153.6 to 173)	165 (155.9 to 174.1)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.798
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-1.728
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.985
upper limit	11.529

Secondary: Difficulty swallowing scores VAS

End point title	Difficulty swallowing scores VAS
End point description:	
Summarised as area under the curve over 7 days using trapezoidal rule with estimates from mixed effects repeated measures model adjusting for symptom at baseline, centre, and delayed antibiotic prescription.	
End point type	Secondary
End point timeframe:	
7 days	

End point values	Dexamethason e	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	193		
Units: points				
arithmetic mean (confidence interval 95%)	134.6 (124 to 145.2)	143.5 (133.2 to 153.8)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	386
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.236
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	-8.904

Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.646
upper limit	5.838

Secondary: Use of OTC or prescribed medication for sore throat

End point title	Use of OTC or prescribed medication for sore throat
End point description:	
End point type	Secondary
End point timeframe:	
7 days	

End point values	Dexamethason e	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	277		
Units: Subjects				
No	156	152		
Yes	50	59		
Missing	82	66		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
Log binomial model adjusted for centre and delayed antibiotic prescription	
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	565
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk ratio (RR)
Point estimate	0.834
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.625
upper limit	1.114

Secondary: Use of OTC or prescribed antibiotics for other reasons

End point title	Use of OTC or prescribed antibiotics for other reasons
End point description:	
End point type	Secondary
End point timeframe:	
7 days	

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	277		
Units: Subjects				
No	201	202		
Yes	5	9		
Missing	82	66		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
Log binomial model adjusted for centre and delayed antibiotic prescription	
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	565
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.581
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.199
upper limit	1.701

Secondary: Use of OTC or prescribed oral or topical analgesia

End point title	Use of OTC or prescribed oral or topical analgesia
End point description:	
End point type	Secondary
End point timeframe:	
7 days	

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	277		
Units: Subjects				
No	59	57		
Yes	147	154		
Missing	82	66		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
Log binomial model adjusted for centre and delayed antibiotic prescription	
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	565
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.983
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.874
upper limit	1.105

Secondary: Use of GP practices, A&E, OOO centres

End point title	Use of GP practices, A&E, OOO centres
End point description:	
Use of any GP practice, A&E OOO centres and telephone contact in the 28 days following the initial trial appointment	
End point type	Secondary
End point timeframe:	
28 days	

End point values	Dexamethasone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	277		
Units: Subjects				
Yes - associated with sore throat	36	25		
No or not associated with sore throat	252	252		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description: Log binomial model adjusted for centre and delayed antibiotic prescription	
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	565
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.175
Method	Log-binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	1.392
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.863
upper limit	2.244

Secondary: Time missed from work or education over 7 days

End point title	Time missed from work or education over 7 days
End point description:	
End point type	Secondary
End point timeframe: 7 days	

End point values	Dexamethason e	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	166		
Units: hours				
arithmetic mean (standard deviation)	6.07 (± 11.3)	5.99 (± 10)		

Statistical analyses

Statistical analysis title	Secondary outcome analysis
Statistical analysis description:	
Linear regression adjusted for centre and delayed antibiotic prescription.	
Comparison groups	Dexamethasone v Placebo
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.846
Method	Regression, Linear
Parameter estimate	Median difference (net)
Point estimate	0.235
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.143
upper limit	2.612

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

During the trial

Adverse event reporting additional description:

Dexamethasone is a commonly used medication in a primary care setting; it has well defined safety profiles and is being used in this trial for authorised indications. As a result of this no non-serious adverse events will be recorded in this study.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Dexamethasone
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

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: Dexamethasone is a commonly used medication in a primary care setting; it has well defined safety profiles and is being used in this trial for authorised indications. As a result of this no non-serious adverse events will be recorded in this study.

Serious adverse events	Dexamethasone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 288 (0.69%)	3 / 277 (1.08%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Hospital admission with parapharyngeal abscess			
subjects affected / exposed	1 / 288 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Hospital admission with pneumonia with subsequent death in the community		
subjects affected / exposed	0 / 288 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Social circumstances			
Death	Additional description: Patient died. Cause of death murder. No further details available		

subjects affected / exposed	1 / 288 (0.35%)	0 / 277 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Tonsillitis			
subjects affected / exposed	0 / 288 (0.00%)	1 / 277 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospital admission with peritonsillar abscess			
subjects affected / exposed	0 / 288 (0.00%)	1 / 277 (0.36%)	
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: 0 %

Non-serious adverse events	Dexamethasone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 288 (0.00%)	0 / 277 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 April 2013	Clarified one the outcome measures and details of the data collection which has already been approved in order to have complete consistency between all our documentation.
08 July 2013	Amendment to the sample size and also extending the follow up process through the text message system and with a thank you of a £10 gift voucher once they return all of the follow up documentation.
02 September 2013	Listed all of our new research sites and have added two further Principal Investigators on the protocol.
13 March 2014	Introducing an upper age limit of 70 to the inclusion criteria.
09 June 2014	Listed all of new research sites. In addition, recruitment period has been extended to the end of December 2014.
30 July 2014	The amendment relates to an increase in the value of the gift card that participants will receive once they have completed and returned their symptom diaries and the addition of a recruiting site. Also have clarified wording within the protocol relating to timelines for reporting SAEs.
03 March 2015	The amendment details the addition of a new research site.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported