Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Supplemental Methods and Results

Methods

Statistical analyses

Analysis of secondary outcomes

Total duration and severity of all symptoms: Plotting the daily symptom score (0 - normal/not affected to 6 - as bad as it could be) against time (up to 28 days), the area under the curve (AUC) was calculated for each symptom for each participant using the trapezium rule.[1] Linear regression was used (adjusting for center and presence of the symptom at baseline) to compare the prednisolone and placebo groups.[1] AUC data and residuals were often skewed, hence log and square root transformations were applied as appropriate. Since conclusions were not altered by these transformations, untransformed data were presented for ease of interpretation.

Cough up to 56 days: participants who had an unresolved cough at 28 days were telephoned weekly by the trial research nurse to establish duration of moderately bad or worse, and any cough. Cox proportional hazard models considered time to resolution of moderately bad or worse cough and time to complete resolution adjusting for center and prior duration of cough.

Duration of abnormal peak flow: for each day (up to 28 days), readings were compared to the expected peak flow for the participant's gender, age and height.[2] Since there is no agreed definition of 'abnormal' peak flow, before these data were examined, the trial team agreed that a reading of less than 80% of the expected peak flow, in either the morning or evening, would be regarded as a day of 'abnormal' peak flow.

Antibiotic consumption: Logistic regression was used (adjusting for center and delayed prescription for antibiotics) to compare the proportion of participants reporting the use of antibiotics by day 7 and day 28.

Adverse events (including re-consultation for a documented deterioration in illness): Adverse events were categorized as: serious; expected (if present in the Summary of Product Characteristics and/or the British National Formulary for prednisolone); unexpected; or related to cough. The occurrence of any adverse event was also compared between the groups. Participants were recorded as having experienced none, one, or more than one event in each of these categories by treatment group and compared using ordinal logistic regression, adjusting for center and baseline impression of illness. The odds ratios of these models represent the likelihood of a worse outcome among the range of possible categories (0, 1, >1 event). Within the severe, expected and unexpected categories, adverse events were further subdivided by type and the number and percentage of participants experiencing each was reported.

Patient satisfaction: On day 28, participants were asked if they agreed or disagreed with two statements relating to patient satisfaction: (i) “my OSAC trial tablets helped me to feel better from my cough” and (ii) “I would want to take my OSAC tablets again if I developed another similar chesty cough in the future”. The proportions of participants responding ‘agree’ (as opposed to ‘neither agree or disagree’ and ‘disagree’) to each statement were compared between the groups in logistic regression models adjusting for center.

Given the number of secondary outcomes and statistical tests performed, a more conservative alpha (significance) level of 0.002 was used to interpret the results of analyses of secondary outcomes (Bonferroni correction, 0.05/ number of tests).[3]

Sensitivity analyses

Missing data and multiple imputation: There was a small degree of missing primary outcome data. In terms of duration of moderately bad or worse cough it was not possible to perform multiple imputation with the primary comparative analysis reported in Table 2. In the primary comparative analysis those participants reporting severity of cough to be <3 on days 1 and 2 had a duration of moderately bad or worse cough of zero and hence were excluded from the Cox Proportional Hazards model. For those with missing severity of cough data for days 1 and/or 2 it was therefore possible that some imputations would lead to a duration of zero and that others would not. This meant that it was possible for the multiple imputations to produce different numbers of zero durations (and hence exclusions from analyses) making amalgamation of the imputed datasets to produce an overall estimate of treatment effect implausible. Hence, duration of moderately bad or worse cough was forced to be one day for all those with a recorded or imputed duration of zero as for the initial sensitivity analysis reported in Web Table 2.

Analyses of the two primary outcomes were performed after multiple imputation (25 datasets) of missing data using a two-fold fully conditional specification algorithm[5] and Rubin’s rules.[6] The two-fold method takes account of the longitudinal and dynamic structure of the data. In the context of the daily symptom diary it imputes missing values conditional on other available data on that same day and conditional on the two days immediately before and after. The imputation models included demographic variables, prognostic factors such as smoking, and values of primary and important secondary outcomes at baseline.

Per-protocol analyses: Full adherence was defined in both groups as having taken all 10 tablets. Adherence was measured in two ways, as a patient-reported outcome included in the diary and from returned blister packets. Consistency between the two measures was examined. Where there were discrepancies between the two measures the lesser number of tablets was assumed to have been taken by the participant. Per-

protocol analyses were carried out for both primary outcomes including only prednisolone and placebo participants taking all 10 tablets.

Day of recruitment: An additional pre-specified sensitivity analysis included controlling for whether a participant had received allocated medication on the day of initial consultation, or the next day. Primary comparative analyses were repeated including an indicator variable for receipt of medication on consultation day/next day.

Subgroup analyses

Formal tests of interaction were carried out to explore a number of potential treatment effect modifiers identified *a priori*: (i) age (dichotomized by median of all participants); (ii) prior cough duration (dichotomized by median of all participants); (iii) presence of wheeze on auscultation; (iv) antibiotic consumption at 7 days; (v) β-agonist consumption in the 24 hours prior to baseline consultation; (vi) smoking status (never vs. ever); (vii) history of hay fever, asthma or eczema; (viii) new diagnoses of asthma or COPD at 3 months*; (ix) diagnosis of whooping cough at 3 months*; and (x) diagnosis of lung cancer at 3 months* (*in the protocol asthma, COPD, whooping cough and lung cancer were mistakenly listed as secondary outcomes). An additional *post-hoc* subgroup analyses was performed considering baseline impression of severity of illness (dichotomized by median of all participants). The trial was not specifically powered for these analyses; interaction tests were therefore performed as hypothesis-generating analyses and interpretation focused on 95% confidence intervals. The resulting interaction effect hazard ratios can be interpreted as the effect of prednisolone compared to placebo in one subgroup relative to the effect in the other subgroup.

Changes to the analysis plan

In the study protocol (see online supplement) the intention was to consider each symptom using time-to-event methods until the severity was scored by the participant as '1'. However, for each symptom, a large proportion of participants initially reported no symptom resulting in large numbers being omitted from analyses. It was therefore agreed (*post-hoc*) to examine differences between the treatment groups by calculating the area under the curve (AUC) for each participant. This is an appropriate approach to consider the overall burden of the symptom over time.[1]

Given the high level of compliance (over 90%) in both groups, 'duration of steroid/tablet use' was not formally compared between the treatment groups in order to reduce the number of statistical hypotheses tests.

In the protocol and original analysis plan (see online supplements) the secondary outcome 'abnormal peak flow' was insufficiently defined as "a peak flow reading that is not within the range of values that would be expected according to a standard predictive algorithm based on gender, height and weight." There is no agreed definition of 'abnormal' peak flow. Before these data were examined, the trial team agreed that a reading of less than 80% of the expected peak flow, in either the morning or evening, would be regarded as a day of 'abnormal' peak flow. During the baseline consultation, participants' peak flow measurement ability was rated as poor, adequate or good. In a *post-hoc* sensitivity analysis those rated as 'poor' were removed from the analysis.

As described earlier a number of patients unexpectedly reported a cough on days 1 and 2 that was not moderately bad or worse and so were excluded from the primary analysis. A sensitivity analysis included these patients by imputing a duration of moderately bad or worse cough of one day. An additional subgroup analysis considering baseline impression of severity of illness was added as deemed to be of clinical importance. An examination of the data demonstrated that some patients were experiencing a moderately bad or worse cough again a few days after resolution. A sensitivity analysis redefined duration of moderately bad or worse cough to be from day 1 to the last day with a value greater than or equal to 3, regardless of values in-between.

The pre-planned per-protocol analysis was analyzed according to the patient's reported consumption of trial tablets. However, some patients failed to return the blister packet which may indicate that they were not fully adherent, despite suggesting otherwise in their diary. An additional *post-hoc* analysis was performed, excluding those not returning the blister packet.

Subgroup analyses specified *a priori* included: (i) new diagnoses of asthma or COPD at 3 months; (ii) diagnosis of whooping cough at 3 months; and (iii) diagnosis of lung cancer at 3 months. No patients were found to have a new diagnosis of COPD, whooping cough or lung cancer at 3 months and only three patients were diagnosed with asthma hence these subgroup analyses were not performed. A *post-hoc* sensitivity analysis considered the effect of removing the three patients diagnosed with asthma and found no effect.

Finally, at the request of the journal additional absolute measures of effect were produced for the time-to-event and binary outcomes.

Results

Sensitivity analyses

Abnormal peak flow – removal of participants whose measurement ability rated 'poor' (post-hoc)

Six patients in the prednisolone group and zero patients in the placebo group were rated poor at measuring their peak flow at baseline. A sensitivity analysis removing these patients from the analysis of duration of abnormal peak flow had no impact on the results (see footnote Table 3).

Including those with no moderately bad or worse cough at baseline (post-hoc)

In total 19 prednisolone and 21 placebo unexpectedly reported the severity of cough as not moderately bad or worse at baseline, imputing a duration of 1 day for these individuals had no impact on the model (Web Table 1).

Duration of moderately bad or worse cough defined to be from day 1 to the last day with a value greater than or equal to 3, regardless of values in-between (post-hoc).

This sensitivity analysis had little impact on the model (Web Table 1).

Day of recruitment

Seven participants (4 prednisolone, 3 placebo) were recruited the day after presenting to their family physician; adjusting for this along with center and baseline cough duration/ severity had no impact on the primary outcomes (Web Table 1).

Missing data

Multiple imputation of missing data had no effect in terms of duration of moderately bad or worse cough or severity of symptoms (Web Table 1).

Per-protocol

Self-reported adherence to study medication was high in both groups, with 92% and 94% of prednisolone and placebo group participants stating they had taken all 10 tablets. Of the 331 participants who returned their blister strip and answered the compliance question in the symptom diary there were only 14 instances (4.3%) where the symptom diary did not agree with the number of tablets returned; in general the blister packets suggested better compliance than the diaries. Assuming the least number of tablets taken (self-reported and returned blister packets), 313 (160 prednisolone, 153 placebo) out of the 334 participants with a duration of moderately bad or worse cough were fully adherent and included in the per-protocol analysis. Of the 370 participants with a symptom severity score, 345 (175 prednisolone, 170 placebo) participants were fully adherent and included in a per-protocol analysis. For both outcomes there was little change (Web Table 1) compared to the primary intention-to-treat analysis.

eTable 1. Sensitivity Analyses for Primary Outcomes

	Duration of moderately bad or worse cough					
	Prednisolone		**Placebo**		**Prednisolone vs. placebo Adjusted for center and baseline[a]**	
	N	**Median (95% CI)**	**N**	**Median (95% CI)**	**HR (95% CI)**	**P value** (alpha=0.05)
Data imputed for those with less severe cough at day 1[b]	192	5 (4, 5)	182	5 (4, 6)	1.11 (0.89,1.39)	0.35
Duration until last day with a value of ≥3	178	7 (5, 8)	169	7 (6, 8)	1.06 (0.85, 1.33)	0.61
Multiple imputation	198	4 (3,5)	200	5 (4,6)	1.11 (0.82,1.50)	0.52
Per-protocol	160	4 (4, 5)	153	5 (4, 6)	1.12 (0.89,1.41)	0.34
Per-protocol[c]	141	5 (4, 5)	132	5 (4, 6)	1.12 (0.88,1.44)	0.35
Adjusting for day of recruitment[d]	173	5 (4, 5)	161	5 (4, 6)	1.12 (0.89,1.40)	0.34
Removal of 3 participants diagnosed with asthma	171	5 (4, 5)	160	5 (4, 6)	1.10 (0.88,1.38)	0.41
	Mean symptom severity[e]					
	Prednisolone		**Placebo**		**Prednisolone vs. placebo Adjusted for center and baseline[a]**	
	N	**Mean (95% CI)**	**N**	**Mean (95% CI)**	**Difference in means (95% CI) [c]**	**P value** (alpha=0.001)
Multiple imputation	198	2.00 (1.98, 2.03)	200	2.20 (2.17, 2.23)	-0.23 (-0.43,-0.02)	0.03
Per-protocol	176	2.01 (1.86, 2.15)	170	2.20 (2.03, 2.36)	-0.21 (-0.41,0.00)[g]	0.05
Per-protocol[c]	155	2.02 (1.86, 2.17)	149	2.21 (2.03, 2.39)	-0.20 (-0.42,0.02)[g]	0.08
Adjusting for day of recruitment[d]	189	1.99 (1.85, 2.13)	181	2.16 (2.00, 2.32)	-0.20 (-0.40,-0.01)[g]	0.06
Removal of 3 participants diagnosed with asthma	187	1.99 (1.85, 2.13)	180	2.15 (1.99, 2.30)	-0.18 (-0.39,0.02)[g]	0.08

[a] Baseline measure for cough is prior duration of cough (1-28 days) and for mean symptom severity score is patient reported illness severity (0 – 10).
[b] Primary analysis (as reported in Table 2) with a value of 1 day imputed for participants (19 prednisolone and 21 placebo group) reporting cough as not moderately bad or worse on day 1
[c] Analysis includes only those who returned their study medication (prednisolone or placebo) blister strip
[d] 7 participants randomized the day after presenting to physician, this variable was missing for 1 placebo participant.
[e] See *Methods, Primary Outcomes* for derivation of mean symptom severity score (minimum of 0 and maximum of 6 (most severe))
[f] Patient reported illness severity missing for 1 prednisolone participant

eTable 2. Adverse Events

	Prednisolone[a] (N=196)	**Placebo (N=198)**	**Prednisolone vs. placebo Adjusted for center and baseline[b]**	
	n (%)	n (%)	OR (95% CI)	P value
Expected[c] adverse events				
0	158 (81%)	167 (84%)	1.25 (0.74, 2.12)	0.41
1	31 (16%)	25 (13%)		
>1	7 (4%)	6 (3%)		
Unexpected[d] adverse events				
0	192 (98%)	194 (98%)	1.07 (0.26, 4.36)	0.93
1	4 (2%)	4 (2%)		
>1	0 (0%)	0 (0%)		
Related to cough				
0	187 (95%)	188 (95%)	0.88 (0.34, 2.24)	0.78
1	9 (5%)	8 (4%)		
>1	0 (0%)	2 (1%)		
Reconsultation for same illness[e]				
0	168 (85%)	170 (86%)	1.04 (0.59, 1.84)	0.89
1	21 (11%)	19 (10%)		
>1	8 (4%)	9 (5%)		

[a] Excludes the duplicate participant who did experience an expected adverse event during their duplicate entry
[b] Ordinal logistic regression, adjusting for center and baseline patient reported illness severity, missing for 1 participant
[c] Expected adverse events were identified using the Summary of Product Characteristics or the British National Formulary
[d] Unexpected adverse events were those that did not constitute as an expected adverse event, cough related event or pre-existing symptom
[e] Data were available for 197 prednisolone participants and 198 placebo participants

eTable 3. Number of Each Type of Adverse Event (Some Patients Experienced More Than One Event)

	Prednisolone[a]	Placebo
Expected[b]		
Anxiety or depression	2	1
Dizziness or faintness	7	0
Gastrointestinal	12	10
Fever	3	5
Fatigue	2	1
Disturbed sleep	3	0
Headache	1	2
Pain in abdomen or chest	5	1
Rash	3	3
Sinusitis	2	2
Sore throat	3	7
Loss of appetite	1	1
Other:	5	6
Head cold started	*1*	*0*
Itchy skin	*1*	*0*
Muscle pain in arm	*1*	*0*
Pain lower leg	*1*	*0*
Tightness in chest	*1*	*0*
"Didn't feel right on tablets"	*0*	*1*
Ache in jaw and mouth	*0*	*1*
Hypersensitivity	*0*	*1*
Palpitations	*0*	*1*
Swollen glands	*0*	*1*
Conjunctivitis	*0*	*1*
TOTAL	49	39
Unexpected[c]		
Dry throat	2	0
Hair loss	0	1
Nosebleed	1	2
Feeling thirsty	0	1
Tinnitus	1	0
TOTAL	4	4

[a]Includes the duplicate participant

[b]Expected adverse events were previously identified in the Summary of Product Characteristics or the British National Formulary

[c]Unexpected adverse events were those that did not constitute as an expected adverse event, cough related event or pre-existing symptom

eTable 4. Subgroup Analyses

	Duration of moderately bad or worse cough						
	Prednisolone		Placebo		Prednisolone vs. placebo Adjusted for center and baseline[a]		
	N	Median (95% CI)	N	Median (95% CI)	Subgroup specific HR (95% CI)	Interaction effect	
						HR (95 CI)	P value
Age (years)[b]							
<48	78	5 (4, 8)	88	6 (5, 7)	0.97 (0.70, 1.34)	1.25 (0.80, 1.97)	0.33
≥48	95	4 (3, 5)	73	5 (4, 6)	1.27 (0.92, 1.75)		
Prior duration of illness[b]							
<12 days	84	5 (4, 6)	83	5 (4, 6)	0.93 (0.68, 1.28)	1.39 (0.89, 2.17)	0.15
≥12 days	89	4 (3, 5)	78	5 (4, 7)	1.31 (0.95, 1.80)		
Presence of wheeze on auscultation							
No	163	4 (4, 5)	150	5 (4, 6)	1.10 (0.87, 1.39)	1.10 (0.43, 2.79)	0.85
Yes	10	5 (1, 10)	11	5 (1, 16)	1.51 (0.52, 4.34)		
Antibiotic consumption (up to 7 days)							
No	158	4 (4, 5)	147	5 (4, 6)	1.13 (0.90, 1.43)	0.73 (0.32, 1.65)	0.45
Yes	14	5 (2,16)	14	7 (4,7)	0.82 (0.32, 2.12)		
β-agonist consumption (24 hours prior to consultation)							
No	164	5 (4, 5)	159	5 (4, 6)	1.13 (0.90, 1.42)	0.31 (0.06, 1.50)	0.14
Yes[c]	9	4 (2, .)	2	1 (1, .)	3.24 (0.30, 34.88)		
Smoking status							
Never	95	4 (3, 5)	84	6 (5, 7)	1.27 (0.93, 1.73)	0.72 (0.46, 1.14)	0.16
Ever	78	5 (4, 6)	76	4 (3, 5)	0.90 (0.64, 1.26)		
History hay fever, asthma or eczema							
No	66	5 (4, 6)	68	5 (4, 7)	0.89 (0.61, 1.28)	1.52 (0.94, 2.44)	0.08
Yes	94	4 (3, 5)	86	5 (4, 6)	1.31 (0.96, 1.79)		
Baseline impression of illness							
<6	72	4 (3, 6)	84	5 (4, 6)	1.13 (0.81, 1.57)	0.99 (0.63, 1.55)	0.95
≥6	101	5 (4, 5)	77	6 (4, 7)	1.11 (0.81, 1.51)		

eTable 4 continued

	Mean symptom severity score[e]						
	Prednisolone		Placebo		Prednisolone vs. placebo Adjusted for center and baseline		
	N	Mean (95% CI)	N	Mean (95% CI)	Subgroup specific difference in means (95% CI)	Interaction effect	
						Difference in means (95 CI);	P value
Age (years)[b]							
<48	80	2.21(1.98, 2.35)	97	2.19 (1.97, 2.41)	-0.02 (-0.33, 0.29)	-0.29 (-0.70, 0.12)	0.17
≥48	109	1.82 (1.65, 2.00)	84	2.13 (1.89, 2.36)	-0.32 (-0.59, -0.04)		
Prior duration of illness[b]							
<12 days	91	2.11 (1.89, 2.33)	90	2.27 (2.05, 2.50)	-0.20 (0.49, 0.09)	-0.00 (-0.41, 0.41)	0.99
≥12 days	98	1.88 (1.70, 2.06)	91	2.04 (1.81, 2.27)	-0.21 (-0.49, 0.08)		
Presence of wheeze on auscultation							
No	178	1.95 (1.81, 2.10)	170	2.14 (1.97, 2.30)	-0.22 (-0.42, -0.01)	0.29 (-0.56, 1.15)	0.50
Yes	11	2.54 (1.71, 3.38)	11	2.53 (1.86, 3.19)	-0.13 (-1.09, 0.84)		
Antibiotic consumption (up to 7 days)							
No	174	1.94 (1.80, 2.08)	166	2.09 (1.93, 2.25)	-0.17 (-0.38, 0.03)	-0.27 (-1.02, 0.48)	0.48
Yes	14	2.57 (1.88, 3.26)	15	2.97 (2.31, 3.63)	-0.70 (-1.58, 0.19)		
β-agonist consumption (24 hours prior to consultation)							
No	180	1.96 (1.81, 2.10)	178	2.17 (2.01, 2.33)	-0.23 (-0.43, -0.02)	0.81 (-0.52, 2.14)	0.23
Yes	9	2.64 (2.04, 3.23)	3	1.54 (0.29, 2.78)	1.05 (-1.07, 3.17)		
Smoking status							
Never	102	2.03 (1.84, 2.21)	96	2.26 (2.03, 2.50)	-0.26 (-0.55, 0.04)	0.13 (-0.28, 0.55)	0.53
Ever	87	1.94 (1.72, 2.16)	84	2.01 (1.80, 2.22)	-0.12 (-0.42, 0.18)		
History hay fever, asthma or eczema							
No	72	1.94 (1.70, 2.18)	74	2.20 (1.94, 2.46)	-0.32 (-0.67, 0.03)	0.23 (-0.20, 0.66)	0.29
Yes	103	2.03 (1.83, 2.22)	100	2.10 (1.88, 2.31)	-0.09 (-0.36, 0.17)		
Baseline impression of illness							
<6	86	1.75 (1.55, 1.95)	98	1.97 (1.77, 2.18)	-0.23 (-0.51, 0.06)	0.04 (-0.38, 0.46)	0.86
≥6	103	2.19 (1.99, 2.38)	83	2.38 (2.13, 2.63)	-0.18 (-0.49, 0.14)		

[a] Baseline measure for cough is prior duration of cough (1-28 days) and for mean symptom severity score is patient reported illness severity (0 – 10).
[b] Dichotomized by median value of all participants
[c] Confidence intervals could not be estimated due to the low number of patients

eReferences

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