Clinical trial results:
What is the clinical and cost effectiveness of oral steroids in the treatment of acute lower respiratory tract infection (LRTI)? A placebo controlled randomised trial

Summary

EudraCT number	2012-000851-15
Trial protocol	GB
Global end of trial date	27 February 2015

Results information

Result version number	v1 (current)
This version publication date	10 May 2018
First version publication date	10 May 2018

Trial information

Trial identification

Sponsor protocol code	UoB1581

Additional study identifiers

ISRCTN number	ISRCTN57309858
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	NHS REC: 12/SW/0180, EudraCT: 2012-000851-15, NIHR CSP: 102138

Notes:

Sponsors

Sponsor organisation name	University of Bristol
Sponsor organisation address	Senate House, Tyndall Avenue, Bristol, United Kingdom, BS8 1TH
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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	18 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 January 2015
Global end of trial reached?	Yes
Global end of trial date	27 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Does the use of oral prednisolone reduce the duration of moderately bad or worse cough and / or the severity of all its associated symptoms on days 2 to 4 by at least 20% when compared to no steroid treatment in adults ≥18 years presenting to primary care with acute LRTI?

Protection of trial subjects:

All Serious Adverse events were reported to the UH Bristol contact and Centre Principal Investigator by a delegated member of the research team within 24 hours of their knowledge of the event.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2012
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: 398
Worldwide total number of subjects	398
EEA total number of subjects	398

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)	336
From 65 to 84 years	62
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted between July 2013 and October 2014. Family physicians and nurses (recruiting clinicians) were trained in study procedures by 4 centres at the Universities of Bristol, Southampton, Nottingham, and Oxford. Fifty-eight family physicians and 50 practice nurses based in 54 family practices assessed patients for suitability.

Pre-assignment

Screening details:

525 patients were assessed for suitability, of whom; 124 were excluded due to ineligibility, 4 declined participation and 401 were randomised.

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	Investigator, Monitor, Subject, Data analyst, Assessor

Blinding implementation details:

The treatment allocation schedule was computer generated by a statistician independent of the trial team in a 1:1 ratio, using a variable block size (4, 6, 8 and 10). Allocated medication was added to numbered participant packs by pharmacists independent of the team. All packs were identical, containing either 20mg oral prednisolone tablets (Galen Pharma GmbH) or placebo tablets matched on dimension, appearance and taste (Piramal Healthcare Ltd).

Arms

Are arms mutually exclusive?	Yes
Arm title	Prednisolone

Arm description:

Participant packs containing ten 20-mg oral prednisolone tablets (Galen Pharma GmbH). Participants were asked to take 2 tablets once daily for 5 days, starting on the day of consultation, if possible before starting any antibiotics (if receiving a "delayed" prescription).

Arm type	Active comparator
Investigational medicinal product name	Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were asked to take 2 tablets once daily for 5 days, starting on the day of consultation, if possible before starting any antibiotics (if receiving a "delayed" prescription).

Arm title	Placebo

Arm description:

Participant packs containing ten 20-mg placebo tablets matched on dimension, appearance and taste (Piramal Healthcare Ltd) to oral prednisolone tablets. Participants were asked to take 2 tablets once daily for 5 days, starting on the day of consultation, if possible before starting any antibiotics (if receiving a "delayed" prescription).

Arm type	Placebo

Investigational medicinal product name	Placebo (no active ingredient)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were asked to take 2 tablets once daily for 5 days, starting on the day of consultation, if possible before stating any antibiotics (if receiving a "delayed" prescription).

Number of subjects in period 1	Prednisolone	Placebo
Started	198	200
Completed	198	200

Baseline characteristics

Reporting groups	
Reporting group title	Prednisolone
Reporting group description:	
Participant packs containing ten 20-mg oral prednisolone tablets (Galen Pharma GmbH). Participants were asked to take 2 tablets once daily for 5 days, starting on the day of consultation, if possible before starting any antibiotics (if receiving a "delayed" prescription).	
Reporting group title	Placebo
Reporting group description:	
Participant packs containing ten 20-mg placebo tablets matched on dimension, appearance and taste (Piramal Healthcare Ltd) to oral prednisolone tablets. Participants were asked to take 2 tablets once daily for 5 days, starting on the day of consultation, if possible before starting any antibiotics (if receiving a "delayed" prescription).	

Reporting group values	Prednisolone	Placebo	Total
Number of subjects	198	200	398
Age categorical			
Greater than or equal to 18 years of age			
Units: Subjects			
Adults (18-64 years)	162	174	336
From 65-84 years	36	26	62
Age continuous			
Units: years			
arithmetic mean	50.0	44.8	
standard deviation	± 16.1	± 15.5	-
Gender categorical			
Units: Subjects			
Female	116	134	250
Male	82	66	148
Centre			
Units: Subjects			
Bristol	118	113	231
Oxford	39	45	84
Southampton	24	21	45
Nottingham	17	21	38
Occupation			
Units: Subjects			
Employed	137	143	280
Unemployed	17	21	38
Retired	41	30	71
Full-time education	3	6	9
Smoking status			
Units: Subjects			
Current	31	38	69
Past	63	55	118
Never	104	106	210
Missing	0	1	1
Ethnicity			
Units: Subjects			

White	188	193	381
Other	10	6	16
Missing	0	1	1
Living with smoker Units: Subjects			
Yes	25	32	57
No	158	163	321
Missing	15	5	20
Personal history of hayfever Units: Subjects			
Yes	41	46	87
No	147	143	290
Missing	10	11	21
Personal history of eczema Units: Subjects			
Yes	30	26	56
No	154	164	318
Missing	14	10	24
Personal history of asthma Units: Subjects			
Yes	10	8	18
No	178	185	363
Missing	10	7	17
Family history of asthma, eczema or hayfever Units: Subjects			
Yes	73	76	149
No	109	113	222
Missing	16	11	27
Influenza vaccine in last 12 months Units: Subjects			
Yes	63	44	107
No	135	156	291
Recruited in winter (Oct-Mar) Units: Subjects			
Yes	112	114	226
No	86	86	172
Sputum present within last 24hrs Units: Subjects			
Yes	149	156	305
No	48	44	92
Missing	1	0	1
Shortness of breath present within last 24hrs Units: Subjects			
Yes	146	133	279
No	52	67	119
Wheeze present within last 24 hrs Units: Subjects			
Yes	88	98	186
No	109	102	211
Missing	1	0	1

Abnormal peak flow (<80% of expected) Units: Subjects			
Yes	87	79	166
No	110	121	231
Missing	1	0	1
Abnormal respiratory rate (>20/min) Units: Subjects			
Yes	2	1	3
No	194	198	392
Missing	2	1	3
Chest retraction or prolonged expiration Units: Subjects			
Yes	0	1	1
No	198	199	397
Wheeze or rhonchi on auscultation Units: Subjects			
Yes	11	11	22
No	187	189	376
Crackles or crepitations on auscultation			
Includes unilateral and bilateral			
Units: Subjects			
Yes	4	6	10
No	194	194	388
Bronchial breathing Units: Subjects			
Yes	0	2	2
No	198	198	396
Taken prescribed beta-agonist in past 24hrs Units: Subjects			
Yes	9	3	12
No	189	197	386
Over the counter drugs taken for current cough Units: Subjects			
Yes	128	139	267
No	70	61	131
Given delayed antibiotic prescription Units: Subjects			
Yes	22	25	47
No	176	175	351
Chest pain present within last 24 hrs Units: Subjects			
Yes	88	97	185
No	110	103	213
Prior duration of cough			
Number of days the patient has been suffering with a cough			
Units: Days			
median	13.0	10.0	
inter-quartile range (Q1-Q3)	7.0 to 20.0	6.0 to 17.5	-
Weight			

Units: kg			
median	77.0	76.0	
inter-quartile range (Q1-Q3)	64.5 to 91.0	66.5 to 90.5	-
Height			
Units: cm			
median	168.0	168.0	
inter-quartile range (Q1-Q3)	161.0 to 175.0	163.0 to 176.0	-
Deprivation			
English Index of Multiple Deprivation scores (range 0-100), higher scores indicate higher levels of deprivation.			
Units: index score (0-100)			
median	11.0	12.0	
inter-quartile range (Q1-Q3)	5.0 to 23.0	5.0 to 23.0	-
Patient reported illness severity score			
Units: scale 0-10			
median	6.0	5.0	
inter-quartile range (Q1-Q3)	5.0 to 7.0	4.0 to 7.0	-
Pulse			
Units: beats per minute			
arithmetic mean	77.8	77.7	
standard deviation	± 12.3	± 11.8	-
Temperature			
Units: Degrees celsius			
arithmetic mean	36.6	36.6	
standard deviation	± 0.5	± 0.4	-
Oxygen saturation			
Units: Percentage			
arithmetic mean	97.5	97.8	
standard deviation	± 1.3	± 1.1	-
Respiratory rate			
Units: per minute			
arithmetic mean	15.4	15.0	
standard deviation	± 2.5	± 2.4	-

End points

End points reporting groups

Reporting group title	Prednisolone
Reporting group description:	
Participant packs containing ten 20-mg oral prednisolone tablets (Galen Pharma GmbH). Participants were asked to take 2 tablets once daily for 5 days, starting on the day of consultation, if possible before starting any antibiotics (if receiving a "delayed" prescription).	
Reporting group title	Placebo
Reporting group description:	
Participant packs containing ten 20-mg placebo tablets matched on dimension, appearance and taste (Piramal Healthcare Ltd) to oral prednisolone tablets. Participants were asked to take 2 tablets once daily for 5 days, starting on the day of consultation, if possible before starting any antibiotics (if receiving a "delayed" prescription).	

Primary: PO: Duration of moderately bad or worse cough (0-28 days)

End point title	PO: Duration of moderately bad or worse cough (0-28 days)
End point description:	
End point type	Primary
End point timeframe:	
From baseline up to 28 days. If the patient was still suffering from a cough by day 28 then they were censored at this time point.	

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	161		
Units: Days				
median (confidence interval 95%)	5 (4 to 5)	5 (4 to 6)		

Statistical analyses

Statistical analysis title	Duration of MBW cough (censored at 28)
Statistical analysis description:	
Adjusted for centre and prior duration of cough	
Comparison groups	Prednisolone v Placebo
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.39

Primary: PO: Severity of symptoms

End point title	PO: Severity of symptoms

End point description:

Mean severity score of the 6 main symptoms (cough, phlegm, shortness of breath, sleep disturbance, feeling generally unwell and activity disturbance) on days 2-4; the mean score was calculated across the symptoms for each day and then the overall mean was calculated with a maximum value of 6.

End point type	Primary

End point timeframe:

On days 2-4

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	181		
Units: Severity (0-6)				
arithmetic mean (confidence interval 95%)	1.99 (1.85 to 2.13)	2.16 (2.00 to 2.32)		

Statistical analyses

Statistical analysis title	Difference in mean symptom severity score

Statistical analysis description:

Adjusted for centre and baseline severity

Comparison groups	Placebo v Prednisolone
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0

Secondary: Mean area under the curve for cough symptoms

End point title	Mean area under the curve for cough symptoms

End point description:

Patients were asked each day to measure the severity score of their cough on a scale of 0 (not affected) - 6 (as bad as it could be). The area under the curve was then calculated for each patient for the total 28 days.

End point type	Secondary

End point timeframe:

0-28 days

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185	179		
Units: severity score per day (0-6)				
arithmetic mean (confidence interval 95%)	40.16 (36.67 to 43.65)	42.88 (38.88 to 46.87)		

Statistical analyses

Statistical analysis title	Cough symptoms - area under the curve

Statistical analysis description:

Area under the curve adjusted for centre and baseline prior duration of cough

Comparison groups	Placebo v Prednisolone
Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.36
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-2.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.66
upper limit	2.8

Notes:

[1] - Although the statistical technique (area under the curve) was not pre-specified the team did say that they would explore the duration and severity of other symptoms in a secondary analysis.

Secondary: Mean area under the curve for phlegm symptoms

End point title	Mean area under the curve for phlegm symptoms

End point description:

Patients were asked each day to measure the severity score of their phlegm on a scale of 0 (not affected) - 6 (as bad as it could be). The area under the curve was then calculated for each patient for the total 28 days.

End point type	Secondary

End point timeframe:

Day 1-28

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	179		
Units: severity score per day (0-6)				
arithmetic mean (confidence interval 95%)	25.48 (22.19 to 28.78)	30.01 (26.40 to 33.61)		

Statistical analyses

Statistical analysis title	Difference in mean area under the curve for phlegm

Statistical analysis description:

Area under the curve adjusted for centre and baseline presence/absence of symptom (previous 24 hours)

Comparison groups	Prednisolone v Placebo
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.09
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.89
upper limit	0.7

Notes:

[2] - Although the statistical technique (area under the curve) was not pre-specified the team did say that they would explore the duration and severity of other symptoms in a secondary analysis.

Secondary: Mean area under the curve for shortness of breath

End point title	Mean area under the curve for shortness of breath

End point description:

End point type	Secondary

End point timeframe:

Patients were asked each day to measure the severity score of their shortness of breath on a scale of 0 (not affected) - 6 (as bad as it could be). The area under the curve was then calculated for each patient for the total 28 days.

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	179		
Units: severity score per day (0-6)				
arithmetic mean (confidence interval 95%)	16.10 (13.25 to 18.95)	18.39 (15.16 to 21.61)		

Statistical analyses

Statistical analysis title	Difference in mean area under the curve for shrtb

Statistical analysis description:

Area under the curve adjusted for centre and baseline presence/absence of symptom (previous 24 hours)

Comparison groups	Prednisolone v Placebo
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.27
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.34
upper limit	1.75

Notes:

[3] - Although the statistical technique (area under the curve) was not pre-specified the team did say that they would explore the duration and severity of other symptoms in a secondary analysis.

Secondary: Mean area under the curve for wheeze

End point title	Mean area under the curve for wheeze

End point description:

Patients were asked each day to measure the severity score of their wheeze on a scale of 0 (not affected) - 6 (as bad as it could be). The area under the curve was then calculated for each patient for the total 28 days.

End point type	Secondary

End point timeframe:

0-28 days

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	179		
Units: severity scores per day (0-6)				
arithmetic mean (confidence interval 95%)	12.32 (9.69 to 14.96)	13.24 (10.37 to 16.11)		

Statistical analyses

Statistical analysis title	Difference in mean area under the curve for wheeze

Statistical analysis description:

Area under the curve adjusted for centre and baseline presence/absence of symptom (previous 24 hours)

Comparison groups	Prednisolone v Placebo
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.92
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.27
upper limit	3.64

Notes:

[4] - Although the statistical technique (area under the curve) was not pre-specified the team did say that they would explore the duration and severity of other symptoms in a secondary analysis.

Secondary: Mean area under the curve for blocked or runny nose

End point title	Mean area under the curve for blocked or runny nose

End point description:

Patients were asked each day to measure the severity score of their blocked/runny nose on a scale of 0 (not affected) - 6 (as bad as it could be). The area under the curve was then calculated for each patient for the total 28 days.

End point type	Secondary

End point timeframe:

0-28 days

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	179		
Units: severity score per day (0-6)				
arithmetic mean (confidence interval 95%)	19.83 (16.38 to 23.28)	20.06 (17.12 to 23.00)		

Statistical analyses

Statistical analysis title	Difference in mean area under the curve for nose

Statistical analysis description:

Area under the curve adjusted for centre and baseline presence/absence of symptom (previous 24 hours)

Comparison groups	Prednisolone v Placebo
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.76
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	5.05

Notes:

[5] - Although the statistical technique (area under the curve) was not pre-specified the team did say that they would explore the duration and severity of other symptoms in a secondary analysis.

Secondary: Mean area under the curve for chest pain

End point title	Mean area under the curve for chest pain

End point description:

Patients were asked each day to measure the severity score of their chest pain on a scale of 0 (not affected) - 6 (as bad as it could be). The area under the curve was then calculated for each patient for the total 28 days.

End point type	Secondary

End point timeframe:

0-28 days

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	179		
Units: severity score per day (0-6)				
arithmetic mean (confidence interval 95%)	6.64 (4.95 to 8.33)	9.59 (6.98 to 12.19)		

Statistical analyses

Statistical analysis title	Difference in mean area under the curve for chestp

Statistical analysis description:

Area under the curve adjusted for centre and baseline presence/absence of symptom (previous 24 hours)

Comparison groups	Prednisolone v Placebo

Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-2.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.83
upper limit	-0.01

Notes:

[6] - Although the statistical technique (area under the curve) was not pre-specified the team did say that they would explore the duration and severity of other symptoms in a secondary analysis.

Secondary: Mean area under the curve for fever

End point title	Mean area under the curve for fever

End point description:

Patients were asked each day to measure the severity score of their fever on a scale of 0 (not affected) - 6 (as bad as it could be). The area under the curve was then calculated for each patient for the total 28 days.

End point type	Secondary

End point timeframe:

0-28 days

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	179		
Units: severity score per day (0-6)				
arithmetic mean (confidence interval 95%)	2.98 (2.05 to 3.91)	3.45 (2.07 to 4.82)		

Statistical analyses

Statistical analysis title	Difference in mean area under the curve for fever

Statistical analysis description:

Area under the curve adjusted for centre and baseline presence/absence of symptom (previous 24 hours)

Comparison groups	Prednisolone v Placebo
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.68
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	1.24

Notes:

[7] - Although the statistical technique (area under the curve) was not pre-specified the team did say that they would explore the duration and severity of other symptoms in a secondary analysis.

Secondary: Mean area under the curve for muscle ache

End point title	Mean area under the curve for muscle ache

End point description:

Patients were asked each day to measure the severity score of their muscle ache on a scale of 0 (not affected) - 6 (as bad as it could be). The area under the curve was then calculated for each patient for the total 28 days.

End point type	Secondary

End point timeframe:

0-28 days

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	179		
Units: severity score per day (0-6)				
arithmetic mean (confidence interval 95%)	8.83 (6.71 to 10.96)	10.29 (7.53 to 13.06)		

Statistical analyses

Statistical analysis title	Difference in mean area under the curve for muscle

Statistical analysis description:

Area under the curve adjusted for centre and baseline presence/absence of symptom (previous 24 hours)

Comparison groups	Prednisolone v Placebo
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.35
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.99
upper limit	1.77

Notes:

[8] - Although the statistical technique (area under the curve) was not pre-specified the team did say that they would explore the duration and severity of other symptoms in a secondary analysis.

Secondary: Mean area under the curve for headache

End point title	Mean area under the curve for headache

End point description:

Patients were asked each day to measure the severity score of their headache on a scale of 0 (not affected) - 6 (as bad as it could be). The area under the curve was then calculated for each patient for the total 28 days.

End point type	Secondary

End point timeframe:

0-28 days

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	179		
Units: severity score per day (0-6)				
arithmetic mean (confidence interval 95%)	10.77 (8.27 to 13.28)	11.83 (8.89 to 14.77)		

Statistical analyses

Statistical analysis title	Difference in mean area under the curve for headac

Statistical analysis description:

Area under the curve adjusted for centre and baseline presence/absence of symptom (previous 24 hours)

Comparison groups	Prednisolone v Placebo
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.74
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.34
upper limit	3.09

Notes:

[9] - Although the statistical technique (area under the curve) was not pre-specified the team did say that they would explore the duration and severity of other symptoms in a secondary analysis.

Secondary: Mean area under the curve for sleep disturbance

End point title	Mean area under the curve for sleep disturbance

End point description:

Patients were asked each day to measure the severity score of their sleep disturbance on a scale of 0

(not affected) - 6 (as bad as it could be). The area under the curve was then calculated for each patient for the total 28 days.

End point type	Secondary

End point timeframe:

0-28 days

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	179		
Units: severity score per day (0-6)				
arithmetic mean (confidence interval 95%)	20.80 (17.66 to 23.94)	22.11 (18.13 to 26.10)		

Statistical analyses

Statistical analysis title	Difference in mean area under the curve for sleep

Statistical analysis description:

Area under the curve adjusted for centre and baseline presence/absence of symptom (previous 24 hours)

Comparison groups	Prednisolone v Placebo
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.76
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	4.1

Notes:

[10] - Although the statistical technique (area under the curve) was not pre-specified the team did say that they would explore the duration and severity of other symptoms in a secondary analysis.

Secondary: Mean area under the curve for feeling generally unwell

End point title	Mean area under the curve for feeling generally unwell

End point description:

Patients were asked each day to measure the severity score of how well they felt in generally on a scale of 0 (not affected) - 6 (as bad as it could be). The area under the curve was then calculated for each patient for the total 28 days.

End point type	Secondary

End point timeframe:

0-28 days

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	179		
Units: severity score per day (0-6)				
arithmetic mean (confidence interval 95%)	19.83 (17.22 to 22.45)	22.68 (19.17 to 26.19)		

Statistical analyses

Statistical analysis title	Difference in mean area under the curve for unwell

Statistical analysis description:

Area under the curve adjusted for centre and baseline presence/absence of symptom (previous 24 hours)

Comparison groups	Prednisolone v Placebo
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.12
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-3.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.38
upper limit	0.89

Notes:

[11] - Although the statistical technique (area under the curve) was not pre-specified the team did say that they would explore the duration and severity of other symptoms in a secondary analysis.

Secondary: Mean area under the curve for activity disturbance

End point title	Mean area under the curve for activity disturbance

End point description:

Patients were asked each day to measure the severity score of their activity disturbance on a scale of 0 (not affected) - 6 (as bad as it could be). The area under the curve was then calculated for each patient for the total 28 days.

End point type	Secondary

End point timeframe:

0-28 days

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	179		
Units: severity score per day (0-6)				
arithmetic mean (confidence interval 95%)	14.29 (12.01 to 16.57)	19.07 (15.40 to 22.74)		

Statistical analyses

Statistical analysis title	Difference in mean area under the curve for active

Statistical analysis description:

Area under the curve adjusted for centre and baseline presence/absence of symptom (previous 24 hours)

Comparison groups	Prednisolone v Placebo
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.02
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-4.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.86
upper limit	-0.69

Notes:

[12] - Although the statistical technique (area under the curve) was not pre-specified the team did say that they would explore the duration and severity of other symptoms in a secondary analysis

Secondary: Duration of moderately bad or worse cough (0-56 days)

End point title	Duration of moderately bad or worse cough (0-56 days)

End point description:

End point type	Secondary

End point timeframe:

From baseline up to 56 days. If the patient was still suffering from a cough by day 56 then they were censored at this time point.

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	161		
Units: Days				
median (confidence interval 95%)	5 (4 to 5)	5 (4 to 6)		

Statistical analyses

Statistical analysis title	Duration of MBW cough (censored at 56)
Statistical analysis description:	
Adjusted for centre and prior duration of cough	
Comparison groups	Prednisolone v Placebo
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.39

Secondary: Duration of cough (0-56 days)

End point title	Duration of cough (0-56 days)
End point description:	
End point type	Secondary
End point timeframe:	
From baseline up to 28 days. If the patients was still suffering from a cough by day 56 then they were censored at this time point.	

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	182		
Units: Days				
median (confidence interval 95%)	18 (17 to 23)	20 (17 to 25)		

Statistical analyses

Statistical analysis title	Duration of cough (censored at 56)
Statistical analysis description:	
Adjusted for centre and prior duration of cough	
Comparison groups	Prednisolone v Placebo

Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.29
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.42

Secondary: Duration of abnormal peak flow (0-28 days)

End point title	Duration of abnormal peak flow (0-28 days)

End point description:

End point type	Secondary

End point timeframe:

From baseline up to 28 days. Counted as the number of days the patient had a peak flow rate that was <80% of their expected level.

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	115		
Units: Days				
median (confidence interval 95%)	10 (7 to 17)	11 (8 to 17)		

Statistical analyses

Statistical analysis title	Duration of abnormal peak flow (censored at 28d)

Statistical analysis description:

Adjusted for centre and prior duration of cough

Comparison groups	Prednisolone v Placebo
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.52

Secondary: Antibiotic use (up to 7 days)

End point title	Antibiotic use (up to 7 days)

End point description:

End point type	Secondary

End point timeframe:

From baseline up to 7 days. Patients were counted if they reported consuming antibiotics on any of the 7 days.

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	182		
Units: Patients				
Yes	15	15		
No	176	167		

Statistical analyses

Statistical analysis title	Odds ratio for the antibiotic consumption (0-7)

Statistical analysis description:

Adjusted for centre and whether the patient was given a delayed antibiotic script at baseline

Comparison groups	Prednisolone v Placebo
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.96
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	2.28

Secondary: Antibiotic use (up to 28 days)

End point title	Antibiotic use (up to 28 days)

End point description:

End point type	Secondary

End point timeframe:

From baseline up to 28 days. Patients were counted if they reported consuming antibiotics on any of the 28 days.

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191	182		
Units: Patients				
Yes	28	34		
No	163	148		

Statistical analyses

Statistical analysis title	Odds ratio for the antibiotic consumption (0-28)

Statistical analysis description:

Adjusted for centre and whether the patients was given a delayed antibiotic script at baseline

Comparison groups	Prednisolone v Placebo
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.39

Secondary: Patient satisfaction (feel better)

End point title	Patient satisfaction (feel better)

End point description:

On day 28, patients were asked if they agreed or disagreed with "my OSAC trial tablets helped me to feel better from my cough". The proportions of participants responding 'agree' (as opposed to 'neither agree or disagree' and 'disagree') were compared between the groups.

End point type	Secondary

End point timeframe:

None. Asked at the end of the symptom diary (day 28).

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	171		
Units: Patients				
Agree	60	43		
Disagree/Neither agree or disagree	118	128		

Statistical analyses

Statistical analysis title	Odds ratio for patient satisfaction (feel better)
Statistical analysis description: Adjusted for centre	
Comparison groups	Prednisolone v Placebo
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	2.34

Secondary: Patient satisfaction (future use)

End point title	Patient satisfaction (future use)
End point description: On day 28, patients were asked if they agreed or disagreed with "my OSAC trial tablets helped me to feel better from my cough". The proportions of participants responding 'agree' (as opposed to 'neither agree or disagree' and 'disagree') were compared between the groups.	
End point type	Secondary
End point timeframe: None. Asked at the end of the symptom diary (day 28).	

End point values	Prednisolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	171		
Units: Patients				
Agree	99	81		
Disagree/Neither agree or disagree	79	90		

Statistical analyses

Statistical analysis title	Odds ratio for patient satisfaction (future use)
Statistical analysis description: Adjusted for centre	
Comparison groups	Prednisolone v Placebo
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	2.08

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events were collected throughout the 28 day follow up period. Non-serious adverse events were collected for the first 7 days only (treatment course=5 days).

Adverse event reporting additional description:

Adverse events were then categorised as expected, unexpected or related to cough.

Assessment type	Systematic

Dictionary used

Dictionary name	SPC and/or BNF
Dictionary version	Latest

Reporting groups

Reporting group title	Prednisolone

Reporting group description:

Participant packs containing ten 20-mg oral prednisolone tablets (Galen Pharma GmbH). Participants were asked to take 2 tablets once daily for 5 days, starting on the day of consultation, if possible before starting any antibiotics (if receiving a "delayed" prescription).

Reporting group title	Placebo

Reporting group description:

Participant packs containing ten 20-mg placebo tablets matched on dimension, appearance and taste (Piramal Healthcare Ltd) to oral prednisolone tablets. Participants were asked to take 2 tablets once daily for 5 days, starting on the day of consultation, if possible before starting any antibiotics (if receiving a "delayed" prescription).

Serious adverse events	Prednisolone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 199 (0.00%)	0 / 200 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Prednisolone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 199 (22.61%)	36 / 200 (18.00%)	
Nervous system disorders			
Dizziness	Additional description: Dizziness or faintness		
subjects affected / exposed	7 / 199 (3.52%)	0 / 200 (0.00%)	
occurrences (all)	7	0	
General disorders and administration site conditions			

Chest pain	Additional description: Pain in abdomen or chest		
subjects affected / exposed	5 / 199 (2.51%)	1 / 200 (0.50%)	
occurrences (all)	5	1	
Throat irritation	Additional description: Reportings of sore throat		
subjects affected / exposed	3 / 199 (1.51%)	7 / 200 (3.50%)	
occurrences (all)	3	7	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	12 / 199 (6.03%)	10 / 200 (5.00%)	
occurrences (all)	12	10	
Infections and infestations			
Fever			
subjects affected / exposed	3 / 199 (1.51%)	5 / 200 (2.50%)	
occurrences (all)	3	5	

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/28829884