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KEYWORDS: Controlled clinical trial, Cough, Demulcent, Diphenhydramine, Simple Linctus

ABSTRACT

OBJECTIVES: To investigate the efficacy and safety of CS1002, an over-the-counter cough treatment containing diphenhydramine, ammonium chloride and levomenthol in a cocoa-based demulcent.

DESIGN: A multicentre, randomised, parallel group, controlled, single-blinded study in subjects with acute upper respiratory tract infection-associated cough.

SETTING: 4 GP surgeries and 14 pharmacies in the UK.

PARTICIPANTS: Subjects aged ≥18 years who self-referred to a general practitioner or pharmacist with acute cough of <7 days' duration. Subject inclusion criterion was cough severity ≥60mm on a 0-100mm visual analogue scale (VAS). 163 subjects were randomised to the study (mean subject age 38 years, 57% females).

INTERVENTIONS: Subjects were randomised to CS1002 or Simple Linctus (SL), a widely used cough treatment, and treatment duration was 7 days or until resolution of cough.

MAIN OUTCOME MEASURES: The primary analysis was intention-to-treat (157 subjects) and comprised cough severity assessed using a VAS after 3 days' treatment. Cough frequency, sleep disruption, health status (Leicester Cough Questionnaire [LCQ-acute]) and cough resolution were also assessed.

RESULTS: After 3 days' treatment, the adjusted mean difference [95% confidence interval] in cough severity VAS between CS1002 and SL was -5.9mm [-14.4,2.7], p=0.18. CS1002 was associated with a greater reduction in cough sleep disruption (mean difference -11.6mm [-20.6,-2.7], p=0.01) and cough frequency (mean difference -8.1mm [-16.2,0.1], p=0.05) compared to SL. There was greater improvement in LCQ-acute quality of life scores with CS1002 compared to SL: mean difference [95% CI] 1.2 [0.05,2.36], p=0.04 after 5 days' treatment. More subjects prematurely stopped treatment due to cough improvement in the CS1002 group (24.4%) compared to SL (10.7%; p=0.02). CS1002 was well-tolerated.

CONCLUSIONS: Although the primary endpoint was not achieved, CS1002 was associated with greater reductions in cough frequency, sleep disruption and improved health status compared to SL.

ABSTRACT WORD COUNT: 288 Words (Maximum: 300 Words)

TRIAL REGISTRATION: EudraCT number 2014-004255-31 protocol publically available at https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-004255-31/GB. The protocol was submitted to the MHRA in December 2014 prior to commencing the study (see attached MHRA approval letter containing the EudraCT number prior to commencing the study) but the MHRA were late in posting the study protocol into the EudraCT/clinical trials register database. No amendments were made to the protocol.

ARTICLE SUMMARY

Strengths and limitations of this study

- A recent Cochrane systematic review of cough medicines highlighted the paucity of randomised controlled trials of antitussive medicines for acute cough.
- This is one of the largest multiple dosing, multi-centre, randomised, controlled trials in subjects with cough to date, and the first to recruit subjects seeking cough medicines at pharmacies and is therefore more likely to represent the broader population with acute cough due to upper respiratory tract infection.
- Subjects were unselected for the category of cough, and included a broad range of subjects with self-reported dry, chesty and tickly cough.
- The study was single-blinded because an active control, Simple Linctus, was used as the comparator but it is possible that there may have been greater differences in efficacy outcome measures if an inactive placebo had been used.
- Our findings highlight the challenges of evaluating cough medicines in a rapidly improving condition and will facilitate the design of future studies of acute cough.

INTRODUCTION

Approximately 1 in 5 people in the United Kingdom (UK) suffer an acute cough over the winter [1] and it is one of the most common reasons for consulting a general practitioner (GP), at a cost to the National Health Service (NHS) of approximately £2 billion per year.[2-4] Although most acute coughs improve spontaneously, many patients use over-the-counter (OTC) medicines. In 2014, £98.7 million was spent in the UK on OTC cough treatments.[5] OTC cough medicines include antitussives, expectorants, mucolytics, antihistamines, decongestants, and numerous drug combinations.[6] There is a lack of data supporting the efficacy of OTC medicines in the treatment of acute cough associated with upper respiratory tract infection (URTI). In 2012, a Cochrane systematic review concluded there was no strong evidence for or against their effectiveness.[6] Methodological flaws in clinical trial design, paucity of placebo-controlled trials, use of un-validated outcome measures, and inefficacy of medicines were some of the reasons for the poor evidence base.

CS1002 is an OTC cough medicine that contains 3 active ingredients: diphenhydramine, levomenthol, and ammonium chloride in a cocoa-based demulcent preparation. Diphenhydramine is an antihistamine that has been reported to reduce the heightened cough reflex sensitivity in subjects with cough associated with an URTI.[7] Menthol and eucalyptus have been used for many centuries for treating coughs and colds.[8] Menthol is obtained from mint oils, mainly peppermint, or made synthetically from coal tar. It has a pungent odour that provides a cooling and soothing effect in the mouth and throat and is often used to relieve congestion.[8] Menthol has also been reported to inhibit cough reflex sensitivity compared to placebo.[9] Ammonium chloride is an acid-forming salt that is thought to exert an expectorant effect by loosening sputum.[10] The effectiveness and mode of action of ammonium chloride remains controversial.[10] The cocoa-based demulcent preparation used

in CS1002 is more viscous than most available OTC cough medicines. Demulcents are thought to reduce cough and cold symptoms because of a soothing effect on the mucus membrane.[11] The aim of this study was to investigate the efficacy of CS1002, an OTC cough medicine for cough associated with URTI, in a randomised controlled trial.

METHODS

Study Design

This multicentre, randomised, parallel group, controlled, single-blinded study was conducted in 4 GP surgeries and 14 pharmacies in the UK between 30 December 2014 and 9 May 2015. The control was a widely used simple linctus (SL) medicine available for acute cough in the UK. The investigators were blinded to the nature of the investigational product by using identical sealed packaging for both medicines. Subjects self-administered their assigned medication outside the pharmacy or GP surgery.

Subjects

Subjects aged ≥18 years who self-referred themselves to a GP or pharmacist with an acute cough of less than 7 days' duration were recruited. Subject inclusion criterion was a severity of at least 60mm on a 0 to 100mm visual analogue scale (VAS). Subject exclusion criteria were (i) subjects with a chronic cough, (ii) current or history of smoking within the past 12 months (including e-cigarettes), (iii) subjects with any relevant hospital stay of >2 days within a 6-month period, (iv) use of any cough or cold treatment for the current cough episode, including antibiotics, (v) productive cough with excessive secretion, (vi) use of angiotensin converting enzyme (ACE) inhibitor medication.

Subject Involvement

Subjects were not involved in the design or conduct of this study.

Ethics and Trial Registration

The protocol was approved by the North West - Greater Manchester South Research Ethics Committee (Reference: 14/NW/1424). The trial protocol was registered prior to commencing

the study in the publically available EudraCT database (Reference: 2014-004255-31) and no protocol amendments were made subsequently. All participants provided written informed consent.

Randomisation

All subjects considered eligible for study participation and who signed a consent form were given a unique randomisation number based on a pre-defined computer-generated randomisation scheme corresponding to a sealed medication pack that contained either CS1002 (2x150mL) or SL (2x150mL). Subjects were allocated treatment using a block randomisation with a block size of 4.

Study Medication

Subjects were randomised to one of the following treatments:

- CS1002: diphenhydramine 14mg/5mL, levomenthol 1.1mg/5mL and ammonium chloride 135mg/5mL in a cocoa-based demulcent preparation.
- SL: citric acid monohydrate 125mg/5mL in a syrup base.

Interventions

The subjects were approached, screened, consented and randomised during their initial consultation with their GP or the pharmacist. Subjects took their study medication orally 4 times daily (5mL in the morning, 5mL at lunchtime, 10mL at teatime, and 10mL at bedtime) for up to 7 days. Subjects were instructed to take the medication regularly until the cough resolved.

Methods of Evaluation

Subjects completed their assessments and compliance with medication in a daily diary. Each subject received a tamper-evident unidentifiable patient pack which was only opened on leaving the site. On completion, the pack was returned in a resealed and unidentifiable state. An independent data management organisation was utilised for data entry and to manage adverse event (AE) reporting. The investigators were blinded to the assignment of treatment and to the outcome assessments. The schedule of study visits is presented in Figure 1. The subjects were asked to complete assessments at baseline (Day 1) and then at the same time of day from Day 2 to Day 8. The study evaluated the efficacy of the study medications by assessing various aspects of acute cough.[12] Cough severity, frequency, and impact on sleep disruption in the previous 24 hours were assessed using a VAS. Health related quality of life (HRQoL) was assessed using the Leicester Cough Questionnaire for acute cough (LCQ-acute).[3,13] The LCQ is a valid and reliable health status measure of acute cough in adults and is responsive to change. It comprises 19 items divided into 3 domains (physical, psychological and social) and uses a 7-point Likert response scale. A higher score indicates a better health status. The LCQ is designed for self-administration and takes less than 5 minutes to complete.[3,14]

Primary Efficacy Endpoint

The primary efficacy endpoint was change from baseline to Day 4 (i.e. after 3 complete days of treatment) in cough severity on a 100mm VAS (ranging from 0=no cough to 100=worst cough ever).

Secondary Efficacy Endpoints

The following pre-specified endpoints were evaluated: (i) change from baseline in cough severity VAS at Days 6 and 8, (ii) change from baseline in cough frequency and cough sleep disruption VAS at Days 4, 6 and 8, (iii) time to resolution of cough symptoms, defined as the day at which cough severity VAS <17mm (the threshold considered to be of minimal severity and the minimally important difference [MID] in acute cough),[12] (iv) change from baseline in LCQ-acute score at Days 4, 6 and 8.

Safety Monitoring

Subjects were advised to reduce the dose of medication if they experienced drowsiness, and to document this in their daily diary. If drowsiness persisted, they were advised to discontinue the medication. Subjects were advised to contact their doctor or a 24-hour help line if they felt unwell. Safety was assessed in terms of the frequency and severity of AEs occurring during the study and this was recorded by the investigator.

Statistical Analysis and Sample Size

The sample size calculation was based on a difference in the change in cough severity VAS of 17mm between subjects treated with CS1002 and SL. Evaluation of the VAS in acute cough has suggested that the MID is 17mm.[12] It was estimated that approximately 180 subjects would be required to achieve a power of 90% to detect a difference between the treatment groups of 17mm, with a standard deviation of 35mm.[12]

The primary analysis was conducted on the intention-to-treat (ITT) population, comprising all randomised subjects who were treated with at least one dose of study medication and provided a baseline and at least one on-treatment assessment of cough severity. No

imputation was used for missing data (i.e. only observed data was used). A mixed model for repeated measures (MMRM) analysis was used to compare the effect of study treatments on cough parameters from baseline. The model included effects for treatment group, day, pooled centre, baseline cough severity, and treatment-by-day and baseline-by-day cough severity interaction terms. Residual plots and a normality test were used to assess normality. The results were also repeated for the per-protocol set (PPS), defined as subjects in the ITT population who did not have an important protocol violation. A sensitivity analysis was also conducted to assess the robustness of the primary efficacy results to the method of handling missing data, using a last observation carried forward (LOCF) approach and a baseline observation carried forward (BOCF) approach for subjects with no on-treatment data. Parametric data was presented as mean and either standard deviation (SD), standard error of the mean (SEM), or 95% confidence intervals (95% CI). Statistical significance was defined as $p \leq 0.05$. The proportions of subjects with cough resolution were compared using a stratified (by centre) Cochran-Mantel-Haenszel test. Time-to-event analysis using a Cox proportional hazards model stratified by centre was used to estimate a hazard ratio.

RESULTS

Subjects

A total of 163 subjects were randomised into the study at 4 GP sites and 14 pharmacy sites. The reasons for screening failures are shown in Figure 2. The ITT population comprised 157 subjects (82 CS1002, 75 SL), and the PPS comprised 142 subjects (75 CS1002, 67 SL) (Figure 2). The baseline characteristics of both treatment groups were well-matched (Table 1). The mean age of the subjects was 38 years, 57% of subjects were female, and 62% of subjects were white (34% Asian and 4% black). The groups were well-matched for the proportion of subjects describing the characteristics of their cough as dry (CS1002 50%; SL 52%), chesty (CS1002 29%; SL 31%) or tickly (CS1002 21%; SL 17%).

Table 1: Subject Demographic and Baseline Characteristics

	CS1002 n (%) N=82	**Simple linctus n (%) N=75**
Gender [N (%)]		
Male	34 (42)	34 (45)
Female	48 (59)	41 (55)
Age [years]		
Mean (SD)	38.5 (17.3)	38.2 (16.6)
Median (range)	31.5 (18, 75)	34.0 (18, 86)
Type of referral [N (%)]		
GP	30 (37)	27 (36)
Pharmacist	52 (63)	48 (64)
Smoking status [N (%)]		
Never smoked	64 (78)	54 (72)
Ex-smoker	18 (22)	21 (28)
Cough characteristics, mean (SD)		
Cough duration [days]	3.0 (1.5)	3.1 (1.6)
Cough severity VAS (mm)	80.4 (10.1)	81.6 (9.9)
Cough frequency VAS (mm)	79.5 (16.1)	76.7 (15.5)
Cough sleep disruption VAS (mm)	75.5 (23.2)	64.6 (29.2)
LCQ-acute scores, mean (SD)		
Total score	10.8 (3.5)	11.4 (3.2)
Physical score	3.7 (1.2)	4.1 (1.1)
Psychological score	3.7 (1.2)	3.9 (1.1)
Social score	3.4 (1.4)	3.5 (1.3)

LCQ = Leicester Cough Questionnaire; VAS = visual analogue scale (using a scale of 0-100 mm)
Based on ITT population

Primary Efficacy Endpoint

Subjects took CS1002 medication for a mean (SD) of 6.2 (2.1) days and SL medication for 6.6 (1.8) days. The mean number of doses of study medication were 22.2 (8.7) for the CS1002 group and 23.7 (8.3) in the SL group. The maximum number of medication doses possible during the study was 28. The weight of the bottles of treatment returned at the end of study was planned to be used to estimate compliance, excluding doses not taken due to early termination from the study due to recovery. The weight of medicine broadly agreed with self-reported consumption stated by subjects receiving CS1002, with a mean (SD) of 94% (17%) vs. 94% (18%) for subjects receiving SL. There was a clinically meaningful improvement in cough severity VAS at Day 4 in both groups (Table 2, Figure 3). The magnitude of the reduction in cough severity score was greater in the CS1002 group compared to the SL group but was not statistically significant; mean (95% CI) difference of 5.9mm (-14.4, 2.7), p=0.18. The PPS and ITT sensitivity analyses with imputations were also consistent with this finding (see Supplementary File).

Secondary Efficacy Endpoints

Cough Severity: There was a progressive decrease in cough severity VAS over the study, with the CS1002 group reporting a greater reduction compared to the SL group between Days 3 to 7 (Figure 3). The between group changes in cough severity VAS did not achieve statistical significance (Table 2 and Figure 3).

Cough Frequency: There was a greater reduction in cough frequency VAS with CS1002 compared to SL at all time points (Figure 4). At Day 4, there was an 8.1mm (95% CI: -16.2, 0.1) greater reduction in cough frequency VAS for CS1002 compared to SL (p=0.05) (Table 2 and Figure 4).

Cough Resolution: By Day 4, 29.3% of subjects in the CS1002 group had achieved cough resolution compared with 17.3% in the SL group (p=0.08) (Table 2). There was no significant difference between the treatment groups regarding median time taken to achieve cough resolution (CS1002 6.5 days, SL 7.0 days, hazard ratio 1.300, p=0.20, Figure 5). In a post-hoc analysis, 20 subjects (24.4%) in the CS1002 group and 10 (10.7%) in SL group stopped treatment by Day 4 due to improvement in cough (p=0.02).

Sleep Disruption: There was a greater reduction in sleep disruption with CS1002 compared to SL at all time points (Figure 6). At Day 4, the magnitude of reduction in cough sleep disruption score was greater for the CS1002 group than for the SL group, mean difference of 11.6mm (95% CCI: -20.6,-2.7), p=0.01 (Figure 6 and Table 2). A summary of all VAS results is provided in Supplementary File Figure 1.

Table 2: Analysis of Key Efficacy Parameters at Day 4

Key Efficacy Assessments	CS1002	Simple linctus
Number of subjects	82	75
Cough severity		
Baseline value (mean±SD)	80.4 (10.1)	81.6 (9.9)
Change from baseline to Day 4: Mean (95% CI)	-38.9 (-45.2,-33.2)	-32.8 (-39.6,-27.0)
Adjusted mean difference (95% CI)	-5.9 (-14.4,2.7)	
p-value	**p=0.18**	
Cough frequency		
Baseline value (mean±SD)	79.5 (16.1)	76.7 (15.5)
Change from baseline to Day 4: Mean (95% CI)	-40.7 (-46.0,-34.6)	-32.1 (-38.1,-26.4)
Adjusted mean difference (95% CI)	-8.1 (-16.2,0.1)	
p-value	**p=0.05**	
Cough resolution		
Day 4 value (n, %)	24 (29.3%)	13 (17.3)
Difference (%)	12%	
p-value	**p=0.08**	
Sleep disruption		
Baseline value (mean±SD)	75.5 (23.2)	64.6 (29.2)
Change from baseline to Day 4; Mean (95% CI)	-42.8 (-46.9,-34.4)	-26.3 (-35.5,-22.6)
Adjusted mean difference (95% CI)	-11.6 (-20.6,-2.7)	
p-value	**p=0.01**	

NB. Negative values indicate a reduction in cough symptoms
Based on ITT population. Adjusted mean difference = difference in between group differences

Health-Related Quality of Life: LCQ-acute total scores increased over time for both treatment groups, indicating an improvement in HRQoL. At Day 6, the magnitude of the improvement was significantly greater in the CS1002 group compared to the SL group (mean difference 1.21 (95% CCI: 0.05, 2.36), p=0.04) (see Supplementary File Figures 2 and 3).

Adverse Events (AEs)

AEs were reported for 17 subjects (20.5%) in the CS1002 group and 21 subjects (27.6%) in the SL group during the study (Table 3). The AEs were generally indicative of the study indication or likely to be associated with URTI, with the majority being mild or moderate

severity. Events classified as severe were only seen in the SL treatment group, and comprised cough, sneezing and joint swelling (all occurring in 1 subject each). No SAEs or deaths were reported. There were no AEs of drowsiness reported during the study. Six subjects (7%) in the CS1002 group and no subjects in the SL group reported in their diary that they reduced the dose of medication due to drowsiness/tiredness. These events were not reported by the subjects as AE. Following the reduction of the dose of medication there were no further reports of drowsiness or tiredness.

Table 3: Adverse Events

AEs, n (%)	CS1002 N=83 Total N (%)	Simple linctus N=79 Total N (%)
Number of subjects with an AE	17 (20.5)	21 (27.6)
Nervous system disorders	7 (8.4)	10 (13.2)
Headache	5 (6.0)	9 (11.8)
Dizziness	1 (1.2)	2 (2.6)
Respiratory, thoracic and mediastinal disorders	8 (9.6)	9 (11.8)
Oropharyngeal pain	2 (2.4)	4 (5.3)
Cough	2 (2.4)	3 (3.9)
Productive cough	3 (3.6)	1 (1.3)
Dyspnoea	0 (0.0)	2 (2.6)
Gastrointestinal disorders	5 (6.0)	2 (2.6)
Diarrhoea	3 (3.6)	0 (0.0)
Abdominal pain upper	2 (2.4)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	5 (6.6)
Pain	0 (0.0)	3 (3.9)
Pyrexia	0 (0.0)	2 (2.6)
Infections and infestations	1 (1.2)	2 (2.6)
Lower respiratory tract infection	0 (0.0)	2 (2.6)

Treated set population. AEs reported for >1 subject.

DISCUSSION

This multicentre, randomised study compared the efficacy and safety of two OTC cough mixtures: CS1002 containing diphenhydramine, ammonium-chloride and levomenthol in a cocoa-based demulcent preparation versus SL containing citric acid monohydrate. This is one of the largest multiple dosing, randomised controlled trials in subjects with URTI-associated cough to date, and the first to recruit subjects seeking cough medicines at pharmacies. The study did not achieve a significant reduction in primary end-point cough severity after 3 days of treatment, but there were greater reductions in cough frequency and sleep disruption and resolution of cough in subjects receiving CS1002 compared to SL.

Our trial represents a significant advance in the study of URTI-associated cough for a number of reasons. A Cochrane systematic review of cough medicines concluded that there was no evidence for or against cough medicines for URTI-associated cough.[6] Previous trials of cough medicines have been hampered by the recruitment of small numbers of subjects, the recruitment of subjects not representative of URTI-associated cough, uncontrolled study design and the use of un-validated endpoints. We conducted a randomised clinical trial that included validated cough outcome measures. Our primary outcome measure, the VAS, is widely used in studies of cough.[15] We recruited subjects with an URTI-associated cough who were otherwise healthy and seeking an antitussive medicine. Our subjects were unselected for the category of cough, and included a broad range of subjects with self-reported dry, chesty and tickly cough. We conducted a large study, recruiting subjects from 18 sites. This is the first study to recruit subjects presenting to pharmacies, and therefore the study population is more likely to resemble the broader population seeking cough medicines. There were few subjects that dropped out of the trial, and therefore our data completeness was good. The efficacy of the interventions was evaluated with widely used and validated

end-points of cough severity VAS and LCQ-acute HRQoL questionnaires.[15,16] We conducted a controlled trial and the comparator was a widely used OTC treatment. SL, like most cough medicines, lacks a strong evidence base. Its efficacy has not been compared to natural recovery, placebo, or to other cough medicines. The rate of reduction of cough severity VAS associated with SL in our study does appear to be greater than that reported for natural recovery.[12] The mechanism of action of SL is poorly understood, but is thought to be related to a demulcent effect and the hyper-salivation resulting from the sugary taste.[11]

There was a clinically significant reduction in primary end-point cough severity VAS at Day 4 in both groups. However, CS1002 did not achieve the primary end-point of a greater reduction in cough severity at Day 4 compared to SL. There were, however, greater reductions in secondary endpoints of sleep disruption and cough frequency, and improvements in HRQoL associated with CS1002 compared to SL. There was also a trend favouring greater resolution of cough at Day 4 with CS1002 compared to SL, with a near doubling of the proportion of subjects whose cough had resolved. This was supported by a post-hoc analysis that found a significantly greater number of subjects had discontinued their medication due to resolution of cough by Day 4 (CS1002, 24.4% vs. SL, 10.7%: p=0.02). The MID for cough outcome measures of frequency VAS, sleep disruption VAS and cough resolution have not been reported in URTI-associated cough, and this should be studied in future to facilitate the clinical interpretation of data. CS1002 was well tolerated, and there were few significant adverse events, including drowsiness. Drowsiness was managed with dose reduction, and no subjects discontinued the medication because of this symptom. Subjects were compliant with both medications, and this was verified by counting the doses of medication returned at the end of the study. The mechanism of action of CS1002 is poorly understood. There are a number of possibilities, which include a reduction in cough reflex

sensitivity,[7] promotion of more restful sleep, and a demulcent action. CS1002 contains a cocoa-flavoured demulcent that is more viscous than most available OTC cough medicines, and this may potentially promote palatability.

There are a number of important limitations with our study. We did not utilise a placebo comparator, and the study was not double-blinded. The limitations of a single-blinded study were reduced by informing the subjects that they were going to receive a cough medicine, but not the characteristics of the medicine. The investigators were blinded to the study because both medicines were contained in identical packaging, and subjects were instructed to commence their medication outside the pharmacy or GP clinic. We used SL as the comparator since this is a widely used cough treatment. It is possible that there may have been greater differences in efficacy outcome measures if we had used an inactive placebo. It is likely that there was also significant natural recovery in our study. Our data highlights the difficulty in evaluating cough medicines in a rapidly resolving condition. We don't know whether the cough at study entry was worsening or improving and this could have impacted on our findings. We were short of our recruitment target of 180 subjects; we recruited 163 subjects. This was due to a delay in the start of the study, and consequently a reduced time window for recruitment during the cough and cold winter season. We think it is unlikely that the slight under-recruitment of subjects would have altered our study conclusions. The reasons for screen failures were not recorded for many patients, particularly at busy pharmacy sites. The reasons were, however, recorded for 2,238 subjects and suggest that a large number of subjects approached had duration of cough greater than 7 days. It is possible that the discontinuation of medication could have reflected lack of efficacy as well as recovery. We didn't investigate the cause of the acute cough, and future studies should possibly assess viruses, pertussis and bacterial causes. We did not assess cough with objective outcome

measures, such as cough frequency monitoring.[16] Recently, there have been significant advances in cough monitoring technology, and this should be possible in future studies.[17]

In conclusion, the OTC cough medicine CS1002 did not achieve a significant reduction in the primary endpoint cough severity, but it was associated with a greater reduction in cough frequency and sleep disruption, and increased resolution of cough leading to early discontinuation of medication and improved HRQoL compared to comparator SL. Further studies should investigate the impact of natural recovery and placebo on cough outcome measures to facilitate the optimal study protocol in URTI-associated cough.

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AUTHORS' CONTRIBUTIONS

SB = Surinder Birring; JB = John Brew; TK = Tony Kilbourn; VE = Viv Edwards; RW = Rosamund Wilson; AM = Alyn Morice

Conception/design of work: SB, JB, TK, VE, RW, AM

Data analysis: RW, VE, JB

Data interpretation: all authors

Drafting manuscript: SB with input from JB, TK, VE, RW and AM. Help was also provided by Debbie Jordan, a professional medical writer.

Review and approval of manuscript: all authors

COMPETING INTERESTS

Surinder Birring has received personal fees from Infirst Healthcare during the conduct of the study for advisory work. Alyn Morice has received personal fees from Infirst Healthcare during the conduct of the study for advisory work. John Brew, Viv Edwards, and Tony Kilbourn are employees of Infirst Healthcare Ltd. Rosamund Wilson is a statistical consultant to Infirst Healthcare.

DATA SHARING STATEMENT

No additional data are available.

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FIGURE LEGENDS

Figure 1: Study Design

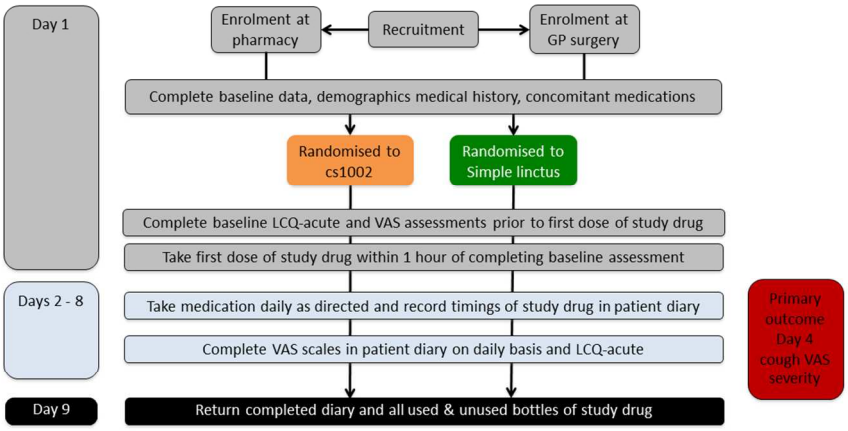
Figure 2: Trial CONSORT Flow Diagram

Figure 3: Change in Cough Severity over Time

Figure 4: Change in Cough Frequency over Time

Figure 5: Resolution of Cough: Cumulative Percentage of Subjects

Figure 6: Change in Cough Sleep Disruption over Time



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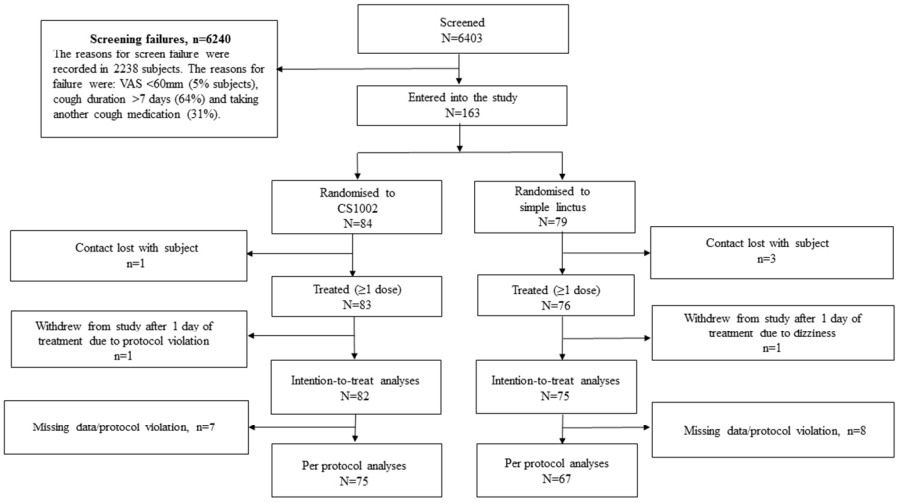

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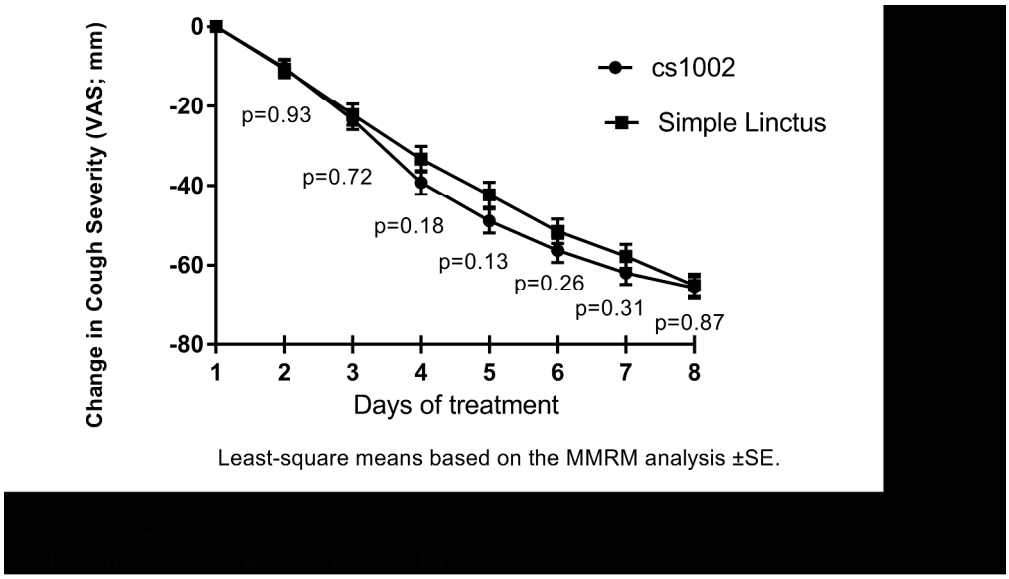
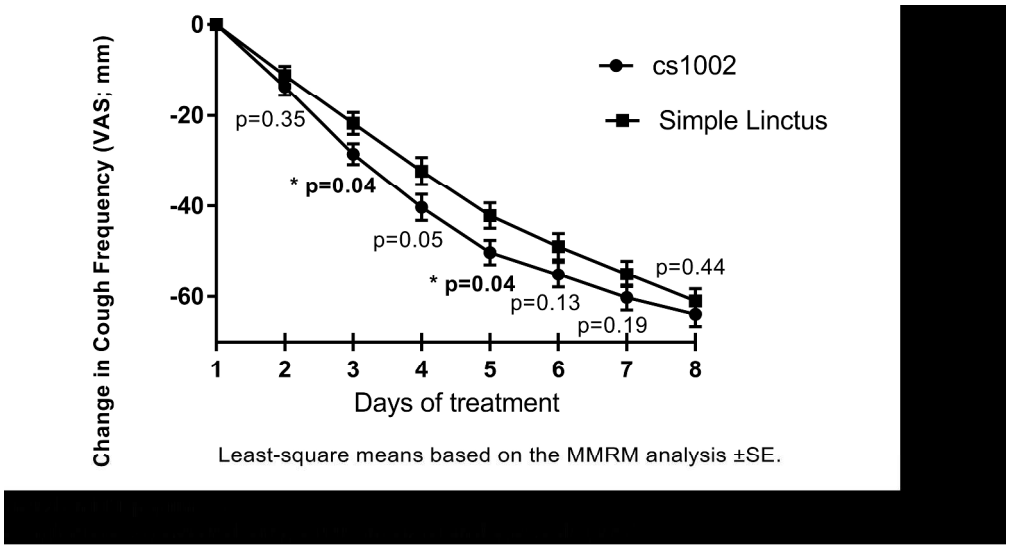


Least-square means based on the MMRM analysis ±SE.



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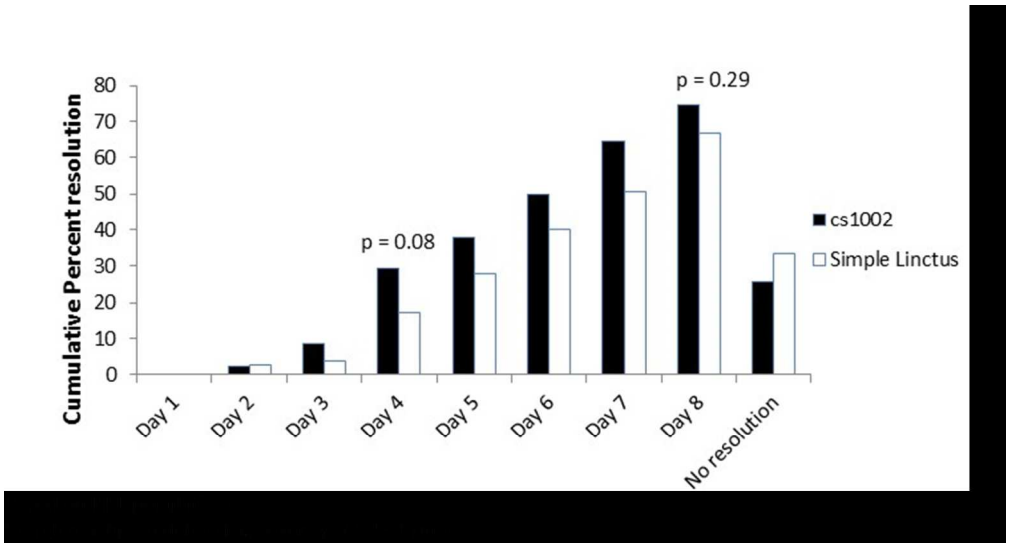

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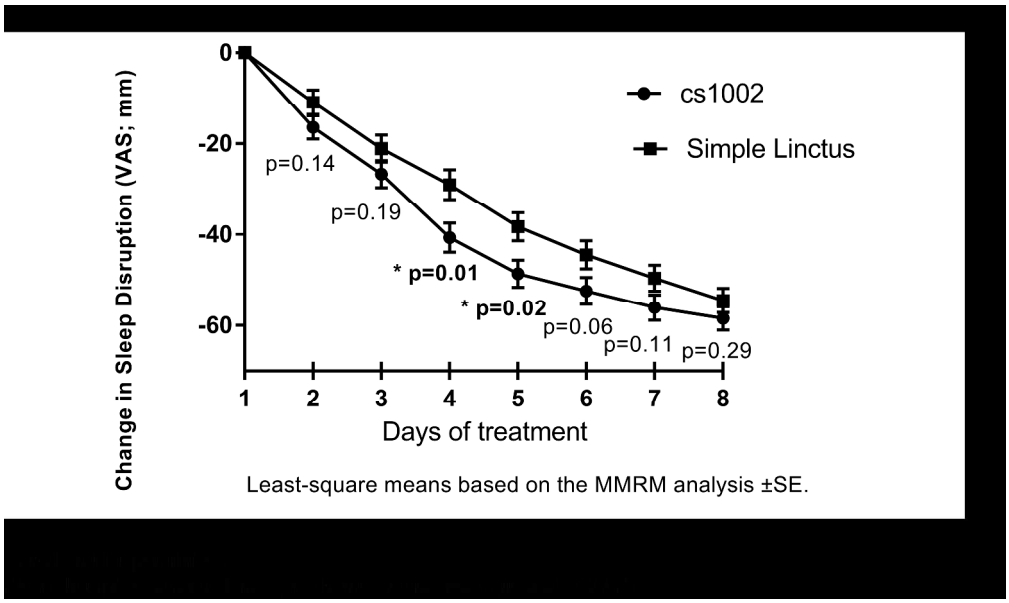

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Supplementary File

Per-protocol Analysis

A supportive analysis of the primary endpoint of the comparison of change in cough severity for CS1002 versus simple linctus from baseline to Day 4 of the study was conducted using the per-protocol set (PPS), as summarised in Supplementary File Table 1. Analysis using the PPS showed similar findings to the primary endpoint analysis, with the 4.6 mm difference in change in cough severity score between groups, not achieving statistical significance (p=0.30).

Supplementary File Table 1: Change in cough severity VAS at Day 4 (Per-Protocol Set)

	CS1002	simple linctus
Number of subjects	75	67
Baseline cough severity VAS, mm Mean (SD)	80.3 (10.0)	81.2 (9.5)
Change in VAS from baseline to Day 4 Mean (SE) Adjusted mean (SE)[1] 95% confidence interval[1]	 -39.4 (3.3) -40.6 (3.1) -46.6, -34.5	 -35.4 (3.1) -36.0 (3.2) -42.4, -29.6
CS1002 vs. simple linctus Adjusted VAS mean difference (SE)[1] 95% confidence interval[1] p-value[1]	 -4.6 (4.4) -13.2, 4.1 0.3009	

Note: Cough severity VAS scores range from 0 (no cough) to 100 (worst cough ever)
Negative values indicate a reduction in cough severity from baseline
[1] ANCOVA analysis on observed data including treatment, day, pooled centre and baseline cough severity terms along with treatment-by-day and baseline-by-day interaction terms

Sensitivity Analysis

Two sensitivity analyses were performed with imputations for missing data. In the first analysis, a last observation carried forward (LOCF) approach for missing data was used in the intention-to-treat (ITT) population. For this analysis if the Day 4 cough severity score was missing (the last on-treatment assessment of cough), the severity prior to Day 4 was carried forward. Analysis using this approach showed similar findings to the primary endpoint analysis (see Supplementary File Table 2), with the analysis of covariance (ANCOVA) demonstrating mean changes in cough severity of -39.2 mm (95% CIs -45.2, -33.2) for CS1002 and -33.7 mm (95% CIs -39.9, -27.4) for simple linctus. The 5.6 mm difference in change in cough severity score between the groups did not achieve statistical significance (p=0.19).

Supplementary File Table 2: Sensitivity analysis of change in cough severity at Day 4 (Last Observation Carried Forward, ITT Population)

	CS1002	simple linctus
Number of subjects	82	75
Baseline cough severity VAS, mm Mean (SD)	80.4 (10.1)	81.6 (9.9)
Change in VAS from baseline to Day 4 Mean (SE) Adjusted mean (SE)[1] 95% confidence interval[1]	-38.4 (3.1) -39.2 (3.0) -45.2, -33.2	-32.8 (3.1) -33.7 (3.2) -39.9, -27.4
CS1002 vs. simple linctus Adjusted VAS mean difference (SE)[1] 95% confidence interval[1] p-value[1]	-5.6 (4.2) -13.9, 2.8 0.1904	

Note: Cough severity VAS scores range from 0 (no cough) to 100 (worst cough ever)
Negative values indicate a reduction in cough severity from baseline
[1] ANCOVA analysis on LOCF data including treatment, day, pooled centre and baseline cough severity terms

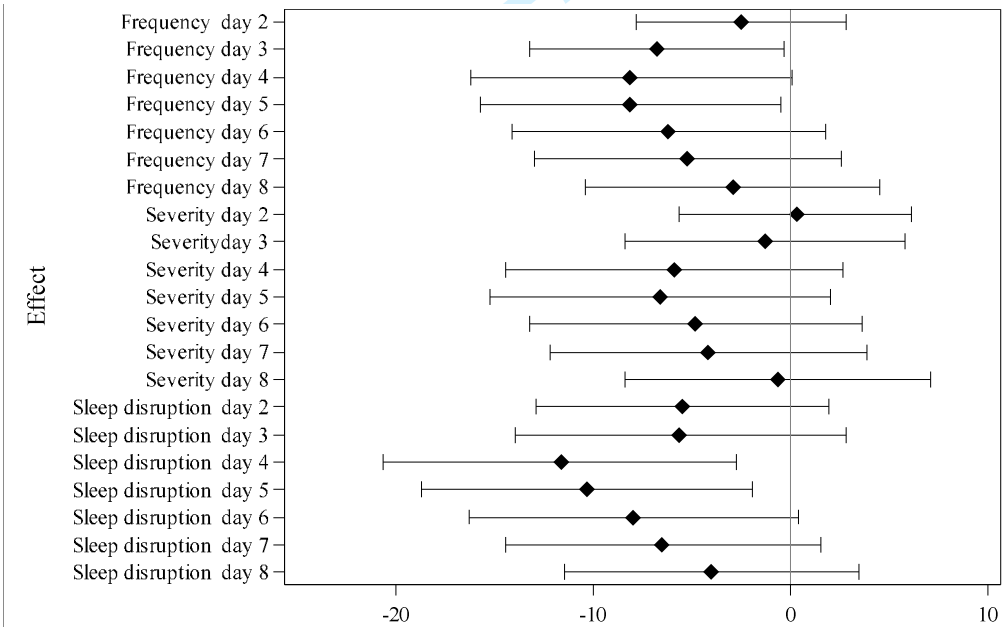
In the second analysis of the randomised set, missing cough VAS data at Day 4 was imputed, with baseline observations carried forward (BOCF). Analysis using this approach showed similar findings to the primary endpoint analysis (see Supplementary File Table 3), with the ANCOVA analysis demonstrating mean changes in cough severity of -38.1 (95% CIs -44.1, -32.1) for CS1002 and -31.5 (95% CIs -37.7, -25.4) for simple linctus. The 6.5 mm difference in change in cough severity score between the treatment groups did not achieve statistical significance (p=0.12).

Supplementary File Table 3: Sensitivity analysis of change in cough severity at Day 4 (Baseline Observation Carried Forward, ITT Population)

	CS1002	simple linctus
Number of subjects	84	79
Baseline cough severity VAS, mm Mean (SD)	80.5 (10.1)	81.5 (10.2)
Change in VAS from baseline to Day 4 Mean (SE) Adjusted mean (SE)[1] 95% confidence interval[1]	-37.5 (3.1) -38.1 (3.0) -44.1, -32.1	-31.2 (3.1) -31.5 (3.1) -37.7, -25.4
CS1002 vs. simple linctus Adjusted VAS mean difference (SE)[1] 95% confidence interval[1] p-value[1]	-6.5 (4.2) -14.9, 1.8 0.1229	

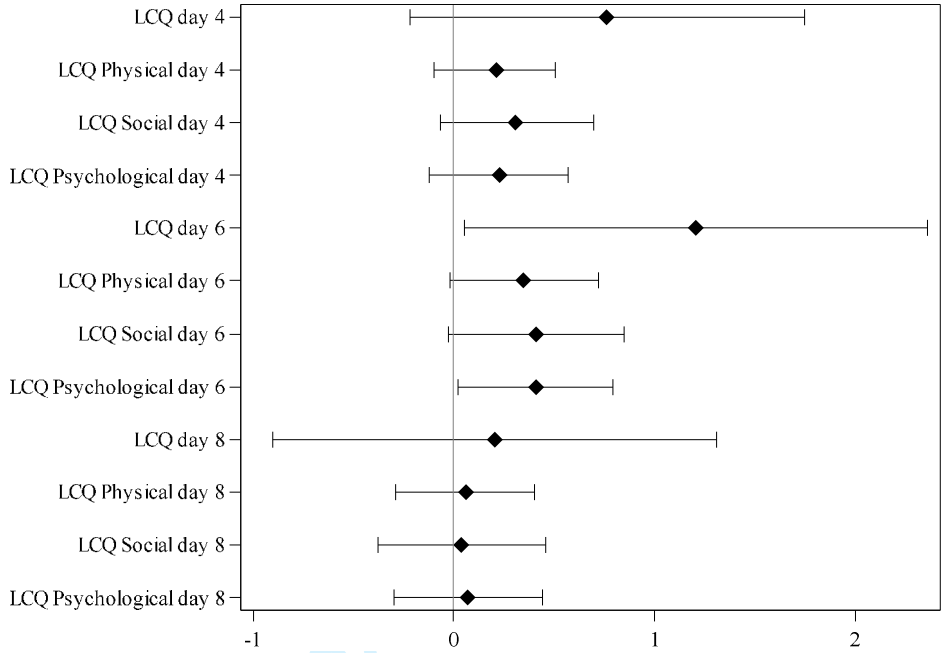
Note: Cough severity VAS scores range from 0 (no cough) to 100 (worst cough ever)
Negative values indicate a reduction in cough severity from baseline
[1] ANCOVA analysis on baseline observation carried forward data including treatment, day, pooled centre and baseline cough severity terms

Supplementary File Figure 1: Forest plot of cough frequency, cough severity and cough sleep disruption VAS scores (Days 2 – 8)



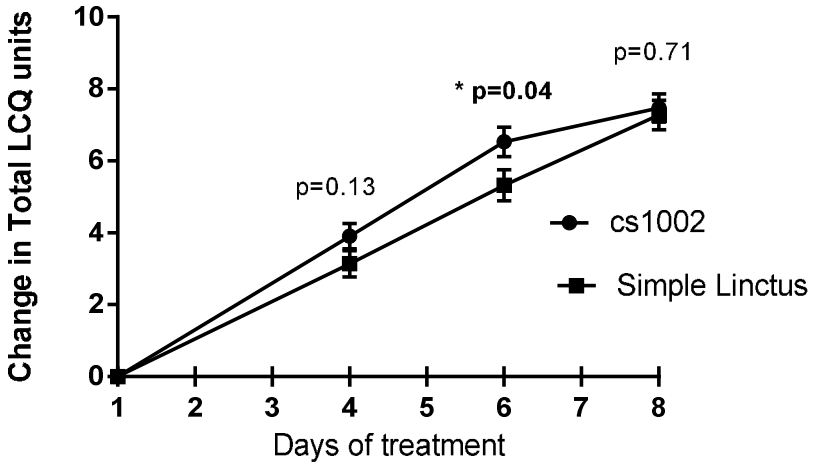
Estimates and 95% CI: Negative values favour CS1002 and positive values favour Simple Linctus.
Based on ITT population

Supplementary File Figure 2: Forest Plot of HRQoL (LCQ) Scores



Estimates and 95% CI: Positive values favour CS1002 and negative values favour Simple Linctus.
ITT population

Supplementary File Figure 3: Change in total LCQ (quality of life) score over time



Least-square means based on the MMRM analysis ±SE.

Based on ITT population
LCQ = Leicester Cough Questionnaire

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Yes
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Page 2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Pages 5 and 6
	2b	Specific objectives or hypotheses	Page 6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Page 8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	4a	Eligibility criteria for participants	Page 7
	4b	Settings and locations where the data were collected	Page 7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Pages 8 and 9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Pages 9 and 10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	Page 10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Page 8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Page 8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Page 8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Pages 8 and 22

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Page 9
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Pages 10 and 11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Page 28
	13b	For each group, losses and exclusions after randomisation, together with reasons	Page 28
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Page 7
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Page 12
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Page 14
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Pages 13, 14 and 15
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Pages 13, 14 and 15
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Pages 15 and 16
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Page 19
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Page 17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Pages 17, 18, 19 and 20
Other information			
Registration	23	Registration number and name of trial registry	Page 3
Protocol	24	Where the full trial protocol can be accessed, if available	Page 3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Page 21

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Clinical Study Protocol IFH-2014-004

Infirst+ HEALTHCARE

CLINICAL STUDY PROTOCOL

A real world, single-blind, randomised study to compare an OTC cough medicine (cs1002) containing diphenhydramine, levomenthol and ammonium chloride with a simple linctus containing citric acid monohydrate in terms of daily cough severity in subjects with acute cough in routine clinical practice.

ROCOCO

Real World evaluation of an **O**TC **co**ugh medicine **co**ntaining diphenhydramine

Protocol Number: IFH-2014-004

EUDRACT Number: 2014-004255-31.

Protocol Version and Date: Version 1. 24 Oct 2014

TEST DRUG: **cs1002**

SPONSOR: **Infirst+ HEALTHCARE Ltd**
45 Beech St, London, United Kingdom, EC2Y 8AD
Telephone: +44 (0) 20 7153 6600
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CHIEF INVESTIGATOR: **Dr Surinder Birring**
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MONITORING CRO: **Prn Clinical Services Ltd**
Grove House, Lutyens Close, Chineham Court, Basingstoke RG24 8AG
Telephone: +44 (0) 1256316551
Fax: +44 (0) 1256 316552

Clinical Study Protocol IFH-2014-004

Protocol Approval

Sponsor Approval

This protocol IFH-2014-004 has been approved by Infirst+ HEALTHCARE:

Protocol Version:	Version 1. 24 Oct 2014
Approver: Dr Sunita Chauhan Responsible Physician (PharSafer) **Print Name** **Sign and date:**	
Approver: Viv Edwards Director of Regulatory & Medical Affairs **Print Name** **Sign and date:**	

Chief Investigator Approval

This protocol IFH-2014-004 has been approved by the Chief Investigator:

Protocol Version:	Version 1. 24 Oct 2014
Approver: Dr Surinder Birring Consultant Respiratory Physician **Print Name:** **Sign and date:**	

Investigator's Agreement

I have read this Infirst+ HEALTHCARE protocol no. IFH-2014-004.

A real world, single-blind, randomised study to compare an OTC cough medicine (cs1002) containing diphenhydramine, levomenthol and ammonium chloride with a simple linctus containing citric acid monohydrate in terms of daily cough severity in subjects with acute cough in routine clinical practice.

I have fully discussed the objectives of this trial and the contents of this protocol with the Sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the trial, without written authorisation from Infirst+ HEALTHCARE. It is, however, permissible to provide information to a patient in order to obtain consent.

I agree to conduct this trial according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines and to conduct the trial in accordance with ICH guidelines on GCP and with the applicable regulatory requirements.

I understand that the sponsor may decide to suspend or prematurely terminate the trial at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the trial I will communicate my intention immediately in writing to the sponsor.

Protocol Version:	Version 1.0
Investigator's Name and address:	_____ _____ _____ _____
Investigator's signature:	_____
Date:	_____ *(DD/MMM/YYYY)*

Emergency Contact List

Serious Adverse Events

In case of a **Serious Adverse Event (SAE)** the Investigator will be able to contact PharSafer at all times:

Principal Contact	Dr Sunita Chauhan (PharSafer)
Address	PharSafer House, White Hart Meadow, Ripley, Surrey, GU23 6ND, UK
Phone (24 hours)	+44 1483 212151
Fax	+44 1483 212178
E-mail	drugsafety@pharsafer.com

For any other safety related issues during normal business hours (09:00 – 17:00 UK GMT), the Investigator must contact the Infirst^{+} HEALTHCARE Responsible Physician:

Dr Sunita Chauhan (PharSafer)

Telephone Number: 01483 - 212167

Mobile Number: 07450 999000

Clinical Study Protocol IFH-2014-004

GLOSSARY OF ABBREVIATIONS	
Abbreviation	**Application**
AUC	Area Under the Curve
ANCOVA	Analysis of Covariance
BP	British Pharmacopoeia
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
ESF	Eligibility Screening Form
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Manufactured Product
LCQ	Leicester Cough Questionnaire
MAOI	Monoamine Oxidase Inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NRS	Numeric Rating Scale
OTC	Over the Counter
PRO	Subject Reported Outcome
PIS	Subject Information Sheet
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
US	United States
VAS	Visual Analogue Scale

Clinical Study Protocol IFH-2014-004

TABLE OF CONTENTS

Clinical Study Protocol IFH-2014-004

1. BACKGROUND AND RATIONALE

1.1 Background

Cough is one of the most common reasons for a subject visiting a physician in General Practice[1, 2, 3]. An acute cough associated with an upper respiratory tract infection rarely requires significant medical intervention, whereas a chronic cough may be associated with a number of underlying diseases [2]. It is therefore essential that any underlying cause of cough is diagnosed and treated [2, 4, 5].

Coughing is an important defensive reflex that enhances clearance of secretions and particulate matter from the airways and protects from the aspiration of foreign materials. The symptoms associated with cough are often debilitating and have a significant impact on quality of life (QoL) [6, 7, 8].

In the United Kingdom in 2010, subjects spent almost £100 million on non-prescription, over the counter (OTC) cough liquids for the self-treatment of their cough symptoms [9]. The range of OTC medicines available for cough includes antitussives, expectorants, mucolytics, antihistamines, antihistamine-decongestant combinations, and other drug combinations [10].

The Proprietary Association of Great Britain recently issued a statement supporting the use of OTC cough medicines, stating that they are safe and that studies support the efficacy of their active ingredients [11]. A Cochrane Review published in 2012 concluded there is no good evidence either for or against the effectiveness of OTC medicines in acute cough [10]. However, the results of the Cochrane Review were compromised by differences in study design, differences in the subject populations studied and by the fact that the data quality was rated as low. Consequently, the Cochrane conclusions should be interpreted with caution. A literature review published in 2007 reported on small studies that showed that diphenhydramine was significantly more effective than placebo at reducing the severity of citric acid induced cough and in ameliorating post infection cough [12]. However, there was no difference between diphenhydramine and placebo in cough associated with pertussis or in cough in children.

Despite the conflicting evidence the use of cough mixtures containing diphenhydramine alone or in combination with other active ingredients is widespread. Diphenhydramine as a stand-alone drug has recently been evaluated by US investigators as having efficacy in human clinical models of cough, and therefore warrants renewed clinical investigation [Error! Reference source not found.13].

1.1.1 Study Drugs

Subjects can find it very difficult to specifically determine the type of cough they have and thereby choose medication that best suits that type of cough. An effective cough medicine that can treat cough empirically may, therefore, be advantageous. In order to achieve this, the cough medicine will need to contain an antihistamine, a decongestant and an expectorant. cs1002 has been developed to provide each of these components in the form of diphenhydramine 14 mg/5 ml (antihistamine), levomenthol 1.1 mg/5 ml (decongestant) and ammonium chloride 135 mg/5 ml (expectorant). The three active components are formulated with excipients and with a cocoa flavour. In addition to improving palatability and hence compliance, the cocoa flavour increases the viscosity and surface adherence of the cough mixture, facilitates coating of the upper respiratory tract, brings the active ingredients into contact with sensitised nerve endings in the throat lining and may thus provide a soothing effect on the cough.

Preparations containing simple linctus are currently recommended by healthcare professionals for the relief of acute cough. Bell's simple linctus (containing citric acid monohydrate 125 mg/5 ml) was therefore, selected as a comparator product. Bell's simple linctus is currently available as an OTC medicine for the relief of cough.

Both products will be administered orally 4 times daily as per the dosing schedule. This is in line with the usual dosage regimen approved for OTC cough medicines that contain diphenhydramine at 14 mg/5 ml. Thus with the dosage used in this study the safety profile is expected to be comparable to that seen with currently available OTC products containing the same concentration of diphenhydramine.

1.2 Rationale for the Study

There is controversy and lack of recent evidence surrounding the efficacy of OTC products used for the treatment of acute cough. In this study the real world effectiveness of an OTC cough medicine (cs1002) designed to provide a novel flavour and additional demulcency for the symptomatic treatment of acute cough, will be evaluated using currently recommended simple linctus as a comparator.

The study will use previously validated methods to evaluate the efficacy of cs1002. Cough severity will be assessed using a Visual Analogue Scale and the impact of treatment on Quality of Life will be assessed using the validated Leicester Cough Questionnaire for acute cough (LCQ-acute) [8].

The study will also evaluate the efficacy of cs1002 on cough frequency and sleep (an important determinant of quality of life) using Visual Analogue Scales.

It is hoped that the use of validated assessment methods in this large scale clinical practice evaluation of cs1002, in a real life prescribing setting, will provide convincing data demonstrating the efficacy of a combination OTC product for treating acute cough, and will answer some of the shortfalls identified by the Cochrane review with previously published studies in this indication. The results of this study will be put into context with the findings of the 2012 Cochrane review [10].

2. OBJECTIVES

2.1 Primary Objectives

To investigate the efficacy of an OTC cough product containing diphenhydramine (cs1002) versus Bell's simple linctus by comparing the change from baseline in cough severity VAS scores after 3 days of treatment (Day 4).

2.2 Secondary Objectives

- To compare the efficacy of an OTC cough product containing diphenhydramine (cs1002) versus Bell's simple linctus by comparing change from baseline Leicester Cough Questionnaire (LCQ-acute) total scores at Days 4, 6 and 8.
- To compare the efficacy of an OTC cough product containing diphenhydramine (cs1002) versus Bell's linctus by assessing change from baseline in cough severity at Day 5, and in cough frequency and sleep quality VAS scores at Days 4, 6 and 8.
- To determine the time to resolution of cough symptoms defined as the day at which cough severity decreases to < 17mm.

3. OVERVIEW OF STUDY DESIGN

This is a multicentre, single-blind randomised study. The IMP is blinded to the Investigator only.

This study will include approximately 180 subjects who self-refer to the Investigator (either a GP or a Pharmacist) with a new onset acute cough which has a maximum of 7 day's duration and a severity of at least 60 mm on a 0–100 mm visual analogue scale (VAS). The basic study design is shown in Figure 1.

Figure 1 Study Flow Diagram

Day 1

- Subject enrolment at GP or Pharmacy Centre.
- Subjects will be given a diary to complete each day and receive instruction on how to complete this.
- Subjects will be given a 24 hour emergency contact number on a 'subject card' and within the diary.
- Subjects will complete baseline data (demographics, medical history and concomitant medications) with the Investigator.
- Subjects will be supplied with cs1002 or Bell's simple linctus according to randomisation.
- Subjects will complete baseline LCQ-acute and VAS assessments before their first dose of study drug.
- Subjects will start taking the study medication within 1 hour of completing their baseline assessments.

Days 2 to 8

- Subjects will take medication daily as directed and record when they have taken the study medicine in their patient diary.
- Subjects will complete an assessment of their symptoms and any additional medications taken.
- Subjects will complete the study assessment scales in the diary on a daily basis, whether they continue to take study medication or not.

Day 9 (End of study)*

- Subjects will meet with the Investigator to return all diary data and bottles, both used and unused, of study drug. Once these are returned the subject will have completed the study.
- If the cough has not resolved completely after 7 days, the subject will be advised to contact their own GP to be assessed.

* Day 9 (+2): If day 9 occurs on a day the Pharmacy / GP surgery is not open, the subject can arrange to return for their end of study assessments on the next Day that the Pharmacy / GP surgery is open (Day 10 or Day 11).

This study will be undertaken to allow the beneficial effectiveness of two OTC cough medicines to be assessed in a 'real-world' clinical practice setting using validated assessment tools.

The centre will be provided with identical looking tamper-evident, sealed boxes of similar weight, containing study medication. Subjects will be given a unique screening number at the

time of signing the informed consent. Once confirmed that they are eligible they will be given a unique randomisation number corresponding to one of the medication packs. The medication packs will remain sealed and only opened by the subjects after they have left the study centre. The IMP pack allocated to the patient will contain either cs1002 or Bells simple Linctus.

The subject will take their allocated study medication orally four times daily for 1-7 days provided they are still experiencing a cough.

Daily dosing will be as follows:

5ml morning dose

5ml lunchtime dose.

10ml teatime dose.

10ml bedtime dose.

The subjects will be given a diary to complete each day during their participation in the study. This will include specific questions on compliance as well as the assessment scales.

Safety will be monitored by asking subjects to keep a record in their diary of any adverse events (AE's) they experience during the study. The data from the subject's diaries regarding AE's will be uploaded by the Investigator within 24 hours of the subject returning the diary. Adverse events will be assessed by PharSafer Associates Ltd.

The primary efficacy endpoint is the change from baseline in cough severity based on VAS scores at Day 4 in subjects receiving cs1002 and Bell's simple linctus.

The secondary efficacy endpoints are a comparison of:

- Change from baseline in LCQ-acute score at Day 4, Day 6 and Day 8 in subjects receiving cs1002 and Bell's simple linctus.
- Change from baseline in cough frequency and sleep quality at Day 4, Day 6 and Day 8 in subjects receiving cs1002 and Bell's simple linctus.
- Change from baseline in cough severity at Day 6.
- AUC analysis of cough severity VAS, frequency VAS and sleep quality VAS from Days 1 to 8 in subjects receiving cs1002 and Bell's simple linctus.

- Time to resolution of cough symptoms defined as the day at which cough severity is < 17mm in subjects receiving cs1002 and Bell's simple linctus.

The primary efficacy endpoint cough severity will be assessed using a 100 mm VAS where 0 = no cough and 100 = worse cough ever. Visual analogue scales of this type have been previously validated for assessing acute cough [15].

The frequency of cough and the impact of cough on sleep disruption will be evaluated using Visual analogue scales.

The LCQ-acute will be used to evaluate cough related quality of life measures. The LCQ-acute is a fully validated scale that assesses 19 aspects of cough divided into three domains (physical, psychological and social). It was specifically designed to assess subject experience within a 24 hour time frame making it suitable for use in the present short term study [8]. An evaluation of the scale showed that subjects are able to complete the questionnaire without difficulty usually in less than 5 minutes.

A longitudinal assessment of measures used to assess acute cough [15] concluded that VAS and the LCQ-acute are both responsive tools for assessing changes during short term treatment validating their use in the present study.

Full details of these rating scales are provided in Appendix 2, 3, 4 and 5.

3.1 End of Study

Subjects will return all used and part used bottles, including the re-sealed outer IMP pack box, to the Investigator who will weigh the bottles and the outer IMP pack box to assess compliance.

Subjects who provide a complete set of data and return their patient diary and used bottle of study medication at the end of the study will receive £25 as reimbursement for their participation in the study (paid by Infirst^{+} HEALTHCARE).

For Pharmacist investigators: If the subject is still symptomatic of their cough the Investigator will advise the subject to visit their GP.

For GP Investigators: If the subject is still symptomatic of their cough the Investigator will continue to provide routine clinical care.

Final analysis is planned when all subjects have completed the study.

4. STUDY POPULATION

4.1 Overview of Target Population

A total of approximately 180 subjects will be enrolled into this study. The study will be run in up to 30 Centre's within the UK. The Centre's will consist of both GP surgeries and Pharmacies.

The Target population will consist of subjects who self-refer to a GP or Pharmacist, with a new onset acute cough, with a maximum of 7 days duration and a severity of at least 60 mm on a 0–100 mm visual analogue scale (VAS) and providing the cough is not associated with any serious underlying medical condition or contraindicated for this study.

Subjects will be allocated to treatment using a computer generated randomisation scheme.

4.1.1 Recruitment Procedures

To raise awareness of the study and provide opportunity for subjects to join the study a poster will be displayed in the reception area of the GP surgery or Pharmacy. Information about the study will also be available in a leaflet form.

Subjects who self-refer to the GP or Pharmacist with a cough, will be asked whether they would like to be involved in the study. If they would like more information, the Investigator will discuss the study with the subject to establish eligibility.

4.2 Enrolment Criteria:

Subjects must fulfil all of the following criteria at enrolment:

4.2.1 Inclusion Criteria

1. Male or female subjects aged 18 years or over.
2. Subject has self-referred to the GP or Pharmacist owing to a new onset acute cough with a maximum of 7 day's duration and a severity of at least 60 mm on a 0–100 mm visual analogue scale (VAS).
3. Willing and able to give informed consent and of complying with the study assessments and any other study procedures.

4.2.2 Exclusion Criteria

1. Pregnant or lactating females.
2. Any relevant hospital stays of more than 2 days, within 6 months before the subject self-refers to the GP or Pharmacist (Day 1). NB: An example of a relevant hospital stay would be for respiratory conditions such as 'lung infection' or 'pneumonia'.

3. Current smokers and those who have smoked within the last two months. This includes the use of e cigarettes.
4. Taken any medication with a cough treatment designation for this cough (whether a prescription drug, an OTC drug or a natural herbal product (e.g. honey, eucalyptus etc.).
5. A productive cough with excessive secretions, regardless of colour.
6. Subjects requiring co-prescription with other treatments for coughs or colds. This includes subjects taking antibiotics.
7. Subjects with known hypersensitivity to any of the ingredients of the study medication.
8. Subjects with chronic cough (i.e. chronic bronchitis in smokers, gastro-oesophageal reflux, asthma, hyper-responsive airways after resolution of respiratory tract infection, COPD, pertussis, aspiration, tumour, tuberculosis or fungal infections).
9. Subjects with prostatic hypertrophy, urinary retention, susceptibility to closed-angle glaucoma, liver disease, fructose intolerance, glucose intolerance, glucose-galactose malabsorption, sucrose-isomaltase insufficiency.
10. Subjects taking monoamine oxidase inhibitors (MAOI) or having taken them within 14 days of entering the study and those requiring ongoing treatment with codeine, other anti-histamines, central nervous system depressants, other anticholinergic medicines (e.g. atropine), anti-psychotics or ACE inhibitors.
11. Treatment with any investigational drug agent during the 30 days before enrolment into the study.

4.3 Concomitant Medication and Treatment

The following interactions are possible with cs1002:

- Additive CNS depressant effects with CNS depressants including barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives and anti-psychotics. Co-prescription of these agents is not permitted during the study.
- Additive CNS depressant effects with alcohol. Alcohol consumption should be used with caution during the study.
- Additive anti-muscarinic effects with other drugs of similar properties such as atropine and some anti-depressants. Co-prescription of these agents is not permitted during the study.

- There is a risk of serotonin syndrome in subjects taking MAOIs or having taken within 14 days of study treatment. Co-prescription of these agents is not permitted during the study.
- Diphenhydramine can inhibit the oxidative metabolism of some drugs.
- Diphenhydramine may enhance the effects of ephedrine. Co-prescription of agents containing ephedrine is not permitted during the study.
- Diphenhydramine may mask the response of the skin to allergenic skin tests and also the ototoxic symptoms associated with certain antibiotics. Co-prescription of antibiotics is not permitted during the study.
- Citric acid may interact with potassium tartrate, carbonates and bicarbonates which therefore should not be administered at the same time.

Subjects will be asked to confirm all medications (prescription and over-the-counter drugs) taken within a 30 day period prior to study screening. The Investigator will record these on the electronic case report form at baseline.

This information will be self-reported by subjects unless the subject regularly collects their medications from the Investigator and thus can be cross checked on the Investigators systems.

4.4 Criteria for Premature Withdrawal of Subjects

The Investigator has the right to withdraw a subject from the study at any time. In addition, subjects have the right to voluntarily withdraw from the study at any time for any reason. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Subject withdrawal of consent at any time.
- Any medical condition that the Investigator or Sponsor determines may jeopardise the subject's safety if he or she continues in the study.
- The Investigator or Sponsor determines it is in the best interest of the subject.

An excessive rate of withdrawals can render a study non-interpretable; therefore, unnecessary withdrawal of subjects should be avoided. Should a subject decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible. Subjects who withdraw from the study will not be replaced.

All reasons for withdrawal must be documented.

4.5 Criteria for Premature Withdrawal Of Study and Centre

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Subject enrolment is unsatisfactory.

The Sponsor will notify the Investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study.

The Sponsor has the right to replace a centre at any time. Reasons for replacing a centre are listed in section 4.6.2.

4.6 Replacement Policy (Ensuring Adequate Numbers of Evaluable Subjects)

4.6.1 For Subjects

Subjects enrolled into the treatment phase of the study will not be replaced.

4.6.2 For Centre's

A centre may be replaced for the following administrative reasons:

- Excessively slow recruitment.
- Poor protocol adherence.
- Inaccurate or incomplete data recording.
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP), as applicable.

5. STUDY PROCEDURES AND ASSESSMENTS

5.1 Schedule of Assessments

The schedule of study procedures is provided in Table 1.

Clinical Study Protocol IFH-2014-004

Table 1: Schedule of Assessments during the study

Assessment	Study Day								
	1	2	3	4	5	6	7	8	9 [a]
Informed Consent	x								
Demographics	x								
Pregnancy Test[b]	x								
Medical History	x								
Cough history	x								
Concomitant Medications	x	x	x	x	x	x	x	x	
Minimum Severity VAS check for eligibility	x								
Eligibility screening form	x								
Cough severity VAS	x	x	x	x	x	x	x	x	
Cough frequency VAS	x	x	x	x	x	x	x	x	
Cough sleep disruption VAS	x	x	x	x	x	x	x	x	
LCQ acute	x			x		x		x	
AE Check Question		x	x	x	x	x	x	x	
Compliance check question		x	x	x	x	x	x	x	
Drug Dispensing	x								
Return of study medication									x
Return of Study Diary									x

[a] Day 9 (+2): If day 9 occurs on a day the Pharmacy / GP surgery is not open, the subject can arrange to return for their end of study assessments on the Day that the Pharmacy / GP Surgery re-opens (Day 10 or Day 11).

[b] Pregnancy Test: If there is a possibility the subject could be pregnant, they will be provided with a home test kit and given the option to return once they have confirmed they are not pregnant, provided they still fulfil all other eligibility criteria they can proceed in the study.

5.2 Day 1 Procedures and Assessments

5.2.1 Screening Examination and Eligibility Screening Form

Subjects will have self-referred to the Investigator with a new onset acute cough. The subjects will be provided with an initial brief introduction to the study using the introduction leaflet and an initial check will take place, asking the subjects how long they have had this cough for and establishing that the subject has a minimum cough severity score, using a severity VAS scale. If the subjects have had their cough for a maximum duration of 7 days and they have a minimum cough severity of at least 60mm, they will be asked if they want to discuss the study further. The subject will be given the PIS to read and the Investigator will discuss this with them. If agreeable the subject signs the informed consent form.

All subjects will be evaluated at their initial presentation to the Investigator to exclude the requirement for emergency treatment. The Investigator will use their experience and expertise, as per their routine clinical practice, to establish whether the patient should seek immediate medical attention and refer them accordingly.

Subjects who fulfil all the inclusion and exclusion criteria will be accepted into the study. The Investigator will confirm the eligibility of the subject to participate in the study.

All subjects must provide written informed consent before any study specific assessments or procedures are performed. An Eligibility Screening Form (ESF) documenting the investigator's assessment of each screened subject with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator. A screen failure log must be maintained by the investigator.

After signing an Informed Consent Form (ICF) the following information will be collected:

1. Demography (age, gender, ethnicity).
2. Brief relevant medical history (smoking history, history of any medical conditions and concomitant medications).
3. Cough history (duration, type of cough and any treatment received).

Each eligible subject will be provided with a diary and 'subject card' containing details of a 24 hour emergency contact number. They will be instructed that in the event of an emergency they should tell the medical staff treating them that they are participating in the study and the medical staff can then call the contact number to liaise with the PharSafer safety team.

The subject cannot take part in this study if there is any possibility they are pregnant. This will be self-reported. If there is a possibility the subject could be pregnant, they will be provided with a home test kit and given the option to return once they have confirmed they are not pregnant, provided they still fulfil all other eligibility criteria they can proceed with the study.

The subjects will be asked to complete the following and before their first dose of study medication.

- Cough severity VAS.
- Cough frequency VAS.
- Cough sleep disruption VAS.

- LCQ-acute.

The Investigator will provide the subject with the study IMP pack in a **sealed package**. This will contain either cs1002 (2 x 150 ml) or simple linctus (2 x 150 ml), according to a pre-defined computer generated, subject randomisation list. This pack will be weighed on the study-calibrated, validated scales and this weight will be documented in the eCRF.

Subjects will be instructed to ensure that they **re-seal** the used study IMP medication box before they return it to their Investigator.

The subject will be asked to start taking the study medication within 1 hour of completing the baseline assessments and advised to continue taking the cough medication four times a day, provided they are still experiencing a cough. Daily dosing will be as follows:

5ml morning dose

5ml lunchtime dose.

10ml teatime dose.

10ml bedtime dose.

Where the subject does not continue taking the study medication for the duration of the study, if their cough has stopped for example or they are experiencing unacceptable adverse effects, they will still be asked to complete all assessments.

The Investigator will instruct the subject on which dose they should start taking and record this in the patient diary; this is dependent on the time of day they complete their baseline assessments. The Investigator will also specify what would be the day and time of the last dose the subject could take on the study and record this in the patient diary. For example: a patient completing their baseline questionnaires at 11am would take a 5ml lunchtime dose as their first dose on Day 1; they would then be instructed that the last dose they could take would be a 5ml lunchtime dose on Day 8.

An appointment will be made for the subject to return on Day 9.

For Pharmacist investigators: An approved letter will be sent to the subjects GP notifying them of their participation, listing the exclusion criteria.

The Investigator will register the subject and transcribe the subject's information into the study electronic case report form (eCRF) on Day 1.

The subject will be offered a text message reminder service. This is a voluntary service initiated by the subject via their mobile phone on day 1. The service reminds subjects to complete their questionnaires at the same time every day.

5.2.2 Days 2 to 8 Procedures and Assessments

The subject will be asked to complete the following questionnaires at the same time of day that they completed the initial baseline assessments.

- Cough severity VAS (daily).
- Cough frequency VAS (daily).
- Cough sleep disruption VAS (daily).
- Compliance question (daily).
- AE question (daily).
- LCQ-acute (Days 4, 6 and 8).

If agreeable, the subject will be sent a text message to remind them to complete the assessments at the same time every day as a prompt.

5.2.3 At the end of the study (Day 9)

The subject will return their used bottles of medication in the medication box and completed diary to the Investigator at a pre-arranged appointment time on Day 9.

For Pharmacist investigators: If the subject is still symptomatic of their cough the Investigator will advise the subject to visit their GP.

For GP Investigators: If the subject is still symptomatic of their cough the Investigator will continue to provide routine clinical care.

If the subject has provided a complete set of diary data (i.e. a minimum of a VAS score for cough severity at Day 4 and LCQ-acute scores at Day 4) they will receive a compensation of £25.

The Investigator will upload the diary information into the eCRF within 24 hours of receipt. The LCQ-acute and the completed VAS scores will be sent via courier to the coordinating data centre.

6. INVESTIGATIONAL MEDICINAL PRODUCT

cs1002 is provided in 150 ml bottles containing a brown syrup solution for oral administration.

Each 5 ml dose contains diphenhydramine (14 mg), levomenthol (1.10 mg) and ammonium chloride (135 mg). The three active components are formulated with excipients and with a cocoa flavour.

Excipients include: sucrose, propylene glycol, nipastat (preservative system), sodium citrate, glycerine, cocoa flavour, purified water.

6.1 Dose and Schedule of IMP: cs1002

cs1002 will be administered orally 4 times daily from Day 1 to 8:

5ml morning dose

5ml lunchtime dose.

10ml teatime dose.

10ml bedtime dose.

If the subject stops coughing they should stop taking their study cough medication.

Refer to Section 6.4 for dose modifications.

The subjects will return the used and part used bottles in the re-sealed package to the Investigator who will weigh the bottles to assess compliance.

The Investigator will instruct the subject on which dose they should start taking; this is dependent on the time of day they complete their baseline assessments. The Investigator will also specify what would be the last dose the subject could take on the study and record this in the patient diary.

6.2 Comparator: Bells Simple Linctus

Bell's simple linctus is provided in 150ml bottles containing a clear, colourless syrup solution with the flavour of anise for oral administration.

Each 5ml dose contains Citric Acid Monohydrate (125mg)..

Excipients include: sucrose, water, polysorbate 20, star anise oil.

6.3 Dosage and Administration of Comparator: Bells Simple Linctus

Bell's simple linctus will be administered orally 4 times daily from Day 1 to 8 as follows:

5ml morning dose

5ml lunchtime dose.

10ml teatime dose.

10ml bedtime dose.

If the subject stops coughing they should stop taking their study cough medication.

Refer to Section 6.4 for dose modifications.

The subjects will return the used and part used bottles to the Investigator who will weigh the bottles to assess compliance.

The Investigator will instruct the subject on which dose they should start taking; this is dependent on the time of day they complete their baseline assessments. The Investigator will also specify what would be the last dose the subject could take on the study and record this in the patient diary.

6.4 Dose Modifications

The most common adverse effects of the active components in cs1002 include CNS effects such as nervous drowsiness (usually diminishes within a few days), paradoxical stimulation, nervous headache, nervous psychomotor impairment; anti-muscarinic effects such as urinary retention, dry mouth, blurred vision, gastrointestinal disturbances and thickened respiratory tract secretions.

Rare side adverse effects of the active components in cs1002 include hypotension, extrapyramidal effects, dizziness , confusion, depression, sleep disturbances, tremor, convulsions, palpitation, arrhythmia, hypersensitivity reactions, blood disorders and liver dysfunction.

The subject will be advised that should they experience unacceptable adverse effects from the study medication they can reduce the dose from 10mls to 5mls. If the unacceptable adverse effects continue they should stop taking the medication.

Specific Dose Guidance

Drowsiness is a known adverse effect of diphenhydramine. Subjects that cannot tolerate a 10ml dose at teatime are advised to reduce this dose from 10mls to 5mls initially and continue with the 10ml bedtime dose.

Subjects that have unacceptable drowsiness adverse effects on a 5ml dose are advised to stop taking the cough medication during the day time, and take 5mls at night.

In the event that this does not reduce the adverse effects to an acceptable level for the subject, the subject is advised to stop taking the study medication. The subject must continue to record all doses of medication taken in the diary provided and is encouraged to contact the safety helpline if they have any concerns.

6.5 Formulation, Packaging and Labelling

All study treatment will be labelled in accordance with current regulatory guidance.

All subjects identified as eligible and who have signed a consent form will be randomised and provided with the study IMP pack in a **sealed package**.

The principal Investigator has overall responsibility for ensuring that study treatment is received and managed in accordance with the protocol and GCP.

For Pharmacist investigators: The study treatments will be dispensed by a qualified pharmacist, any delegation by the Principal Investigator to another Pharmacist at the Pharmacy centre, must be documented.

For GP investigators: The study treatment may be dispensed directly by the GP Investigator in accordance with the applicable regulatory requirements. The GP Investigator may delegate the responsibility for dispensing the IMP to a local pharmacist.

The Investigator or appropriately delegated pharmacist will be responsible for entering the subject number on the study treatment at the time of dispensing.
The Sponsor will be permitted upon request to audit the supplies storage and dispensing procedures and records.

6.6 Accountability and Assessment of Compliance

A sealed IMP pack will be supplied to all eligible subjects who have consented to take part. This pack will be weighed on the study-calibrated, validated scales when dispensed and this weight will be documented in the eCRF

Subjects will be advised **not** to open the IMP pack whilst in the pharmacy or GP surgery.

Subjects will be instructed to ensure that they have resealed the used study IMP pack before they return to their GP surgery or Pharmacy.

Subjects will be asked to complete a compliance check question in the diary on a daily basis and return all used and unused containers on Day 9 after the end of the 7 day treatment period as a measure of compliance.

The returned IMP pack will be weighed on the same study calibrated validated scales and this will be documented in the eCRF for compliance.

6.7 Destruction of the IMP and comparator

At the end of the study, after all drug accountability has been completed and the last patient has completed the study, all used and unused study treatment packs will be destroyed on site, following approval of the site's local drug destruction policy. If the site is unable to destroy on site, used and unused treatment pack will be shipped back to a nominated contractor for destruction on behalf of Infirst^{+} HEALTHCARE.

Local or institutional regulations may require immediate destruction of used investigational product for safety reasons. In these cases, it may be acceptable for investigational site staff to destroy dispensed investigational product before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned and destroyed. Written authorization must be obtained from the sponsor before destruction.

6.8 IMP Unblinding

The IMP is blinded to the Investigator only.

If for any reason the Investigator does not remain blinded to the IMP, the Investigator must inform the study team immediately.

Should it become necessary to break the blind to the Investigator on the grounds of safety, the Investigator will contact the safety centre on the 24 hour telephone safety line (Telephone: +44 1483 212151).

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 Adverse Events

7.1.1 Clinical AEs

An Adverse Event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and

unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adverse Event data will be collected in the patient diaries from the first dose of study medication through to the end of day 8. Any adverse events reported to the investigator after this time in relation to the study drug would be reported by the Investigator to the Sponsor through spontaneous reporting.

7.1.2 Serious Adverse Events (SAEs)

A Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires in subject hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect
- Medically Significant Events (IMEs)

The study will comply with all local regulatory requirements and adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A.

Serious Adverse Event data will be collected from the first dose of study medication through to resolution of the SAE. Any adverse events reported to the investigator after this time in relation to the study drug would be reported by the Investigator to the Sponsor through spontaneous reporting.

In case of urgent safety queries please contact:

Principal Contact	Dr Sunita Chauhan (PharSafer)
Address	PharSafer House, White Hart Meadow, Ripley, Surrey, GU23 6ND, UK
Phone (24 hours)	+44 1483 212151
Fax	+44 1483 212178
E-mail	drugsafety@pharsafer.com

This study will be conducted in the UK only and therefore follow UK reporting requirements.

7.2 Warnings and Precautions

cs1002 is contraindicated in:

- Subjects who are hypersensitive to any of the ingredients.
- Subjects receiving ongoing treatment with codeine or anti-histamines.
- Subjects receiving central nervous system depressants, other anticholinergic medicines (e.g. atropine) or anti-psychotics.
- Subjects receiving MAOI therapy within the previous 14 days prior to consent.
- Subjects receiving ACE inhibitors.

The following warnings and precautions should be adhered to:

- Do not combine with other treatments for coughs and colds (whether a prescription drug, an OTC drug or a natural herbal product (e.g. honey, eucalyptus etc.).
- Diphenhydramine can cause drowsiness. If affected, subjects should be advised not to drive or operate machinery.

Excipient Warnings:

- Glycerol may cause headache, stomach upset and diarrhoea.
- Parahydroxybenzoates may cause allergic reactions (possibly delayed) and exceptionally bronchospasm.
- Propylene Glycol may cause intoxication similar to that produced by alcohol consumption. Subjects are therefore advised to take any alcohol with caution.
- It is possible that citric acid ingested in large quantities or frequently may cause gastric irritation, or erosion of dental enamel.

Bells Simple Linctus contraindications:

- Subjects who are hypersensitive to any of the ingredients.

Warnings

- Product contains sucrose; this should be taken into account in patients with diabetes mellitus. Patients with hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isolatase insufficiency should not take this medicine.
- It is possible that citric acid ingested in large quantities or frequently may cause gastric irritation, or erosion of dental enamel.

8. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a randomised, single-blind, active-controlled, multicentre study to compare cs1002 to Bell's simple linctus.

8.1 Analysis Sets

Treated set (TS): The treated set will consist of all subjects who were randomised and treated with at least one dose of study drug. This set of subjects will be used for the assessment of safety.

Full analysis set (FAS): The full analysis set will consist of all randomised subjects who were treated with at least one dose of study drug and had a baseline assessment of cough severity. This set of subjects will be used for the primary assessment of efficacy.

Per protocol set (PPS): The per protocol set will consist of all randomised subjects included in the FAS that did not have an important protocol violation. This set of subjects will be used for a supportive assessment of efficacy. Examples of important protocol violations are:

- Violations of eligibility criteria that may impact on efficacy or safety.
- Treatment non-compliance as per Protocol.
- Prohibited medication use.
- Incorrect trial medication taken (mis-randomisation).
- Insufficient efficacy data

Further details on the definition of the PPS will be provided in the Statistical Analysis Plan (SAP) prior to unblinding.

8.2 Null and Alternative Hypotheses

The confirmatory analysis will compare cs1002 to Bell's simple linctus with respect to the primary endpoint of change from baseline to Day 4 in cough severity, in the FAS. The null hypothesis of no difference in cough severity between the two treatment groups will be tested at a two-sided alpha-level of 5%. The alternative hypothesis is that there is a difference in cough severity between the two treatment groups. If the null hypothesis can be rejected in favour of the alternative hypothesis the observed difference between the treatment groups will be considered statistically significant.

All statistical testing will be two-sided and performed at the 5% significance level. Where appropriate, p-values will be supported with 95% confidence intervals (CIs) to help describe the magnitude and precision of treatment effect estimates.

As the confirmatory analysis is based on a single treatment group comparison for a single endpoint no alpha adjustment for multiplicity is required.

8.3 Planned Analysis

8.3.1 Primary Analysis

A mixed model for repeated measures (MMRM) analysis will be used to test the effect of cs1002 on the change from baseline to Day 4 in cough severity compared to Bell's simple linctus. All cough severity data recorded during the study will be included in the model. The model will include effects for treatment group, daycentre (pooled if necessary), baseline cough severity and the treatment by day and treatment by baseline cough severity interaction terms. The adjusted treatment group difference at Day 4 and corresponding 95% CI will be presented along with the p-value. In the absence of missing data the MMRM analysis equates to the corresponding analysis of covariance (ANCOVA).

A sensitivity analysis will be performed to examine whether treatment effects are dependent upon centre by including a treatment by centre interaction term in the model. If the interaction term is found to be statistically significant ($p<0.05$) further investigation into the source of the interaction will be performed and appropriate measures taken.

Residual plots and a normality test will be used to assess normality assumptions. If normality assumptions are not met then an appropriate transformation (e.g. log transformation) or non-parametric analysis will be used

If pooling of centres is required, a detailed strategy for pooling will be determined in a blinded fashion and detailed in the Statistical Analysis Plan (SAP).

The primary analysis will be performed on the FAS with a supportive analysis performed on the PPS to help assess the robustness of the primary analysis.

Exploratory subgroup analyses will be performed on the FAS only for the following subgroups:

- Self-diagnosed type of cough (chesty, dry or tickly).
- Gender.
- Age.
- Referral (GP, Pharmacist).

Other subgroups may be identified in the SAP prior to unblinding.

8.3.2 Secondary Analyses

The following secondary analyses will be performed:

Leicester Cough Questionnaire

The changes from baseline to Day 4, Day 6 and Day 8 in the LCQ acute score and each individual domain (physical, psychological and social) will compared across the treatment groups using the same analysis methodology as for the primary analysis.

Cough Frequency

The change from baseline to Days 4, 6 and 8 in cough frequency will be compared across the treatment groups using the same analysis methodology as for the primary analysis.

In addition the area under the curve (AUC) for cough frequency across Days 1 to 8 will be compared across the treatment groups using the same MMRM as above.

Cough Severity

The change from baseline to Day 6 in cough severity will be compared across the treatment groups using the same analysis methodology as for the primary analysis.

In addition the AUC for cough frequency across Days 1 to 8 will be compared across the treatment groups using the same MMRM as above. The proportion of patients with resolution

of cough severity, defined as the first day at which the severity score is <17 mm will be displayed by each day of the study. These data will be compared across treatment groups using a stratified (by centre) Cochran-Mantel-Haenszel test. In order to include all patients in the analysis, those with no resolution of symptoms during Days 1 to 8 will be included in a separate category ordered after Day 8. If analytical assumptions hold a more formal time to event analysis via a Cox proportional hazards model and log-rank test will be used as an alternative.

Sleep Disruption

The AUC for sleep disruption across Days 1 to 8 will be compared across the treatment groups using the same MMRM analysis as above.

8.3.3 Safety Analyses

All treated subjects will be included in the safety analysis. In general, safety analyses will be descriptive in nature, no hypothesis testing is planned.

AEs will be coded according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The frequency of subjects with AEs will be summarised by maximum severity, treatment, primary system organ class (SOC) and preferred term (PT) for each of the following AE tables:

- All AEs.
- Drug related AEs.
- AEs leading to treatment discontinuation.
- Serious AEs.

All AEs recorded during the on-treatment period will be summarised.

8.3.4 Interim Analysis

Due to the uncertainty in the variability assumed in the sample size calculation (see Section 8.5) a blinded estimation of variation will be performed when approximately 50% of subjects have received 3 days of treatment (Day 4 of the study). The estimation will be made on any available primary endpoint data at this time; it will be done in a blinded fashion pooling the data across treatment groups. As no unblinding is occurring and only the pooled variability is being estimated the overall type I error rate (5%) is preserved and no adjustment is required.

No decrease in the planned sample size will be performed even if the estimated variability is lower than that assumed in the original calculation. In order to preserve the power of the study the planned sample size will only be increased if the interim estimate of variability is more than 5 mm above that in the sample size estimation.

8.4 Handling of Missing Data

Every effort will be made to collect complete efficacy data from all randomised subjects and given the short study duration the degree of missing data is expected to be relatively low. Descriptive summaries of efficacy data will be produced on non-missing data only so that the degree of data completion across the treatment groups can be easily assessed.

The main efficacy analyses will use an MMRM approach to analysis, for these analyses information from the observed outcomes (non-missing data) are used to provide information about the unobserved outcomes (missing data), so missing data is not an issue.

To assess the robustness of the primary efficacy results to the method of handling missing data a sensitivity analysis will be performed using ANCOVA methodology. For this analysis subjects with a missing cough severity score at Day 3 will have their last on-treatment assessment prior to Day 4 carried forward.

8.5 Determination of Sample Size

The sample size is based on being able to claim superiority of cs1002 over Bell's simple linctus; in terms of the change from baseline to Day 4 in cough severity. For this endpoint superiority is defined as a difference of at least 17 mm between subjects treated with cs1002 and those treated with Bell's simple linctus.

There is uncertainty in the standard deviation for cough severity with literature suggesting it could be somewhere between 25 and 35 mm[15]. Table 2 presents the number of evaluable subjects required per treatment group to detect a difference between the treatment groups of 17 mm using a two-sided 5% alpha-level with 90% power, for a selection of standard deviations.

Table 2: Sample Sizes for Testing Cough Severity (FAS)

Alpha (2-sided) [%]	Power [%]	SD=25	SD=30	SD=35
5	90	47	67	91

Approximately 180 subjects will be randomised in order to achieve a power of 90% for detecting a difference between the treatment groups of 17 mm with a common standard deviation of 35 mm.

Sample size calculations are based on an allocation ratio between treatment groups of 1:1 and were derived using nQuery Advisor (version 7).

9. DATA COLLECTION, MANAGEMENT AND QUALITY ASSURANCE

Subject data will be collected by the investigator using electronic Case Report Forms (eCRFs) as part of the Medrio™ data management system.

Quality of Life questionnaires and VAS scores will be completed by the Subject on paper and entered into Medrio by the Investigator and Exp-e-Data (UK) data entry staff.

Discrepancy checks will be programmed according to definitions in the Data Handling Manual and data queries will be generated during the data entry process in order to confirm the validity, consistency and completeness of the data.

10. ETHICAL ASPECTS

10.1 Local Regulations/Declaration of Helsinki

This study will be conducted in full conformance with the principles of the "Declaration of Helsinki (sixth revision 1996)". The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997). The investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC) and the protocol. In addition the study will adhere to all local regulatory requirements.

10.2 Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain written informed consent from each subject participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. Due to the nature of the study, using OTC medication, it will be acceptable for consent to be taken on the day the subject self refers to the Investigator.

The Case Report Forms for this study contain a section for documenting informed subject consent, and this must be completed appropriately by the Investigator. If new safety information results in significant changes in the risk benefit assessment, the consent form should be reviewed and updated if necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

10.3 Independent Ethics Committees (IEC)

This protocol and any accompanying material provided to the subject (such as subject information sheets or descriptions of the study used to obtain informed consent) as well as any advertising or compensation given to the subject, will be submitted by the investigator to an Independent Ethics Committee. Approval from the committee must be obtained before starting the study, and should be documented in a letter to the investigator specifying the date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of the Independent Ethics Committee approval must also be submitted by the investigator to the Committee in accordance with local procedures and regulatory requirements.

10.4 Financial Disclosure

The investigator(s) will provide the Sponsor with sufficient accurate financial information by completing a Financial Disclosure Form to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The investigator is responsible to promptly update any information provided to the Sponsor if relevant changes occur in the course of the investigation and for 1 year following the completion of the study (last subject, last visit).

11. CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between an appropriate representative of the sponsor and the investigator. Protocol modifications must be prepared by a representative of the sponsor and initially reviewed and approved by the Medical Manager and Biostatistician.

All protocol modifications must be submitted to the appropriate Independent Ethics Committee for information and approval in accordance with local requirements, and to Regulatory Agencies

if required. Approval must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g. change in monitor(s), change of telephone number(s).

12. CONDITIONS FOR TERMINATING THE STUDY

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures to be put in place on an individual study basis after review and consultation. In terminating the study, the sponsor and the investigator will ensure that adequate consideration is given to the protection of the subject's interests.

13. STUDY DOCUMENTATION, CRFS AND RECORD KEEPING

13.1 Investigator Files/Retention of Documents

Records and documents pertaining to the conduct of this study, including eCRFs, PRO data, Informed Consent Forms, clinical or hospital charts, laboratory test results, and medication records, must be retained by the principal Investigator after completion or discontinuation of the study, or for the length of time required by the sponsor, relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

13.2 Source Documents and Background Data

Study monitors will perform ongoing data review including source document verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorised centre personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which subject data are recorded and documented for the first time. They include, but are not limited to, subject reported outcomes, evaluation checklists, copies of transcriptions that are certified after verification as being accurate and complete, subject files and records kept at pharmacies.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 13.1.

To facilitate source data verification, the Investigators and institutions must provide Infirst+ HEALTHCARE or their designee access to applicable source documents and reports from study related monitoring, Sponsor audits, and IRB/EC review.

13.3 Case Report Forms or Electronic Case Report Forms

For each subject enrolled, an Electronic Case Report Form must be completed by the Investigator or an authorized delegate from the centre staff.

All Data will be held in compliance with all appropriate EU and FDA Statutes, Directives and Guidelines.

13.4 Confidentiality of study Documents and Subject Records

Data collected during this study may be used to support the development, registration or marketing of cs1002. InFirst+ HEALTHCARE will control all data collected during the study, and will abide by the EU Directive on Data Privacy concerning the processing and use of patients' personal data. For the purpose of data privacy legislation, InFirst HEALTHCARE will be the data controller.

After patients have consented to take part in the study their medical records and the data collected during the study will be reviewed by InFirst HEALTHCARE and/or its representatives. These records and data may, in addition, be reviewed by the following: independent auditors who validate the data on behalf of InFirst HEALTHCARE; third parties with whom InFirst HEALTHCARE may develop, register or market cs1002 national or local regulatory authorities and the IRB(s)/IEC(s) which gave their approval for this study to proceed.

Although patients will be known by a unique number, their initials and date of birth may also be collected and used to assist InFirst+ HEALTHCARE to verify the accuracy of the data. The results of this study containing the unique number, initials, date of birth and relevant medical information including ethnicity may be recorded and transferred to and used in other countries

throughout the world, which may not afford the same level of protection that applies within the EU. The purpose of any such transfer would be to support regulatory submissions made by InFirst HEALTHCARE in order to market cs1002 in other countries.

13.5 Audit / Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the UK Medicines and Healthcare products Regulatory Agency (MHRA), InFirst HEALTHCARE or its representatives, interested commercial parties and the IRB/IEC for each study site.

14. INDEMNITY / LIABILITY AND INSURANCE

Infirst+ HEALTHCARE will adhere to the recommendations of the Association of British Pharmaceutical Industry (ABPI) Guidelines. If appropriate, a copy of the Indemnity document will be supplied to the Investigator before study initiation. Infirst+ HEALTHCARE will ensure that suitable insurance cover is in place prior to the start of the study. An insurance certificate shall be supplied to the monitoring CRO.

15. CLINICAL STUDY REPORT (CSR)

A clinical study report will be written and distributed to Health Authorities and Independent Ethics Committee as required by applicable regulatory requirements.

16. PUBLICATION POLICY

All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by Infirst+ HEALTHCARE, in advance of submission. The review is aimed at protecting Infirst+ HEALTHCARE's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results or other information, generated or created in relation to the study shall be set out in the agreement between each Investigator and the CRO/ Infirst+ HEALTHCARE.

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18. APPENDICES

18.1 Appendix 1 Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Recommendations guiding physicians
in biomedical research involving human subjects
Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected. Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8 In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible

to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE
(Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

18.2 Appendix 2 Leicester Cough Questionnaire for Acute Cough (LCQ-acute)

This Questionnaire must only be used for reference only and not photocopied for subject use.

This questionnaire is designed to assess the impact of cough on various aspects of your life. Read each question carefully and answer by CIRCLING the response that best applies to you. Please answer ALL questions, as honestly as you can.

1. In the last 24-hours, have you had chest or stomach pains as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

2. In the last 24-hours, have you been bothered by sputum (phlegm) production when you cough?

1	2	3	4	5	6	7
Every time	Most times	Several times	Some times	Occasionally	Rarely	Never

3. In the last 24-hours, have you been tired because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

4. In the last 24-hours, have felt in control of your cough?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time

5. How often during the last 24-hours have you felt embarrassed by your coughing?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

6. In the last 24-hours, my cough has made me feel anxious

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

7. In the last 24-hours, my cough has interfered with my job, or other daily tasks

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

8. In the last 24-hours, I felt that my cough interfered with the overall enjoyment of my life

1	2	3	4	5	6	7

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

9. In the last 2 weeks, exposure to paints or fumes has made me cough

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

10. In the last 24-hours, has your cough disturbed your sleep?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

11. In the last 24-hours, how many times have you had coughing bouts?

1	2	3	4	5	6	7
All the time (continuously)	Most times of during the day	Several times during the day	Some times during the day	Occasionally through the day	Rarely	None

12. In the last 24-hours, my cough has made me feel frustrated

1	2	3	4	5	6	7
All of the time	Most of	A good bit	Some of	A little of the	Hardly any	None of

	the time	of the time	the time	time	of the time	the time

13. In the last 24-hours, my cough has made me feel fed up

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

14. In the last 24-hours, have you suffered from a hoarse voice as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

15. In the last 24-hours, have you had a lot of energy?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time

16. In the last 24-hours, have you worried that your cough may indicate a serious illness?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

17. In the last 24-hours, have you been concerned that other people think something is wrong with you, because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

18. In the last 24-hours, my cough has interrupted conversation or telephone calls

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

19. In the last 24-hours, I feel that my cough has annoyed my partner, family or friends

1	2	3	4	5	6	7
Every time I cough	Most times when I cough	Several times when I cough	Some times when I cough	Occasionally when I cough	Rarely	Never

Thank you for completing this questionnaire.

LCQ Scoring

1. Domains (questions):

Physical: 1,2,3,9,10,11,14,15

Psychological 4,5,6,12,13,16,17

Social: 7,8,18,19

2. Domain Scores: total score from items in domain / number of items in domain (range 1–7)

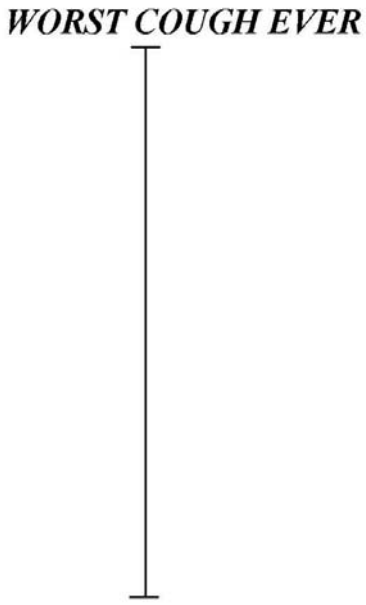
3. Total Scores: Addition of domain scores (range 3–21)

18.3 Appendix 3 Cough Severity Visual Analogue Scale

This Visual Analogue Scale must only be used for reference only and not photocopied for subject use.

Cough Severity Visual Analogue Scale

Please put a cross on the line to indicate the severity of your cough in the past 24-hours.



18.4 Appendix 4 Cough Frequency Visual Analogue Scale

This Visual Analogue Scale must only be used for reference only and not photocopied for subject use.

Cough Frequency Visual Analogue Scale

Please put a cross on the line to indicate how often you coughed in the past 24-hours.

COUGHED CONSTANTLY

NEVER COUGHED

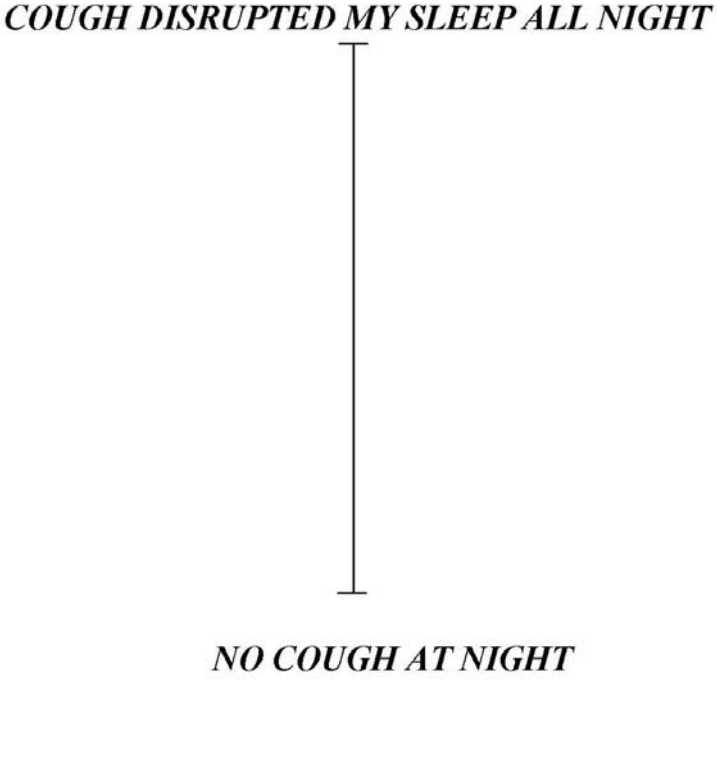
18.5 Appendix 5 Cough Sleep Disruption Visual Analogue Scale

This Visual Analogue Scale must only be used for reference only and not photocopied for subject use.

Cough Sleep Disruption Visual Analogue Scale

Please put a cross on the line to indicate how much your cough disrupted your sleep in the past 24-hours.

COUGH DISRUPTED MY SLEEP ALL NIGHT



NO COUGH AT NIGHT

Clinical Study Protocol IFH-2014-004

BMJ Open

THE ROCOCO STUDY: A REAL WORLD EVALUATION OF AN OVER THE COUNTER MEDICINE IN ACUTE COUGH (A MULTICENTRE, RANDOMISED, CONTROLLED STUDY)

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Primary Subject Heading:	Respiratory medicine
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WORD COUNT: 3,334 WORDS (4000 WORD COUNT LIMIT)

THE ROCOCO STUDY: A **R**EAL WORLD EVALUATION OF AN **O**VER THE **CO**UNTER MEDICINE IN ACUTE **CO**UGH (A MULTICENTRE, RANDOMISED, CONTROLLED STUDY)

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ABSTRACT

OBJECTIVES: To investigate the efficacy and safety of CS1002, an over-the-counter cough treatment containing diphenhydramine, ammonium chloride and levomenthol in a cocoa-based demulcent.

DESIGN: A multicentre, randomised, parallel group, controlled, single-blinded study in subjects with acute upper respiratory tract infection-associated cough.

SETTING: 4 GP surgeries and 14 pharmacies in the UK.

PARTICIPANTS: Subjects aged ≥18 years who self-referred to a general practitioner or pharmacist with acute cough of <7 days' duration. Subject inclusion criterion was cough severity ≥60mm on a 0-100mm visual analogue scale (VAS). Exclusion criteria included current smokers or history of smoking within the past 12 months (including e-cigarettes). 163 subjects were randomised to the study (mean subject age 38 years, 57% females).**INTERVENTIONS:** Subjects were randomised to CS1002 (Unicough) or Simple Linctus (SL), a widely used cough treatment, and treatment duration was 7 days or until resolution of cough.

MAIN OUTCOME MEASURES: The primary analysis was intention-to-treat (157 subjects) and comprised cough severity assessed using a VAS after 3 days' treatment (Day 4). Cough frequency, sleep disruption, health status (Leicester Cough Questionnaire [LCQ-acute]) and cough resolution were also assessed.

RESULTS: After 3 days' treatment, the adjusted mean difference [95% confidence interval] in cough severity VAS between CS1002 and SL was -5.9mm [-14.4,2.7], p=0.18. CS1002 was associated with a greater reduction in cough sleep disruption (mean difference -11.6mm [-20.6,-2.7], p=0.01) and cough frequency (mean difference -8.1mm [-16.2,0.1], p=0.05) compared to SL. There was greater improvement in LCQ-acute quality of life scores with CS1002 compared to SL: mean difference [95% CI] 1.2 [0.05,2.36], p=0.04 after 5 days'

treatment. More subjects prematurely stopped treatment due to cough improvement in the CS1002 group (24.4%) compared to SL (10.7%; p=0.02). Adverse events were comparable between CS1002 (20.5%) and SL (27.6%) and largely related to the study indication. Six subjects (7%) in the CS1002 group reduced the dose of medication due to drowsiness/tiredness, which subsequently resolved. These events were not reported by subjects as AEs..

CONCLUSIONS: Although the primary endpoint was not achieved, CS1002 was associated with greater reductions in cough frequency, sleep disruption and improved health status compared to SL.

ABSTRACT WORD COUNT: 288 Words (Maximum: 300 Words)

TRIAL REGISTRATION: EudraCT number 2014-004255-31 protocol publically available at https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-004255-31/GB. The protocol was submitted to the MHRA in December 2014 prior to commencing the study (see attached MHRA approval letter containing the EudraCT number prior to commencing the study) but the MHRA were late in posting the study protocol into the EudraCT/clinical trials register database. No amendments were made to the protocol.

ARTICLE SUMMARY

Strengths and limitations of this study

- A recent Cochrane systematic review of cough medicines found no good evidence for or against the effectiveness of OTC medications in acute cough. .
- This is one of the largest multiple dosing, multi-centre, randomised, controlled trials in subjects with cough to date, and the first to recruit subjects seeking cough medicines at pharmacies and is therefore more likely to represent the broader population with acute cough due to upper respiratory tract infection.
- Subjects were unselected for the category of cough, and included a broad range of subjects with self-reported dry, chesty and tickly cough.
- The study was single-blinded because an active control, Simple Linctus, was used as the comparator but it is possible that there may have been greater differences in efficacy outcome measures if an inactive placebo had been used.
- Our findings highlight the challenges of evaluating cough medicines in a rapidly improving condition and will facilitate the design of future studies of acute cough.

INTRODUCTION

Approximately 1 in 5 people in the United Kingdom (UK) suffer an acute cough over the winter [1] and it is one of the most common reasons for consulting a general practitioner (GP), at a cost to the National Health Service (NHS) of approximately £2 billion per year.[2-4] Although most acute coughs improve spontaneously, many patients use over-the-counter (OTC) medicines. In 2014, £98.7 million was spent in the UK on OTC cough treatments.[5] OTC cough medicines include antitussives, expectorants, mucolytics, antihistamines, decongestants, and numerous drug combinations.[6] There is a lack of data supporting the efficacy of OTC medicines in the treatment of acute cough associated with upper respiratory tract infection (URTI). In 2012, a Cochrane systematic review concluded there was no strong evidence for or against their effectiveness.[6] Methodological flaws in clinical trial design, paucity of placebo-controlled trials, use of un-validated outcome measures, and inefficacy of medicines were some of the reasons for the poor evidence base.

CS1002 is an OTC cough medicine that contains 3 active ingredients: diphenhydramine, levomenthol, and ammonium chloride in a cocoa-based demulcent preparation. Diphenhydramine is an antihistamine that has been reported to reduce the heightened cough reflex sensitivity in subjects with cough associated with an URTI.[7] Menthol and eucalyptus have been used for many centuries for treating coughs and colds.[8] Menthol is obtained from mint oils, mainly peppermint, or made synthetically from coal tar. It has a pungent odour that provides a cooling and soothing effect in the mouth and throat and is often used to relieve congestion.[8] Menthol has also been reported to inhibit cough reflex sensitivity compared to placebo.[9] Ammonium chloride is an acid-forming salt that is thought to exert an expectorant effect by loosening sputum.[10] The effectiveness and mode of action of ammonium chloride remains controversial.[10] The cocoa-based demulcent preparation used

in CS1002 is more viscous than most available OTC cough medicines. Demulcents are thought to reduce cough and cold symptoms because of a soothing effect on the mucus membrane.[11] The aim of this study was to investigate the efficacy of CS1002, an OTC cough medicine for cough associated with URTI, in a randomised controlled trial.

METHODS

Study Design

This multicentre, randomised, parallel group, controlled, single-blinded study was conducted in 4 GP surgeries and 14 pharmacies in the UK between 30 December 2014 and 9 May 2015. The control was a widely used simple linctus (SL) medicine available for acute cough in the UK. The investigators were blinded to the nature of the investigational product by using identical sealed packaging for both medicines. Subjects self-administered their assigned medication outside the pharmacy or GP surgery.

Subjects

Subjects aged ≥18 years who self-referred themselves to a GP or pharmacist with an acute cough of less than 7 days' duration were recruited. Subject inclusion criterion was a severity of at least 60mm on a 0 to 100mm visual analogue scale (VAS). Subject exclusion criteria were (i) subjects with a chronic cough, (ii) current or history of smoking within the past 12 months (including e-cigarettes), (iii) subjects with any relevant hospital stay of >2 days within a 6-month period, (iv) use of any cough or cold treatment for the current cough episode, including antibiotics, (v) productive cough with excessive secretion, (vi) use of angiotensin converting enzyme (ACE) inhibitor medication.

Subject Involvement

Subjects were not involved in the design or conduct of this study.

Ethics and Trial Registration

The protocol was approved by the North West - Greater Manchester South Research Ethics Committee (Reference: 14/NW/1424). The trial protocol was registered prior to commencing

the study in the publically available EudraCT database (Reference: 2014-004255-31) and no protocol amendments were made subsequently. All participants provided written informed consent.

Randomisation

All subjects considered eligible for study participation and who signed a consent form were given a unique randomisation number based on a pre-defined computer-generated randomisation scheme corresponding to a sealed medication pack that contained either CS1002 (2x150mL) or SL (2x150mL). Subjects were allocated treatment using a block randomisation with a block size of 4.

Study Medication

Subjects were randomised to one of the following treatments:

- CS1002 (Unicough): diphenhydramine 14mg/5mL, levomenthol 1.1mg/5mL and ammonium chloride 135mg/5mL in a cocoa-based demulcent preparation.
- SL: citric acid monohydrate 125mg/5mL in a syrup base.

Interventions

The subjects were approached, screened, consented and randomised during their initial consultation with their GP or the pharmacist. Subjects took their study medication orally 4 times daily (5mL in the morning, 5mL at lunchtime, 10mL at teatime, and 10mL at bedtime) for up to 7 days. Subjects were instructed to take the medication regularly until the cough resolved.

Methods of Evaluation

Subjects completed their assessments and compliance with medication in a daily diary. Each subject received a tamper-evident unidentifiable patient pack which was only opened on leaving the site. On completion, the pack was returned in a resealed and unidentifiable state. An independent data management organisation was utilised for data entry and to manage adverse event (AE) reporting. The investigators were blinded to the assignment of treatment and to the outcome assessments. The schedule of study visits is presented in Figure 1. The subjects were asked to complete assessments at baseline (Day 1) and then at the same time of day from Day 2 to Day 8. The study evaluated the efficacy of the study medications by assessing various aspects of acute cough.[12] Cough severity, frequency, and impact on sleep disruption in the previous 24 hours were assessed using a VAS. Health related quality of life (HRQoL) was assessed using the Leicester Cough Questionnaire for acute cough (LCQ-acute).[3,13] The LCQ is a valid and reliable health status measure of acute cough in adults and is responsive to change. It comprises 19 items divided into 3 domains (physical, psychological and social) and uses a 7-point Likert response scale. A higher score indicates a better health status. The LCQ is designed for self-administration and takes less than 5 minutes to complete.[3,14]

Primary Efficacy Endpoint

The primary efficacy endpoint was change from baseline to Day 4 (i.e. after 3 complete days of treatment) in cough severity on a 100mm VAS (ranging from 0=no cough to 100=worst cough ever).

Secondary Efficacy Endpoints

The following pre-specified endpoints were evaluated: (i) change from baseline in cough severity VAS at Days 6 and 8, (ii) change from baseline in cough frequency and cough sleep disruption VAS at Days 4, 6 and 8, (iii) time to resolution of cough symptoms, defined as the day at which cough severity VAS <17mm (the threshold considered to be of minimal severity and the minimally important difference [MID] in acute cough),[12] (iv) change from baseline in LCQ-acute score at Days 4, 6 and 8.

Safety Monitoring

Subjects were advised to reduce the dose of medication if they experienced drowsiness, and to document this in their daily diary. If drowsiness persisted, they were advised to discontinue the medication. Subjects were advised to contact their doctor or a 24-hour help line if they felt unwell. Safety was assessed in terms of the frequency and severity of AEs occurring during the study and this was recorded by the investigator.

Statistical Analysis and Sample Size

The sample size calculation was based on a difference in the change in cough severity VAS of 17mm between subjects treated with CS1002 and SL. Evaluation of the VAS in acute cough has suggested that the MID is 17mm.[12] It was estimated that approximately 180 subjects would be required to achieve a power of 90% to detect a difference between the treatment groups of 17mm, with a standard deviation of 35mm.[12]

The primary analysis was conducted on the intention-to-treat (ITT) population, comprising all randomised subjects who were treated with at least one dose of study medication and provided a baseline and at least one on-treatment assessment of cough severity. No

imputation was used for missing data (i.e. only observed data was used). A mixed model for repeated measures (MMRM) analysis was used to compare the effect of study treatments on cough parameters from baseline. The model included effects for treatment group, day, pooled centre, baseline cough severity, and treatment-by-day and baseline-by-day cough severity interaction terms. Residual plots and a normality test were used to assess normality. The results were also repeated for the per-protocol set (PPS), defined as subjects in the ITT population who did not have an important protocol violation. A sensitivity analysis was also conducted to assess the robustness of the primary efficacy results to the method of handling missing data, using a last observation carried forward (LOCF) approach and a baseline observation carried forward (BOCF) approach for subjects with no on-treatment data. Parametric data was presented as mean and either standard deviation (SD), standard error of the mean (SEM), or 95% confidence intervals (95% CI). Statistical significance was defined as $p \leq 0.05$. The proportions of subjects with cough resolution were compared using a stratified (by centre) Cochran-Mantel-Haenszel test. Time-to-event analysis using a Cox proportional hazards model stratified by centre was used to estimate a hazard ratio.

RESULTS

Subjects

A total of 163 subjects were randomised into the study at 4 GP sites and 14 pharmacy sites. The reasons for screening failures are shown in Figure 2. The ITT population comprised 157 subjects (82 CS1002, 75 SL), and the PPS comprised 142 subjects (75 CS1002, 67 SL) (Figure 2). The baseline characteristics of both treatment groups were well-matched (Table 1). The mean age of the subjects was 38 years, 57% of subjects were female, and 62% of subjects were white (34% Asian and 4% black). The groups were well-matched for the proportion of subjects describing the characteristics of their cough as dry (CS1002 50%; SL 52%), chesty (CS1002 29%; SL 31%) or tickly (CS1002 21%; SL 17%).

Table 1: Subject Demographic and Baseline Characteristics

	CS1002 n (%) N=82	**Simple linctus n (%) N=75**
Gender [N (%)]		
Male	34 (42)	34 (45)
Female	48 (59)	41 (55)
Age [years]		
Mean (SD)	38.5 (17.3)	38.2 (16.6)
Median (range)	31.5 (18, 75)	34.0 (18, 86)
Type of referral [N (%)]		
GP	30 (37)	27 (36)
Pharmacist	52 (63)	48 (64)
Smoking status [N (%)]		
Never smoked	64 (78)	54 (72)
Ex-smoker	18 (22)	21 (28)
Cough characteristics, mean (SD)		
Cough duration [days]	3.0 (1.5)	3.1 (1.6)
Cough severity VAS (mm)	80.4 (10.1)	81.6 (9.9)
Cough frequency VAS (mm)	79.5 (16.1)	76.7 (15.5)
Cough sleep disruption VAS (mm)	75.5 (23.2)	64.6 (29.2)
LCQ-acute scores, mean (SD)		
Total score	10.8 (3.5)	11.4 (3.2)
Physical score	3.7 (1.2)	4.1 (1.1)
Psychological score	3.7 (1.2)	3.9 (1.1)
Social score	3.4 (1.4)	3.5 (1.3)

LCQ = Leicester Cough Questionnaire; VAS = visual analogue scale (using a scale of 0-100 mm)
Based on ITT population

Primary Efficacy Endpoint

Subjects took CS1002 medication for a mean (SD) of 6.2 (2.1) days and SL medication for 6.6 (1.8) days. The mean number of doses of study medication were 22.2 (8.7) for the CS1002 group and 23.7 (8.3) in the SL group. The maximum number of medication doses possible during the study was 28. The weight of the bottles of treatment returned at the end of study was planned to be used to estimate compliance, excluding doses not taken due to early termination from the study due to recovery. The weight of medicine broadly agreed with self-reported consumption stated by subjects receiving CS1002, with a mean (SD) of 94% (17%) vs. 94% (18%) for subjects receiving SL. There was a clinically meaningful improvement in cough severity VAS at Day 4 in both groups (Table 2, Figure 3). The magnitude of the reduction in cough severity score was greater in the CS1002 group compared to the SL group but was not statistically significant; mean (95% CI) difference of 5.9mm (-14.4, 2.7), p=0.18. The PPS and ITT sensitivity analyses with imputations were also consistent with this finding (see Supplementary File).

Secondary Efficacy Endpoints

Cough Severity: There was a progressive decrease in cough severity VAS over the study, with the CS1002 group reporting a greater reduction compared to the SL group between Days 3 to 7 (Figure 3). The between group changes in cough severity VAS did not achieve statistical significance (Table 2 and Figure 3).

Cough Frequency: There was a greater reduction in cough frequency VAS with CS1002 compared to SL at all time points (Figure 4). At Day 4, there was an 8.1mm (95% CI: -16.2, 0.1) greater reduction in cough frequency VAS for CS1002 compared to SL (p=0.05) (Table 2 and Figure 4).

Cough Resolution: By Day 4, 29.3% of subjects in the CS1002 group had achieved cough resolution compared with 17.3% in the SL group (p=0.08) (Table 2). There was no significant difference between the treatment groups regarding median time taken to achieve cough resolution (CS1002 6.5 days, SL 7.0 days, hazard ratio 1.300, p=0.20, Figure 5). In a post-hoc analysis, 20 subjects (24.4%) in the CS1002 group and 10 (10.7%) in SL group stopped treatment by Day 4 due to improvement in cough (p=0.02).

Sleep Disruption: There was a greater reduction in sleep disruption with CS1002 compared to SL at all time points (Figure 6). At Day 4, the magnitude of reduction in cough sleep disruption score was greater for the CS1002 group than for the SL group, mean difference of 11.6mm (95% CCI: -20.6,-2.7), p=0.01 (Figure 6 and Table 2). A summary of all VAS results is provided in Supplementary File Figure 1.

Table 2: Analysis of Key Efficacy Parameters at Day 4

Key Efficacy Assessments	CS1002	Simple linctus
Number of subjects	82	75
Cough severity		
Baseline value (mean±SD)	80.4 (10.1)	81.6 (9.9)
Change from baseline to Day 4: Mean (95% CI)	-38.9 (-45.2,-33.2)	-32.8 (-39.6,-27.0)
Adjusted mean difference (95% CI)	-5.9 (-14.4,2.7)	
p-value	**p=0.18**	
Cough frequency		
Baseline value (mean±SD)	79.5 (16.1)	76.7 (15.5)
Change from baseline to Day 4: Mean (95% CI)	-40.7 (-46.0,-34.6)	-32.1 (-38.1,-26.4)
Adjusted mean difference (95% CI)	-8.1 (-16.2,0.1)	
p-value	**p=0.05**	
Cough resolution		
Day 4 value (n, %)	24 (29.3%)	13 (17.3)
Difference (%)	12%	
p-value	**p=0.08**	
Sleep disruption		
Baseline value (mean±SD)	75.5 (23.2)	64.6 (29.2)
Change from baseline to Day 4; Mean (95% CI)	-42.8 (-46.9,-34.4)	-26.3 (-35.5,-22.6)
Adjusted mean difference (95% CI)	-11.6 (-20.6,-2.7)	
p-value	**p=0.01**	

NB. Negative values indicate a reduction in cough symptoms
Based on ITT population. Adjusted mean difference = difference in between group differences

Health-Related Quality of Life: LCQ-acute total scores increased over time for both treatment groups, indicating an improvement in HRQoL. At Day 6, the magnitude of the improvement was significantly greater in the CS1002 group compared to the SL group (mean difference 1.21 (95% CCI: 0.05, 2.36), p=0.04) (see Supplementary File Figures 2 and 3).

Adverse Events (AEs)

AEs were reported for 17 subjects (20.5%) in the CS1002 group and 21 subjects (27.6%) in the SL group during the study (Table 3). The AEs were generally indicative of the study indication or likely to be associated with URTI, with the majority being mild or moderate

severity. Events classified as severe were only seen in the SL treatment group, and comprised cough, sneezing and joint swelling (all occurring in 1 subject each). No SAEs or deaths were reported. There were no AEs of drowsiness reported during the study. Six subjects (7%) in the CS1002 group and no subjects in the SL group reported in their diary that they reduced the dose of medication due to drowsiness/tiredness. These events were not reported by the subjects as AE. Following the reduction of the dose of medication there were no further reports of drowsiness or tiredness.

Table 3: Adverse Events

AEs, n (%)	CS1002 N=83 Total N (%)	Simple linctus N=79 Total N (%)
Number of subjects with an AE	17 (20.5)	21 (27.6)
Nervous system disorders	7 (8.4)	10 (13.2)
Headache	5 (6.0)	9 (11.8)
Dizziness	1 (1.2)	2 (2.6)
Respiratory, thoracic and mediastinal disorders	8 (9.6)	9 (11.8)
Oropharyngeal pain	2 (2.4)	4 (5.3)
Cough	2 (2.4)	3 (3.9)
Productive cough	3 (3.6)	1 (1.3)
Dyspnoea	0 (0.0)	2 (2.6)
Gastrointestinal disorders	5 (6.0)	2 (2.6)
Diarrhoea	3 (3.6)	0 (0.0)
Abdominal pain upper	2 (2.4)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	5 (6.6)
Pain	0 (0.0)	3 (3.9)
Pyrexia	0 (0.0)	2 (2.6)
Infections and infestations	1 (1.2)	2 (2.6)
Lower respiratory tract infection	0 (0.0)	2 (2.6)

Treated set population. AEs reported for >1 subject.

DISCUSSION

This multicentre, randomised study compared the efficacy and safety of two OTC cough mixtures: CS1002 containing diphenhydramine, ammonium-chloride and levomenthol in a cocoa-based demulcent preparation versus SL containing citric acid monohydrate. This is one of the largest multiple dosing, randomised controlled trials in subjects with URTI-associated cough to date, and the first to recruit subjects seeking cough medicines at pharmacies. The study did not achieve a significant reduction in primary end-point cough severity after 3 days of treatment, but there were greater reductions in cough frequency and sleep disruption and resolution of cough in subjects receiving CS1002 compared to SL.

Our trial represents a significant advance in the study of URTI-associated cough for a number of reasons. A Cochrane systematic review of cough medicines concluded that there was no evidence for or against cough medicines for URTI-associated cough.[6] Previous trials of cough medicines have been hampered by the recruitment of small numbers of subjects, the recruitment of subjects not representative of URTI-associated cough, uncontrolled study design and the use of un-validated endpoints. We conducted a randomised clinical trial that included validated cough outcome measures. Our primary outcome measure, the VAS, is widely used in studies of cough.[15] We recruited subjects with an URTI-associated cough who were otherwise healthy and seeking an antitussive medicine. Our subjects were unselected for the category of cough, and included a broad range of subjects with self-reported dry, chesty and tickly cough. We conducted a large study, recruiting subjects from 18 sites. This is the first study to recruit subjects presenting to pharmacies, and therefore the study population is more likely to resemble the broader population seeking cough medicines. There were few subjects that dropped out of the trial, and therefore our data completeness was good. The efficacy of the interventions was evaluated with widely used and validated

end-points of cough severity VAS and LCQ-acute HRQoL questionnaires.[15,16] We conducted a controlled trial and the comparator was a widely used OTC treatment. SL, which costs less than many OTC medicines to purchase but like most cough medicines, it lacks a strong evidence base. Its efficacy has not been compared to natural recovery, placebo, or to other cough medicines. The rate of reduction of cough severity VAS associated with SL in our study does appear to be greater than that reported for natural recovery.[12] The mechanism of action of SL is poorly understood, but is thought to be related to a demulcent effect and the hyper-salivation resulting from the sugary taste.[11]

There was a clinically significant reduction in primary end-point cough severity VAS at Day 4 in both groups. However, CS1002 did not achieve the primary end-point of a greater reduction in cough severity at Day 4 compared to SL. There were, however, greater reductions in secondary endpoints of sleep disruption and cough frequency, and improvements in HRQoL associated with CS1002 compared to SL. There was also a trend favouring greater resolution of cough at Day 4 with CS1002 compared to SL, with a near doubling of the proportion of subjects whose cough had resolved. This was supported by a post-hoc analysis that found a significantly greater number of subjects had discontinued their medication due to resolution of cough by Day 4 (CS1002, 24.4% vs. SL, 10.7%: p=0.02). The MID for cough outcome measures of frequency VAS, sleep disruption VAS and cough resolution have not been reported in URTI-associated cough, and this should be studied in future to facilitate the clinical interpretation of data. CS1002 was well tolerated, and there were few significant adverse events, including drowsiness. Drowsiness was managed with dose reduction, and no subjects discontinued the medication because of this symptom. Subjects were compliant with both medications, and this was verified by counting the doses of medication returned at the end of the study. The mechanism of action of CS1002 is poorly

understood. There are a number of possibilities, which include a reduction in cough reflex sensitivity,[7] promotion of more restful sleep, and a demulcent action. CS1002 contains a cocoa-flavoured demulcent that is more viscous than most available OTC cough medicines, and this may potentially promote palatability.

There are a number of important limitations with our study. We did not utilise a placebo comparator, and the study was not double-blinded. The limitations of a single-blinded study were reduced by informing the subjects that they were going to receive a cough medicine, but not the characteristics of the medicine. The investigators were blinded to the study because both medicines were contained in identical packaging, and subjects were instructed to commence their medication outside the pharmacy or GP clinic. We used SL as the comparator since this is a widely used cough treatment. It is possible that there may have been greater differences in efficacy outcome measures if we had used an inactive placebo. Another option for comparator that should be considered in future studies is the demulcent used in CS1002. It is likely that there was also significant natural recovery in our study. Our data highlights the difficulty in evaluating cough medicines in a rapidly resolving condition. We don't know whether the cough at study entry was worsening or improving and this could have impacted on our findings. We were short of our recruitment target of 180 subjects; we recruited 163 subjects. This was due to a delay in the start of the study, and consequently a reduced time window for recruitment during the cough and cold winter season. We think it is unlikely that the slight under-recruitment of subjects would have altered our study conclusions. The reasons for screen failures were not recorded for many patients, particularly at busy pharmacy sites. The reasons were, however, recorded for 2,238 subjects and suggest that a large number of subjects approached had duration of cough greater than 7 days. It is possible that the discontinuation of medication could have reflected lack of efficacy as well as

recovery. We didn't investigate the cause of the acute cough, and future studies should possibly assess viruses, pertussis and bacterial causes. We did not assess cough with objective outcome measures, such as cough frequency monitoring.[16] Recently, there have been significant advances in cough monitoring technology, and this should be possible in future studies.[17]

In conclusion, the OTC cough medicine CS1002 did not achieve a significant reduction in the primary endpoint cough severity, but it was associated with a greater reduction in cough frequency and sleep disruption, and increased resolution of cough leading to early discontinuation of medication and improved HRQoL compared to comparator SL. Further studies should investigate the impact of natural recovery and placebo on cough outcome measures to facilitate the optimal study protocol in URTI-associated cough.

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AUTHORS' CONTRIBUTIONS

SB = Surinder Birring; JB = John Brew; TK = Tony Kilbourn; VE = Viv Edwards; RW = Rosamund Wilson; AM = Alyn Morice

Conception/design of work: SB, JB, TK, VE, RW, AM

Data analysis: RW, VE, JB

Data interpretation: all authors

Drafting manuscript: SB with input from JB, TK, VE, RW and AM. Help was also provided by Debbie Jordan, a professional medical writer.

Review and approval of manuscript: all authors

COMPETING INTERESTS

Surinder Birring has received personal fees from Infirst Healthcare during the conduct of the study for advisory work. Alyn Morice has received personal fees from Infirst Healthcare during the conduct of the study for advisory work. John Brew, Viv Edwards, and Tony Kilbourn are employees of Infirst Healthcare Ltd. Rosamund Wilson is a statistical consultant to Infirst Healthcare.

DATA SHARING STATEMENT

No additional data are available.

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FIGURE LEGENDS

Figure 1: Study Design

Figure 2: Trial CONSORT Flow Diagram

Figure 3: Change in Cough Severity over Time

Figure 4: Change in Cough Frequency over Time

Figure 5: Resolution of Cough: Cumulative Percentage of Subjects

Figure 6: Change in Cough Sleep Disruption over Time

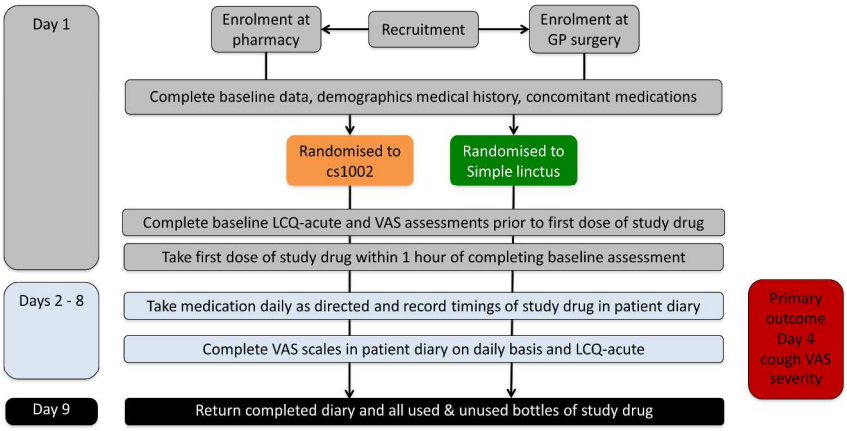

Figure 1: Study Design

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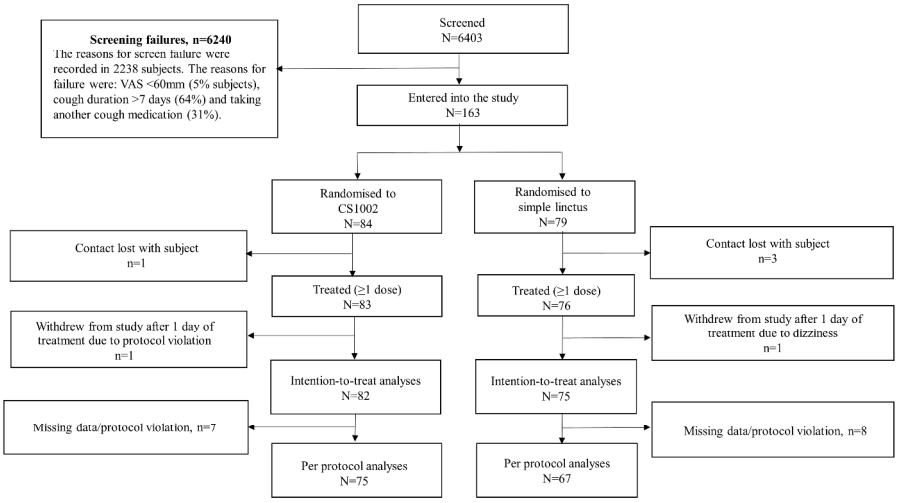
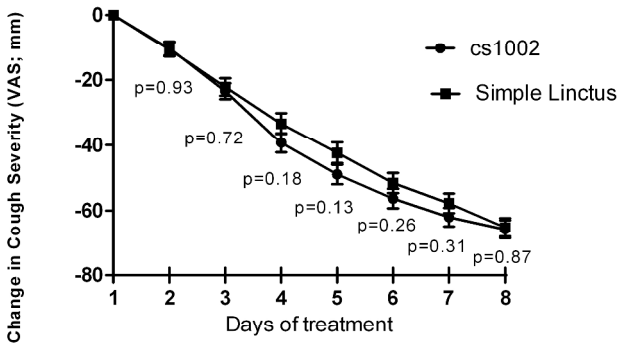


Figure 2: Trial CONSORT Flow Diagram

338x190mm (300 x 300 DPI)



Based on ITT population
Cough severity assessed using a 100 mm visual analogue scale (VAS)

Figure 3: Change in Cough Severity over Time

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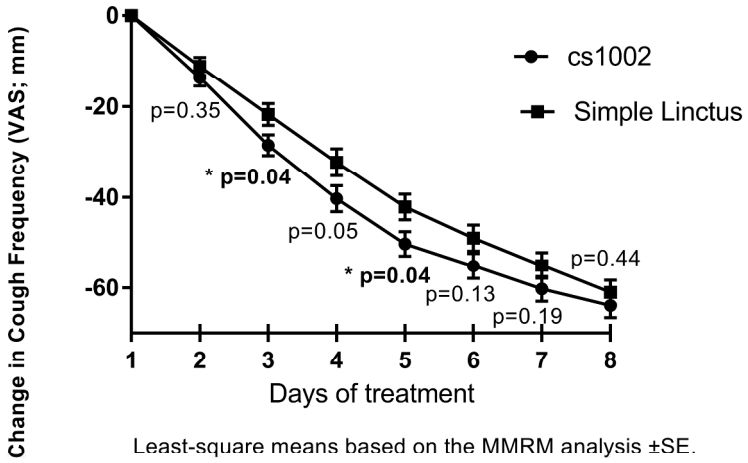

Based on ITT population
Cough frequency assessed using a 100 mm visual analogue scale (VAS)

Figure 4: Change in Cough Frequency over Time

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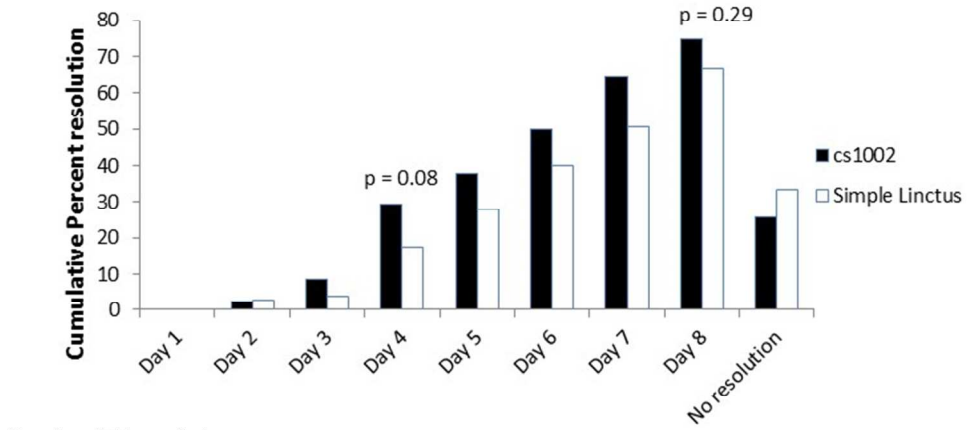
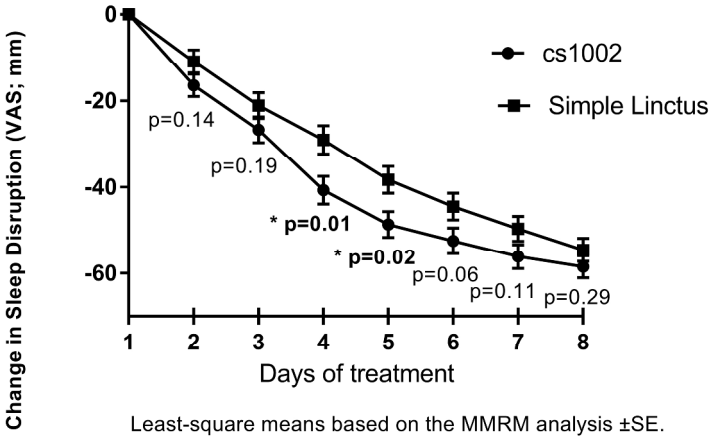


Based on ITT population
Cough resolution defined as severity VAS ≤17mm

Figure 5: Resolution of Cough: Cumulative Percentage of Subjects

338x190mm (300 x 300 DPI)



Least-square means based on the MMRM analysis ±SE.

Based on ITT population
Sleep disruption assessed using a 100 mm visual analogue scale (VAS)

Figure 6: Change in Cough Sleep Disruption over Time

338x190mm (300 x 300 DPI)

Supplementary File

Per-protocol Analysis

A supportive analysis of the primary endpoint of the comparison of change in cough severity for CS1002 versus simple linctus from baseline to Day 4 of the study was conducted using the per-protocol set (PPS), as summarised in Supplementary File Table 1. Analysis using the PPS showed similar findings to the primary endpoint analysis, with the 4.6 mm difference in change in cough severity score between groups, not achieving statistical significance (p=0.30).

Supplementary File Table 1: Change in cough severity VAS at Day 4 (Per-Protocol Set)

	CS1002	simple linctus
Number of subjects	75	67
Baseline cough severity VAS, mm Mean (SD)	80.3 (10.0)	81.2 (9.5)
Change in VAS from baseline to Day 4 Mean (SE) Adjusted mean (SE)[1] 95% confidence interval[1]	-39.4 (3.3) -40.6 (3.1) -46.6, -34.5	-35.4 (3.1) -36.0 (3.2) -42.4, -29.6
CS1002 vs. simple linctus Adjusted VAS mean difference (SE)[1] 95% confidence interval[1] p-value[1]	-4.6 (4.4) -13.2, 4.1 0.3009	

Note: Cough severity VAS scores range from 0 (no cough) to 100 (worst cough ever)
Negative values indicate a reduction in cough severity from baseline
[1] ANCOVA analysis on observed data including treatment, day, pooled centre and baseline cough severity terms along with treatment-by-day and baseline-by-day interaction terms

Sensitivity Analysis

Two sensitivity analyses were performed with imputations for missing data. In the first analysis, a last observation carried forward (LOCF) approach for missing data was used in the intention-to-treat (ITT) population. For this analysis if the Day 4 cough severity score was missing (the last on-treatment assessment of cough), the severity prior to Day 4 was carried forward. Analysis using this approach showed similar findings to the primary endpoint analysis (see Supplementary File Table 2), with the analysis of covariance (ANCOVA) demonstrating mean changes in cough severity of -39.2 mm (95% CIs -45.2, -33.2) for CS1002 and -33.7 mm (95% CIs -39.9, -27.4) for simple linctus. The 5.6 mm difference in change in cough severity score between the groups did not achieve statistical significance (p=0.19).

Supplementary File Table 2: Sensitivity analysis of change in cough severity at Day 4 (Last Observation Carried Forward, ITT Population)

	CS1002	simple linctus
Number of subjects	82	75
Baseline cough severity VAS, mm Mean (SD)	80.4 (10.1)	81.6 (9.9)
Change in VAS from baseline to Day 4 Mean (SE) Adjusted mean (SE)[1] 95% confidence interval[1]	-38.4 (3.1) -39.2 (3.0) -45.2, -33.2	-32.8 (3.1) -33.7 (3.2) -39.9, -27.4
CS1002 vs. simple linctus Adjusted VAS mean difference (SE)[1] 95% confidence interval[1] p-value[1]	-5.6 (4.2) -13.9, 2.8 0.1904	

Note: Cough severity VAS scores range from 0 (no cough) to 100 (worst cough ever)
Negative values indicate a reduction in cough severity from baseline
[1] ANCOVA analysis on LOCF data including treatment, day, pooled centre and baseline cough severity terms

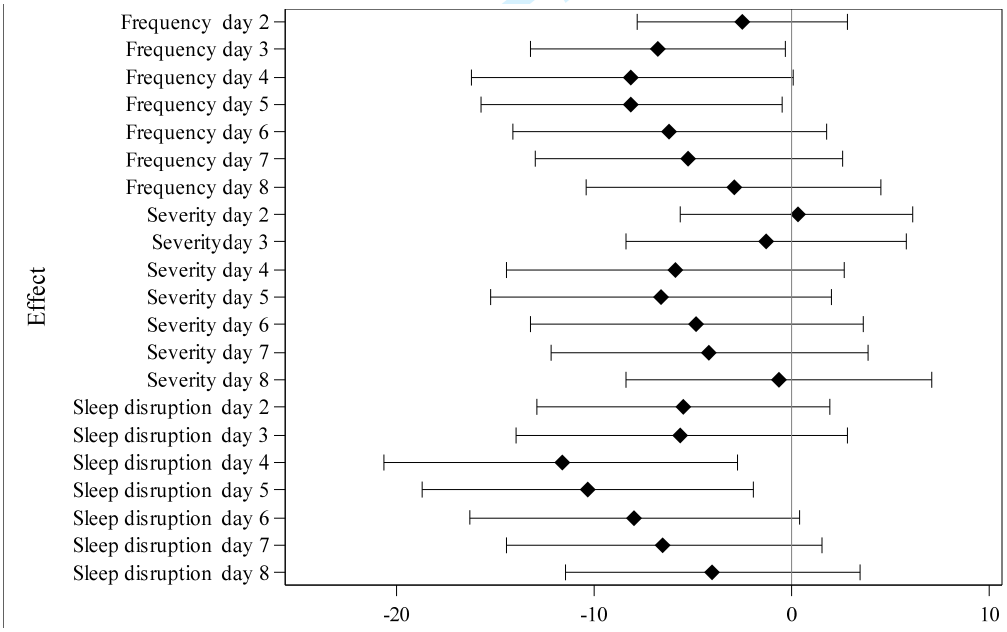
In the second analysis of the randomised set, missing cough VAS data at Day 4 was imputed, with baseline observations carried forward (BOCF). Analysis using this approach showed similar findings to the primary endpoint analysis (see Supplementary File Table 3), with the ANCOVA analysis demonstrating mean changes in cough severity of -38.1 (95% CIs -44.1, -32.1) for CS1002 and -31.5 (95% CIs -37.7, -25.4) for simple linctus. The 6.5 mm difference in change in cough severity score between the treatment groups did not achieve statistical significance (p=0.12).

Supplementary File Table 3: Sensitivity analysis of change in cough severity at Day 4 (Baseline Observation Carried Forward, ITT Population)

	CS1002	simple linctus
Number of subjects	84	79
Baseline cough severity VAS, mm Mean (SD)	80.5 (10.1)	81.5 (10.2)
Change in VAS from baseline to Day 4 Mean (SE) Adjusted mean (SE)[1] 95% confidence interval[1]	-37.5 (3.1) -38.1 (3.0) -44.1, -32.1	-31.2 (3.1) -31.5 (3.1) -37.7, -25.4
CS1002 vs. simple linctus Adjusted VAS mean difference (SE)[1] 95% confidence interval[1] p-value[1]	-6.5 (4.2) -14.9, 1.8 0.1229	

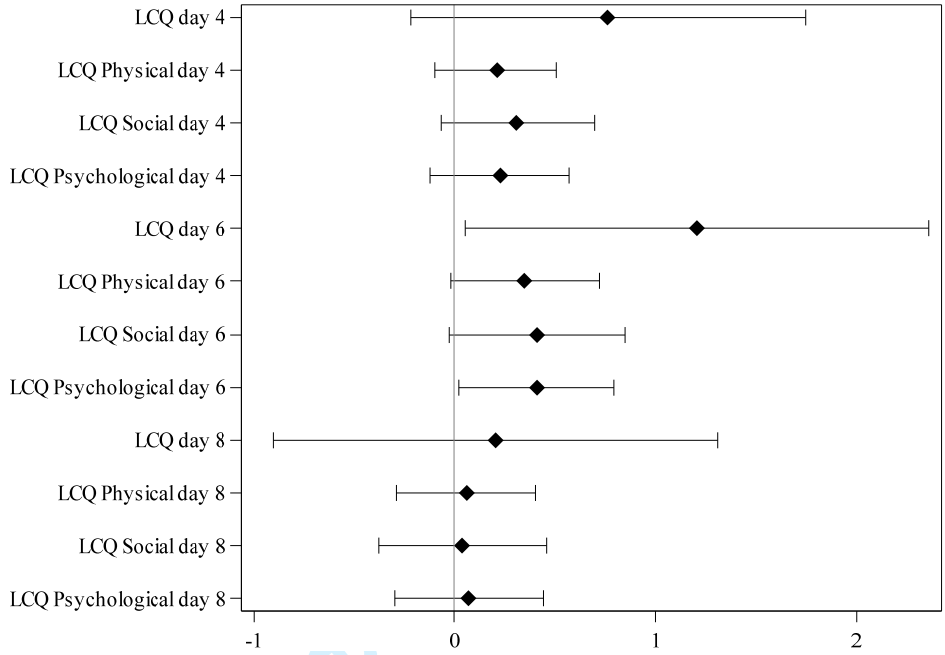
Note: Cough severity VAS scores range from 0 (no cough) to 100 (worst cough ever)
Negative values indicate a reduction in cough severity from baseline
[1] ANCOVA analysis on baseline observation carried forward data including treatment, day, pooled centre and baseline cough severity terms

Supplementary File Figure 1: Forest plot of cough frequency, cough severity and cough sleep disruption VAS scores (Days 2 – 8)



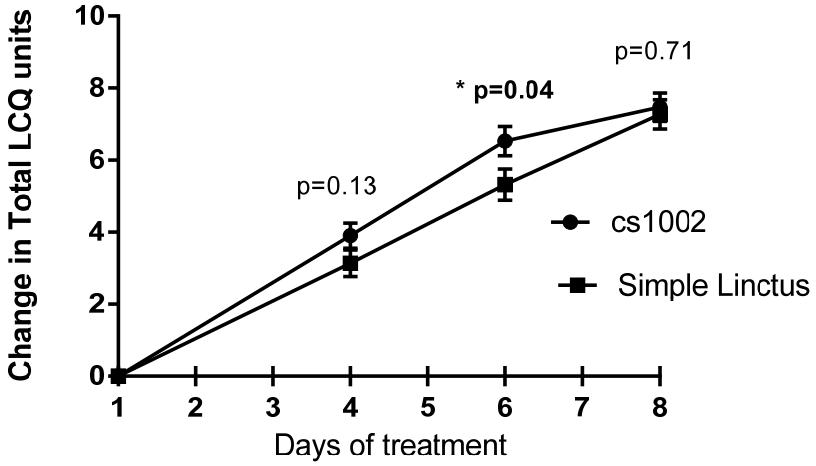
Estimates and 95% CI: Negative values favour CS1002 and positive values favour Simple Linctus.
Based on ITT population

Supplementary File Figure 2: Forest Plot of HRQoL (LCQ) Scores



Estimates and 95% CI: Positive values favour CS1002 and negative values favour Simple Linctus.
ITT population

Supplementary File Figure 3: Change in total LCQ (quality of life) score over time



Least-square means based on the MMRM analysis ±SE.

Based on ITT population
LCQ = Leicester Cough Questionnaire

Clinical Study Protocol IFH-2014-004

Infirst+ HEALTHCARE

CLINICAL STUDY PROTOCOL

A real world, single-blind, randomised study to compare an OTC cough medicine (cs1002) containing diphenhydramine, levomenthol and ammonium chloride with a simple linctus containing citric acid monohydrate in terms of daily cough severity in subjects with acute cough in routine clinical practice.

ROCOCO

Real World evaluation of an **O**TC **co**ugh medicine **co**ntaining diphenhydramine

Protocol Number: IFH-2014-004

EUDRACT Number: 2014-004255-31.

Protocol Version and Date: Version 1. 24 Oct 2014

TEST DRUG: **cs1002**

SPONSOR: **Infirst+ HEALTHCARE Ltd**
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Telephone: +44 (0) 20 7153 6600
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CHIEF INVESTIGATOR: **Dr Surinder Birring**
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Grove House, Lutyens Close, Chineham Court, Basingstoke RG24 8AG
Telephone: +44 (0) 1256316551
Fax: +44 (0) 1256 316552

Protocol Approval

Sponsor Approval

This protocol IFH-2014-004 has been approved by Infirst+ HEALTHCARE:

Protocol Version:	Version 1. 24 Oct 2014
Approver: Dr Sunita Chauhan Responsible Physician (PharSafer) **Print Name** **Sign and date:**	
Approver: Viv Edwards Director of Regulatory & Medical Affairs **Print Name** **Sign and date:**	

Chief Investigator Approval

This protocol IFH-2014-004 has been approved by the Chief Investigator:

Protocol Version:	Version 1. 24 Oct 2014
Approver: Dr Surinder Birring Consultant Respiratory Physician **Print Name:** **Sign and date:**	

Investigator's Agreement

I have read this Infirst+ HEALTHCARE protocol no. IFH-2014-004.

A real world, single-blind, randomised study to compare an OTC cough medicine (cs1002) containing diphenhydramine, levomenthol and ammonium chloride with a simple linctus containing citric acid monohydrate in terms of daily cough severity in subjects with acute cough in routine clinical practice.

I have fully discussed the objectives of this trial and the contents of this protocol with the Sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the trial, without written authorisation from Infirst+ HEALTHCARE. It is, however, permissible to provide information to a patient in order to obtain consent.

I agree to conduct this trial according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines and to conduct the trial in accordance with ICH guidelines on GCP and with the applicable regulatory requirements.

I understand that the sponsor may decide to suspend or prematurely terminate the trial at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the trial I will communicate my intention immediately in writing to the sponsor.

Protocol Version:	Version 1.0
Investigator's Name and address:	_____ _____ _____ _____
Investigator's signature:	_____
Date:	_____ *(DD/MMM/YYYY)*

Emergency Contact List

Serious Adverse Events

In case of a **Serious Adverse Event (SAE)** the Investigator will be able to contact PharSafer at all times:

Principal Contact	Dr Sunita Chauhan (PharSafer)
Address	PharSafer House, White Hart Meadow, Ripley, Surrey, GU23 6ND, UK
Phone (24 hours)	+44 1483 212151
Fax	+44 1483 212178
E-mail	drugsafety@pharsafer.com

For any other safety related issues during normal business hours (09:00 – 17:00 UK GMT), the Investigator must contact the Infirst^{+} HEALTHCARE Responsible Physician:

Dr Sunita Chauhan (PharSafer)

Telephone Number: 01483 - 212167

Mobile Number: 07450 999000

Clinical Study Protocol IFH-2014-004

GLOSSARY OF ABBREVIATIONS	
Abbreviation	**Application**
AUC	Area Under the Curve
ANCOVA	Analysis of Covariance
BP	British Pharmacopoeia
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
ESF	Eligibility Screening Form
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Manufactured Product
LCQ	Leicester Cough Questionnaire
MAOI	Monoamine Oxidase Inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NRS	Numeric Rating Scale
OTC	Over the Counter
PRO	Subject Reported Outcome
PIS	Subject Information Sheet
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
US	United States
VAS	Visual Analogue Scale

Clinical Study Protocol IFH-2014-004

TABLE OF CONTENTS

Clinical Study Protocol IFH-2014-004

1. BACKGROUND AND RATIONALE

1.1 Background

Cough is one of the most common reasons for a subject visiting a physician in General Practice[1, 2, 3]. An acute cough associated with an upper respiratory tract infection rarely requires significant medical intervention, whereas a chronic cough may be associated with a number of underlying diseases [2]. It is therefore essential that any underlying cause of cough is diagnosed and treated [2, 4, 5].

Coughing is an important defensive reflex that enhances clearance of secretions and particulate matter from the airways and protects from the aspiration of foreign materials. The symptoms associated with cough are often debilitating and have a significant impact on quality of life (QoL) [6, 7, 8].

In the United Kingdom in 2010, subjects spent almost £100 million on non-prescription, over the counter (OTC) cough liquids for the self-treatment of their cough symptoms [9]. The range of OTC medicines available for cough includes antitussives, expectorants, mucolytics, antihistamines, antihistamine-decongestant combinations, and other drug combinations [10].

The Proprietary Association of Great Britain recently issued a statement supporting the use of OTC cough medicines, stating that they are safe and that studies support the efficacy of their active ingredients [11]. A Cochrane Review published in 2012 concluded there is no good evidence either for or against the effectiveness of OTC medicines in acute cough [10]. However, the results of the Cochrane Review were compromised by differences in study design, differences in the subject populations studied and by the fact that the data quality was rated as low. Consequently, the Cochrane conclusions should be interpreted with caution. A literature review published in 2007 reported on small studies that showed that diphenhydramine was significantly more effective than placebo at reducing the severity of citric acid induced cough and in ameliorating post infection cough [12]. However, there was no difference between diphenhydramine and placebo in cough associated with pertussis or in cough in children.

Despite the conflicting evidence the use of cough mixtures containing diphenhydramine alone or in combination with other active ingredients is widespread. Diphenhydramine as a stand-alone drug has recently been evaluated by US investigators as having efficacy in human clinical models of cough, and therefore warrants renewed clinical investigation [Error! Reference source not found.13].

1.1.1 Study Drugs

Subjects can find it very difficult to specifically determine the type of cough they have and thereby choose medication that best suits that type of cough. An effective cough medicine that can treat cough empirically may, therefore, be advantageous. In order to achieve this, the cough medicine will need to contain an antihistamine, a decongestant and an expectorant. cs1002 has been developed to provide each of these components in the form of diphenhydramine 14 mg/5 ml (antihistamine), levomenthol 1.1 mg/5 ml (decongestant) and ammonium chloride 135 mg/5 ml (expectorant). The three active components are formulated with excipients and with a cocoa flavour. In addition to improving palatability and hence compliance, the cocoa flavour increases the viscosity and surface adherence of the cough mixture, facilitates coating of the upper respiratory tract, brings the active ingredients into contact with sensitised nerve endings in the throat lining and may thus provide a soothing effect on the cough.

Preparations containing simple linctus are currently recommended by healthcare professionals for the relief of acute cough. Bell's simple linctus (containing citric acid monohydrate 125 mg/5 ml) was therefore, selected as a comparator product. Bell's simple linctus is currently available as an OTC medicine for the relief of cough.

Both products will be administered orally 4 times daily as per the dosing schedule. This is in line with the usual dosage regimen approved for OTC cough medicines that contain diphenhydramine at 14 mg/5 ml. Thus with the dosage used in this study the safety profile is expected to be comparable to that seen with currently available OTC products containing the same concentration of diphenhydramine.

1.2 Rationale for the Study

There is controversy and lack of recent evidence surrounding the efficacy of OTC products used for the treatment of acute cough. In this study the real world effectiveness of an OTC cough medicine (cs1002) designed to provide a novel flavour and additional demulcency for the symptomatic treatment of acute cough, will be evaluated using currently recommended simple linctus as a comparator.

The study will use previously validated methods to evaluate the efficacy of cs1002. Cough severity will be assessed using a Visual Analogue Scale and the impact of treatment on Quality of Life will be assessed using the validated Leicester Cough Questionnaire for acute cough (LCQ-acute) [8].

The study will also evaluate the efficacy of cs1002 on cough frequency and sleep (an important determinant of quality of life) using Visual Analogue Scales.

It is hoped that the use of validated assessment methods in this large scale clinical practice evaluation of cs1002, in a real life prescribing setting, will provide convincing data demonstrating the efficacy of a combination OTC product for treating acute cough, and will answer some of the shortfalls identified by the Cochrane review with previously published studies in this indication. The results of this study will be put into context with the findings of the 2012 Cochrane review [10].

2. OBJECTIVES

2.1 Primary Objectives

To investigate the efficacy of an OTC cough product containing diphenhydramine (cs1002) versus Bell's simple linctus by comparing the change from baseline in cough severity VAS scores after 3 days of treatment (Day 4).

2.2 Secondary Objectives

- To compare the efficacy of an OTC cough product containing diphenhydramine (cs1002) versus Bell's simple linctus by comparing change from baseline Leicester Cough Questionnaire (LCQ-acute) total scores at Days 4, 6 and 8.
- To compare the efficacy of an OTC cough product containing diphenhydramine (cs1002) versus Bell's linctus by assessing change from baseline in cough severity at Day 5, and in cough frequency and sleep quality VAS scores at Days 4, 6 and 8.
- To determine the time to resolution of cough symptoms defined as the day at which cough severity decreases to < 17mm.

3. OVERVIEW OF STUDY DESIGN

This is a multicentre, single-blind randomised study. The IMP is blinded to the Investigator only.

This study will include approximately 180 subjects who self-refer to the Investigator (either a GP or a Pharmacist) with a new onset acute cough which has a maximum of 7 day's duration and a severity of at least 60 mm on a 0–100 mm visual analogue scale (VAS). The basic study design is shown in Figure 1.

Figure 1 Study Flow Diagram

Day 1

- Subject enrolment at GP or Pharmacy Centre.
- Subjects will be given a diary to complete each day and receive instruction on how to complete this.
- Subjects will be given a 24 hour emergency contact number on a 'subject card' and within the diary.
- Subjects will complete baseline data (demographics, medical history and concomitant medications) with the Investigator.
- Subjects will be supplied with cs1002 or Bell's simple linctus according to randomisation.
- Subjects will complete baseline LCQ-acute and VAS assessments before their first dose of study drug.
- Subjects will start taking the study medication within 1 hour of completing their baseline assessments.

Days 2 to 8

- Subjects will take medication daily as directed and record when they have taken the study medicine in their patient diary.
- Subjects will complete an assessment of their symptoms and any additional medications taken.
- Subjects will complete the study assessment scales in the diary on a daily basis, whether they continue to take study medication or not.

Day 9 (End of study)*

- Subjects will meet with the Investigator to return all diary data and bottles, both used and unused, of study drug. Once these are returned the subject will have completed the study.
- If the cough has not resolved completely after 7 days, the subject will be advised to contact their own GP to be assessed.

* Day 9 (+2): If day 9 occurs on a day the Pharmacy / GP surgery is not open, the subject can arrange to return for their end of study assessments on the next Day that the Pharmacy / GP surgery is open (Day 10 or Day 11).

This study will be undertaken to allow the beneficial effectiveness of two OTC cough medicines to be assessed in a 'real-world' clinical practice setting using validated assessment tools.

The centre will be provided with identical looking tamper-evident, sealed boxes of similar weight, containing study medication. Subjects will be given a unique screening number at the

time of signing the informed consent. Once confirmed that they are eligible they will be given a unique randomisation number corresponding to one of the medication packs. The medication packs will remain sealed and only opened by the subjects after they have left the study centre. The IMP pack allocated to the patient will contain either cs1002 or Bells simple Linctus.

The subject will take their allocated study medication orally four times daily for 1-7 days provided they are still experiencing a cough.

Daily dosing will be as follows:

5ml morning dose

5ml lunchtime dose.

10ml teatime dose.

10ml bedtime dose.

The subjects will be given a diary to complete each day during their participation in the study. This will include specific questions on compliance as well as the assessment scales.

Safety will be monitored by asking subjects to keep a record in their diary of any adverse events (AE's) they experience during the study. The data from the subject's diaries regarding AE's will be uploaded by the Investigator within 24 hours of the subject returning the diary. Adverse events will be assessed by PharSafer Associates Ltd.

The primary efficacy endpoint is the change from baseline in cough severity based on VAS scores at Day 4 in subjects receiving cs1002 and Bell's simple linctus.

The secondary efficacy endpoints are a comparison of:

- Change from baseline in LCQ-acute score at Day 4, Day 6 and Day 8 in subjects receiving cs1002 and Bell's simple linctus.
- Change from baseline in cough frequency and sleep quality at Day 4, Day 6 and Day 8 in subjects receiving cs1002 and Bell's simple linctus.
- Change from baseline in cough severity at Day 6.
- AUC analysis of cough severity VAS, frequency VAS and sleep quality VAS from Days 1 to 8 in subjects receiving cs1002 and Bell's simple linctus.

- Time to resolution of cough symptoms defined as the day at which cough severity is < 17mm in subjects receiving cs1002 and Bell's simple linctus.

The primary efficacy endpoint cough severity will be assessed using a 100 mm VAS where 0 = no cough and 100 = worse cough ever. Visual analogue scales of this type have been previously validated for assessing acute cough [15].

The frequency of cough and the impact of cough on sleep disruption will be evaluated using Visual analogue scales.

The LCQ-acute will be used to evaluate cough related quality of life measures. The LCQ-acute is a fully validated scale that assesses 19 aspects of cough divided into three domains (physical, psychological and social). It was specifically designed to assess subject experience within a 24 hour time frame making it suitable for use in the present short term study [8]. An evaluation of the scale showed that subjects are able to complete the questionnaire without difficulty usually in less than 5 minutes.

A longitudinal assessment of measures used to assess acute cough [15] concluded that VAS and the LCQ-acute are both responsive tools for assessing changes during short term treatment validating their use in the present study.

Full details of these rating scales are provided in Appendix 2, 3, 4 and 5.

3.1 End of Study

Subjects will return all used and part used bottles, including the re-sealed outer IMP pack box, to the Investigator who will weigh the bottles and the outer IMP pack box to assess compliance.

Subjects who provide a complete set of data and return their patient diary and used bottle of study medication at the end of the study will receive £25 as reimbursement for their participation in the study (paid by Infirst+ HEALTHCARE).

For Pharmacist investigators: If the subject is still symptomatic of their cough the Investigator will advise the subject to visit their GP.

For GP Investigators: If the subject is still symptomatic of their cough the Investigator will continue to provide routine clinical care.

Final analysis is planned when all subjects have completed the study.

4. STUDY POPULATION

4.1 Overview of Target Population

A total of approximately 180 subjects will be enrolled into this study. The study will be run in up to 30 Centre's within the UK. The Centre's will consist of both GP surgeries and Pharmacies.

The Target population will consist of subjects who self-refer to a GP or Pharmacist, with a new onset acute cough, with a maximum of 7 days duration and a severity of at least 60 mm on a 0–100 mm visual analogue scale (VAS) and providing the cough is not associated with any serious underlying medical condition or contraindicated for this study.

Subjects will be allocated to treatment using a computer generated randomisation scheme.

4.1.1 Recruitment Procedures

To raise awareness of the study and provide opportunity for subjects to join the study a poster will be displayed in the reception area of the GP surgery or Pharmacy. Information about the study will also be available in a leaflet form.

Subjects who self-refer to the GP or Pharmacist with a cough, will be asked whether they would like to be involved in the study. If they would like more information, the Investigator will discuss the study with the subject to establish eligibility.

4.2 Enrolment Criteria:

Subjects must fulfil all of the following criteria at enrolment:

4.2.1 Inclusion Criteria

1. Male or female subjects aged 18 years or over.
2. Subject has self-referred to the GP or Pharmacist owing to a new onset acute cough with a maximum of 7 day's duration and a severity of at least 60 mm on a 0–100 mm visual analogue scale (VAS).
3. Willing and able to give informed consent and of complying with the study assessments and any other study procedures.

4.2.2 Exclusion Criteria

1. Pregnant or lactating females.
2. Any relevant hospital stays of more than 2 days, within 6 months before the subject self-refers to the GP or Pharmacist (Day 1). NB: An example of a relevant hospital stay would be for respiratory conditions such as 'lung infection' or 'pneumonia'.

3. Current smokers and those who have smoked within the last two months. This includes the use of e cigarettes.
4. Taken any medication with a cough treatment designation for this cough (whether a prescription drug, an OTC drug or a natural herbal product (e.g. honey, eucalyptus etc.).
5. A productive cough with excessive secretions, regardless of colour.
6. Subjects requiring co-prescription with other treatments for coughs or colds. This includes subjects taking antibiotics.
7. Subjects with known hypersensitivity to any of the ingredients of the study medication.
8. Subjects with chronic cough (i.e. chronic bronchitis in smokers, gastro-oesophageal reflux, asthma, hyper-responsive airways after resolution of respiratory tract infection, COPD, pertussis, aspiration, tumour, tuberculosis or fungal infections).
9. Subjects with prostatic hypertrophy, urinary retention, susceptibility to closed-angle glaucoma, liver disease, fructose intolerance, glucose intolerance, glucose-galactose malabsorption, sucrose-isomaltase insufficiency.
10. Subjects taking monoamine oxidase inhibitors (MAOI) or having taken them within 14 days of entering the study and those requiring ongoing treatment with codeine, other anti-histamines, central nervous system depressants, other anticholinergic medicines (e.g. atropine), anti-psychotics or ACE inhibitors.
11. Treatment with any investigational drug agent during the 30 days before enrolment into the study.

4.3 Concomitant Medication and Treatment

The following interactions are possible with cs1002:

- Additive CNS depressant effects with CNS depressants including barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives and anti-psychotics. Co-prescription of these agents is not permitted during the study.
- Additive CNS depressant effects with alcohol. Alcohol consumption should be used with caution during the study.
- Additive anti-muscarinic effects with other drugs of similar properties such as atropine and some anti-depressants. Co-prescription of these agents is not permitted during the study.

- There is a risk of serotonin syndrome in subjects taking MAOIs or having taken within 14 days of study treatment. Co-prescription of these agents is not permitted during the study.
- Diphenhydramine can inhibit the oxidative metabolism of some drugs.
- Diphenhydramine may enhance the effects of ephedrine. Co-prescription of agents containing ephedrine is not permitted during the study.
- Diphenhydramine may mask the response of the skin to allergenic skin tests and also the ototoxic symptoms associated with certain antibiotics. Co-prescription of antibiotics is not permitted during the study.
- Citric acid may interact with potassium tartrate, carbonates and bicarbonates which therefore should not be administered at the same time.

Subjects will be asked to confirm all medications (prescription and over-the-counter drugs) taken within a 30 day period prior to study screening. The Investigator will record these on the electronic case report form at baseline.

This information will be self-reported by subjects unless the subject regularly collects their medications from the Investigator and thus can be cross checked on the Investigators systems.

4.4 Criteria for Premature Withdrawal of Subjects

The Investigator has the right to withdraw a subject from the study at any time. In addition, subjects have the right to voluntarily withdraw from the study at any time for any reason. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Subject withdrawal of consent at any time.
- Any medical condition that the Investigator or Sponsor determines may jeopardise the subject's safety if he or she continues in the study.
- The Investigator or Sponsor determines it is in the best interest of the subject.

An excessive rate of withdrawals can render a study non-interpretable; therefore, unnecessary withdrawal of subjects should be avoided. Should a subject decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible. Subjects who withdraw from the study will not be replaced.

All reasons for withdrawal must be documented.

4.5 Criteria for Premature Withdrawal Of Study and Centre

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Subject enrolment is unsatisfactory.

The Sponsor will notify the Investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study.

The Sponsor has the right to replace a centre at any time. Reasons for replacing a centre are listed in section 4.6.2.

4.6 Replacement Policy (Ensuring Adequate Numbers of Evaluable Subjects)

4.6.1 For Subjects

Subjects enrolled into the treatment phase of the study will not be replaced.

4.6.2 For Centre's

A centre may be replaced for the following administrative reasons:

- Excessively slow recruitment.
- Poor protocol adherence.
- Inaccurate or incomplete data recording.
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP), as applicable.

5. STUDY PROCEDURES AND ASSESSMENTS

5.1 Schedule of Assessments

The schedule of study procedures is provided in Table 1.

Clinical Study Protocol IFH-2014-004

Table 1: Schedule of Assessments during the study

Assessment	Study Day								
	1	2	3	4	5	6	7	8	9 [a]
Informed Consent	x								
Demographics	x								
Pregnancy Test[b]	x								
Medical History	x								
Cough history	x								
Concomitant Medications	x	x	x	x	x	x	x	x	
Minimum Severity VAS check for eligibility	x								
Eligibility screening form	x								
Cough severity VAS	x	x	x	x	x	x	x	x	
Cough frequency VAS	x	x	x	x	x	x	x	x	
Cough sleep disruption VAS	x	x	x	x	x	x	x	x	
LCQ acute	x			x		x		x	
AE Check Question		x	x	x	x	x	x	x	
Compliance check question		x	x	x	x	x	x	x	
Drug Dispensing	x								
Return of study medication									x
Return of Study Diary									x

[a] Day 9 (+2): If day 9 occurs on a day the Pharmacy / GP surgery is not open, the subject can arrange to return for their end of study assessments on the Day that the Pharmacy / GP Surgery re-opens (Day 10 or Day 11).

[b] Pregnancy Test: If there is a possibility the subject could be pregnant, they will be provided with a home test kit and given the option to return once they have confirmed they are not pregnant, provided they still fulfil all other eligibility criteria they can proceed in the study.

5.2 Day 1 Procedures and Assessments

5.2.1 Screening Examination and Eligibility Screening Form

Subjects will have self-referred to the Investigator with a new onset acute cough. The subjects will be provided with an initial brief introduction to the study using the introduction leaflet and an initial check will take place, asking the subjects how long they have had this cough for and establishing that the subject has a minimum cough severity score, using a severity VAS scale. If the subjects have had their cough for a maximum duration of 7 days and they have a minimum cough severity of at least 60mm, they will be asked if they want to discuss the study further. The subject will be given the PIS to read and the Investigator will discuss this with them. If agreeable the subject signs the informed consent form.

All subjects will be evaluated at their initial presentation to the Investigator to exclude the requirement for emergency treatment. The Investigator will use their experience and expertise, as per their routine clinical practice, to establish whether the patient should seek immediate medical attention and refer them accordingly.

Subjects who fulfil all the inclusion and exclusion criteria will be accepted into the study. The Investigator will confirm the eligibility of the subject to participate in the study.

All subjects must provide written informed consent before any study specific assessments or procedures are performed. An Eligibility Screening Form (ESF) documenting the investigator's assessment of each screened subject with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator. A screen failure log must be maintained by the investigator.

After signing an Informed Consent Form (ICF) the following information will be collected:

1. Demography (age, gender, ethnicity).
2. Brief relevant medical history (smoking history, history of any medical conditions and concomitant medications).
3. Cough history (duration, type of cough and any treatment received).

Each eligible subject will be provided with a diary and 'subject card' containing details of a 24 hour emergency contact number. They will be instructed that in the event of an emergency they should tell the medical staff treating them that they are participating in the study and the medical staff can then call the contact number to liaise with the PharSafer safety team.

The subject cannot take part in this study if there is any possibility they are pregnant. This will be self-reported. If there is a possibility the subject could be pregnant, they will be provided with a home test kit and given the option to return once they have confirmed they are not pregnant, provided they still fulfil all other eligibility criteria they can proceed with the study.

The subjects will be asked to complete the following and before their first dose of study medication.

- Cough severity VAS.
- Cough frequency VAS.
- Cough sleep disruption VAS.

- LCQ-acute.

The Investigator will provide the subject with the study IMP pack in a **sealed package**. This will contain either cs1002 (2 x 150 ml) or simple linctus (2 x 150 ml), according to a pre-defined computer generated, subject randomisation list. This pack will be weighed on the study-calibrated, validated scales and this weight will be documented in the eCRF.

Subjects will be instructed to ensure that they **re-seal** the used study IMP medication box before they return it to their Investigator.

The subject will be asked to start taking the study medication within 1 hour of completing the baseline assessments and advised to continue taking the cough medication four times a day, provided they are still experiencing a cough. Daily dosing will be as follows:

5ml morning dose

5ml lunchtime dose.

10ml teatime dose.

10ml bedtime dose.

Where the subject does not continue taking the study medication for the duration of the study, if their cough has stopped for example or they are experiencing unacceptable adverse effects, they will still be asked to complete all assessments.

The Investigator will instruct the subject on which dose they should start taking and record this in the patient diary; this is dependent on the time of day they complete their baseline assessments. The Investigator will also specify what would be the day and time of the last dose the subject could take on the study and record this in the patient diary. For example: a patient completing their baseline questionnaires at 11am would take a 5ml lunchtime dose as their first dose on Day 1; they would then be instructed that the last dose they could take would be a 5ml lunchtime dose on Day 8.

An appointment will be made for the subject to return on Day 9.

For Pharmacist investigators: An approved letter will be sent to the subjects GP notifying them of their participation, listing the exclusion criteria.

The Investigator will register the subject and transcribe the subject's information into the study electronic case report form (eCRF) on Day 1.

The subject will be offered a text message reminder service. This is a voluntary service initiated by the subject via their mobile phone on day 1. The service reminds subjects to complete their questionnaires at the same time every day.

5.2.2 Days 2 to 8 Procedures and Assessments

The subject will be asked to complete the following questionnaires at the same time of day that they completed the initial baseline assessments.

- Cough severity VAS (daily).
- Cough frequency VAS (daily).
- Cough sleep disruption VAS (daily).
- Compliance question (daily).
- AE question (daily).
- LCQ-acute (Days 4, 6 and 8).

If agreeable, the subject will be sent a text message to remind them to complete the assessments at the same time every day as a prompt.

5.2.3 At the end of the study (Day 9)

The subject will return their used bottles of medication in the medication box and completed diary to the Investigator at a pre-arranged appointment time on Day 9.

For Pharmacist investigators: If the subject is still symptomatic of their cough the Investigator will advise the subject to visit their GP.

For GP Investigators: If the subject is still symptomatic of their cough the Investigator will continue to provide routine clinical care.

If the subject has provided a complete set of diary data (i.e. a minimum of a VAS score for cough severity at Day 4 and LCQ-acute scores at Day 4) they will receive a compensation of £25.

The Investigator will upload the diary information into the eCRF within 24 hours of receipt. The LCQ-acute and the completed VAS scores will be sent via courier to the coordinating data centre.

6. INVESTIGATIONAL MEDICINAL PRODUCT

cs1002 is provided in 150 ml bottles containing a brown syrup solution for oral administration.

Each 5 ml dose contains diphenhydramine (14 mg), levomenthol (1.10 mg) and ammonium chloride (135 mg). The three active components are formulated with excipients and with a cocoa flavour.

Excipients include: sucrose, propylene glycol, nipastat (preservative system), sodium citrate, glycerine, cocoa flavour, purified water.

6.1 Dose and Schedule of IMP: cs1002

cs1002 will be administered orally 4 times daily from Day 1 to 8:

5ml morning dose

5ml lunchtime dose.

10ml teatime dose.

10ml bedtime dose.

If the subject stops coughing they should stop taking their study cough medication.

Refer to Section 6.4 for dose modifications.

The subjects will return the used and part used bottles in the re-sealed package to the Investigator who will weigh the bottles to assess compliance.

The Investigator will instruct the subject on which dose they should start taking; this is dependent on the time of day they complete their baseline assessments. The Investigator will also specify what would be the last dose the subject could take on the study and record this in the patient diary.

6.2 Comparator: Bells Simple Linctus

Bell's simple linctus is provided in 150ml bottles containing a clear, colourless syrup solution with the flavour of anise for oral administration.

Each 5ml dose contains Citric Acid Monohydrate (125mg)..

Excipients include: sucrose, water, polysorbate 20, star anise oil.

6.3 Dosage and Administration of Comparator: Bells Simple Linctus

Bell's simple linctus will be administered orally 4 times daily from Day 1 to 8 as follows:

5ml morning dose

5ml lunchtime dose.

10ml teatime dose.

10ml bedtime dose.

If the subject stops coughing they should stop taking their study cough medication.

Refer to Section 6.4 for dose modifications.

The subjects will return the used and part used bottles to the Investigator who will weigh the bottles to assess compliance.

The Investigator will instruct the subject on which dose they should start taking; this is dependent on the time of day they complete their baseline assessments. The Investigator will also specify what would be the last dose the subject could take on the study and record this in the patient diary.

6.4 Dose Modifications

The most common adverse effects of the active components in cs1002 include CNS effects such as nervous drowsiness (usually diminishes within a few days), paradoxical stimulation, nervous headache, nervous psychomotor impairment; anti-muscarinic effects such as urinary retention, dry mouth, blurred vision, gastrointestinal disturbances and thickened respiratory tract secretions.

Rare side adverse effects of the active components in cs1002 include hypotension, extrapyramidal effects, dizziness , confusion, depression, sleep disturbances, tremor, convulsions, palpitation, arrhythmia, hypersensitivity reactions, blood disorders and liver dysfunction.

The subject will be advised that should they experience unacceptable adverse effects from the study medication they can reduce the dose from 10mls to 5mls. If the unacceptable adverse effects continue they should stop taking the medication.

Specific Dose Guidance

Drowsiness is a known adverse effect of diphenhydramine. Subjects that cannot tolerate a 10ml dose at teatime are advised to reduce this dose from 10mls to 5mls initially and continue with the 10ml bedtime dose.

Subjects that have unacceptable drowsiness adverse effects on a 5ml dose are advised to stop taking the cough medication during the day time, and take 5mls at night.

In the event that this does not reduce the adverse effects to an acceptable level for the subject, the subject is advised to stop taking the study medication. The subject must continue to record all doses of medication taken in the diary provided and is encouraged to contact the safety helpline if they have any concerns.

6.5 Formulation, Packaging and Labelling

All study treatment will be labelled in accordance with current regulatory guidance.

All subjects identified as eligible and who have signed a consent form will be randomised and provided with the study IMP pack in a **sealed package**.

The principal Investigator has overall responsibility for ensuring that study treatment is received and managed in accordance with the protocol and GCP.

For Pharmacist investigators: The study treatments will be dispensed by a qualified pharmacist, any delegation by the Principal Investigator to another Pharmacist at the Pharmacy centre, must be documented.

For GP investigators: The study treatment may be dispensed directly by the GP Investigator in accordance with the applicable regulatory requirements. The GP Investigator may delegate the responsibility for dispensing the IMP to a local pharmacist.

The Investigator or appropriately delegated pharmacist will be responsible for entering the subject number on the study treatment at the time of dispensing.
The Sponsor will be permitted upon request to audit the supplies storage and dispensing procedures and records.

6.6 Accountability and Assessment of Compliance

A sealed IMP pack will be supplied to all eligible subjects who have consented to take part. This pack will be weighed on the study-calibrated, validated scales when dispensed and this weight will be documented in the eCRF

Subjects will be advised **not** to open the IMP pack whilst in the pharmacy or GP surgery.

Subjects will be instructed to ensure that they have resealed the used study IMP pack before they return to their GP surgery or Pharmacy.

Subjects will be asked to complete a compliance check question in the diary on a daily basis and return all used and unused containers on Day 9 after the end of the 7 day treatment period as a measure of compliance.

The returned IMP pack will be weighed on the same study calibrated validated scales and this will be documented in the eCRF for compliance.

6.7 Destruction of the IMP and comparator

At the end of the study, after all drug accountability has been completed and the last patient has completed the study, all used and unused study treatment packs will be destroyed on site, following approval of the site's local drug destruction policy. If the site is unable to destroy on site, used and unused treatment pack will be shipped back to a nominated contractor for destruction on behalf of Infirst^{+} HEALTHCARE.

Local or institutional regulations may require immediate destruction of used investigational product for safety reasons. In these cases, it may be acceptable for investigational site staff to destroy dispensed investigational product before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned and destroyed. Written authorization must be obtained from the sponsor before destruction.

6.8 IMP Unblinding

The IMP is blinded to the Investigator only.

If for any reason the Investigator does not remain blinded to the IMP, the Investigator must inform the study team immediately.

Should it become necessary to break the blind to the Investigator on the grounds of safety, the Investigator will contact the safety centre on the 24 hour telephone safety line (Telephone: +44 1483 212151).

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 Adverse Events

7.1.1 Clinical AEs

An Adverse Event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and

unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adverse Event data will be collected in the patient diaries from the first dose of study medication through to the end of day 8. Any adverse events reported to the investigator after this time in relation to the study drug would be reported by the Investigator to the Sponsor through spontaneous reporting.

7.1.2 Serious Adverse Events (SAEs)

A Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires in subject hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect
- Medically Significant Events (IMEs)

The study will comply with all local regulatory requirements and adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A.

Serious Adverse Event data will be collected from the first dose of study medication through to resolution of the SAE. Any adverse events reported to the investigator after this time in relation to the study drug would be reported by the Investigator to the Sponsor through spontaneous reporting.

In case of urgent safety queries please contact:

Principal Contact	Dr Sunita Chauhan (PharSafer)
Address	PharSafer House, White Hart Meadow, Ripley, Surrey, GU23 6ND, UK
Phone (24 hours)	+44 1483 212151
Fax	+44 1483 212178
E-mail	drugsafety@pharsafer.com

This study will be conducted in the UK only and therefore follow UK reporting requirements.

7.2 Warnings and Precautions

cs1002 is contraindicated in:

- Subjects who are hypersensitive to any of the ingredients.
- Subjects receiving ongoing treatment with codeine or anti-histamines.
- Subjects receiving central nervous system depressants, other anticholinergic medicines (e.g. atropine) or anti-psychotics.
- Subjects receiving MAOI therapy within the previous 14 days prior to consent.
- Subjects receiving ACE inhibitors.

The following warnings and precautions should be adhered to:

- Do not combine with other treatments for coughs and colds (whether a prescription drug, an OTC drug or a natural herbal product (e.g. honey, eucalyptus etc.).
- Diphenhydramine can cause drowsiness. If affected, subjects should be advised not to drive or operate machinery.

Excipient Warnings:

- Glycerol may cause headache, stomach upset and diarrhoea.
- Parahydroxybenzoates may cause allergic reactions (possibly delayed) and exceptionally bronchospasm.
- Propylene Glycol may cause intoxication similar to that produced by alcohol consumption. Subjects are therefore advised to take any alcohol with caution.
- It is possible that citric acid ingested in large quantities or frequently may cause gastric irritation, or erosion of dental enamel.

Bells Simple Linctus contraindications:

- Subjects who are hypersensitive to any of the ingredients.

Warnings

- Product contains sucrose; this should be taken into account in patients with diabetes mellitus. Patients with hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isolatase insufficiency should not take this medicine.
- It is possible that citric acid ingested in large quantities or frequently may cause gastric irritation, or erosion of dental enamel.

8. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a randomised, single-blind, active-controlled, multicentre study to compare cs1002 to Bell's simple linctus.

8.1 Analysis Sets

Treated set (TS): The treated set will consist of all subjects who were randomised and treated with at least one dose of study drug. This set of subjects will be used for the assessment of safety.

Full analysis set (FAS): The full analysis set will consist of all randomised subjects who were treated with at least one dose of study drug and had a baseline assessment of cough severity. This set of subjects will be used for the primary assessment of efficacy.

Per protocol set (PPS): The per protocol set will consist of all randomised subjects included in the FAS that did not have an important protocol violation. This set of subjects will be used for a supportive assessment of efficacy. Examples of important protocol violations are:

- Violations of eligibility criteria that may impact on efficacy or safety.
- Treatment non-compliance as per Protocol.
- Prohibited medication use.
- Incorrect trial medication taken (mis-randomisation).
- Insufficient efficacy data

Further details on the definition of the PPS will be provided in the Statistical Analysis Plan (SAP) prior to unblinding.

8.2 Null and Alternative Hypotheses

The confirmatory analysis will compare cs1002 to Bell's simple linctus with respect to the primary endpoint of change from baseline to Day 4 in cough severity, in the FAS. The null hypothesis of no difference in cough severity between the two treatment groups will be tested at a two-sided alpha-level of 5%. The alternative hypothesis is that there is a difference in cough severity between the two treatment groups. If the null hypothesis can be rejected in favour of the alternative hypothesis the observed difference between the treatment groups will be considered statistically significant.

All statistical testing will be two-sided and performed at the 5% significance level. Where appropriate, p-values will be supported with 95% confidence intervals (CIs) to help describe the magnitude and precision of treatment effect estimates.

As the confirmatory analysis is based on a single treatment group comparison for a single endpoint no alpha adjustment for multiplicity is required.

8.3 Planned Analysis

8.3.1 Primary Analysis

A mixed model for repeated measures (MMRM) analysis will be used to test the effect of cs1002 on the change from baseline to Day 4 in cough severity compared to Bell's simple linctus. All cough severity data recorded during the study will be included in the model. The model will include effects for treatment group, daycentre (pooled if necessary), baseline cough severity and the treatment by day and treatment by baseline cough severity interaction terms. The adjusted treatment group difference at Day 4 and corresponding 95% CI will be presented along with the p-value. In the absence of missing data the MMRM analysis equates to the corresponding analysis of covariance (ANCOVA).

A sensitivity analysis will be performed to examine whether treatment effects are dependent upon centre by including a treatment by centre interaction term in the model. If the interaction term is found to be statistically significant ($p<0.05$) further investigation into the source of the interaction will be performed and appropriate measures taken.

Residual plots and a normality test will be used to assess normality assumptions. If normality assumptions are not met then an appropriate transformation (e.g. log transformation) or non-parametric analysis will be used

If pooling of centres is required, a detailed strategy for pooling will be determined in a blinded fashion and detailed in the Statistical Analysis Plan (SAP).

The primary analysis will be performed on the FAS with a supportive analysis performed on the PPS to help assess the robustness of the primary analysis.

Exploratory subgroup analyses will be performed on the FAS only for the following subgroups:

- Self-diagnosed type of cough (chesty, dry or tickly).
- Gender.
- Age.
- Referral (GP, Pharmacist).

Other subgroups may be identified in the SAP prior to unblinding.

8.3.2 Secondary Analyses

The following secondary analyses will be performed:

Leicester Cough Questionnaire

The changes from baseline to Day 4, Day 6 and Day 8 in the LCQ acute score and each individual domain (physical, psychological and social) will compared across the treatment groups using the same analysis methodology as for the primary analysis.

Cough Frequency

The change from baseline to Days 4, 6 and 8 in cough frequency will be compared across the treatment groups using the same analysis methodology as for the primary analysis.

In addition the area under the curve (AUC) for cough frequency across Days 1 to 8 will be compared across the treatment groups using the same MMRM as above.

Cough Severity

The change from baseline to Day 6 in cough severity will be compared across the treatment groups using the same analysis methodology as for the primary analysis.

In addition the AUC for cough frequency across Days 1 to 8 will be compared across the treatment groups using the same MMRM as above. The proportion of patients with resolution

of cough severity, defined as the first day at which the severity score is <17 mm will be displayed by each day of the study. These data will be compared across treatment groups using a stratified (by centre) Cochran-Mantel-Haenszel test. In order to include all patients in the analysis, those with no resolution of symptoms during Days 1 to 8 will be included in a separate category ordered after Day 8. If analytical assumptions hold a more formal time to event analysis via a Cox proportional hazards model and log-rank test will be used as an alternative.

Sleep Disruption

The AUC for sleep disruption across Days 1 to 8 will be compared across the treatment groups using the same MMRM analysis as above.

8.3.3 Safety Analyses

All treated subjects will be included in the safety analysis. In general, safety analyses will be descriptive in nature, no hypothesis testing is planned.

AEs will be coded according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The frequency of subjects with AEs will be summarised by maximum severity, treatment, primary system organ class (SOC) and preferred term (PT) for each of the following AE tables:

- All AEs.
- Drug related AEs.
- AEs leading to treatment discontinuation.
- Serious AEs.

All AEs recorded during the on-treatment period will be summarised.

8.3.4 Interim Analysis

Due to the uncertainty in the variability assumed in the sample size calculation (see Section 8.5) a blinded estimation of variation will be performed when approximately 50% of subjects have received 3 days of treatment (Day 4 of the study). The estimation will be made on any available primary endpoint data at this time; it will be done in a blinded fashion pooling the data across treatment groups. As no unblinding is occurring and only the pooled variability is being estimated the overall type I error rate (5%) is preserved and no adjustment is required.

No decrease in the planned sample size will be performed even if the estimated variability is lower than that assumed in the original calculation. In order to preserve the power of the study the planned sample size will only be increased if the interim estimate of variability is more than 5 mm above that in the sample size estimation.

8.4 Handling of Missing Data

Every effort will be made to collect complete efficacy data from all randomised subjects and given the short study duration the degree of missing data is expected to be relatively low. Descriptive summaries of efficacy data will be produced on non-missing data only so that the degree of data completion across the treatment groups can be easily assessed.

The main efficacy analyses will use an MMRM approach to analysis, for these analyses information from the observed outcomes (non-missing data) are used to provide information about the unobserved outcomes (missing data), so missing data is not an issue.

To assess the robustness of the primary efficacy results to the method of handling missing data a sensitivity analysis will be performed using ANCOVA methodology. For this analysis subjects with a missing cough severity score at Day 3 will have their last on-treatment assessment prior to Day 4 carried forward.

8.5 Determination of Sample Size

The sample size is based on being able to claim superiority of cs1002 over Bell's simple linctus; in terms of the change from baseline to Day 4 in cough severity. For this endpoint superiority is defined as a difference of at least 17 mm between subjects treated with cs1002 and those treated with Bell's simple linctus.

There is uncertainty in the standard deviation for cough severity with literature suggesting it could be somewhere between 25 and 35 mm[15]. Table 2 presents the number of evaluable subjects required per treatment group to detect a difference between the treatment groups of 17 mm using a two-sided 5% alpha-level with 90% power, for a selection of standard deviations.

Table 2: Sample Sizes for Testing Cough Severity (FAS)

Alpha (2-sided) [%]	Power [%]	SD=25	SD=30	SD=35
5	90	47	67	91

Approximately 180 subjects will be randomised in order to achieve a power of 90% for detecting a difference between the treatment groups of 17 mm with a common standard deviation of 35 mm.

Sample size calculations are based on an allocation ratio between treatment groups of 1:1 and were derived using nQuery Advisor (version 7).

9. DATA COLLECTION, MANAGEMENT AND QUALITY ASSURANCE

Subject data will be collected by the investigator using electronic Case Report Forms (eCRFs) as part of the Medrio™ data management system.

Quality of Life questionnaires and VAS scores will be completed by the Subject on paper and entered into Medrio by the Investigator and Exp-e-Data (UK) data entry staff.

Discrepancy checks will be programmed according to definitions in the Data Handling Manual and data queries will be generated during the data entry process in order to confirm the validity, consistency and completeness of the data.

10. ETHICAL ASPECTS

10.1 Local Regulations/Declaration of Helsinki

This study will be conducted in full conformance with the principles of the "Declaration of Helsinki (sixth revision 1996)". The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997). The investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC) and the protocol. In addition the study will adhere to all local regulatory requirements.

10.2 Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain written informed consent from each subject participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. Due to the nature of the study, using OTC medication, it will be acceptable for consent to be taken on the day the subject self refers to the Investigator.

The Case Report Forms for this study contain a section for documenting informed subject consent, and this must be completed appropriately by the Investigator. If new safety information results in significant changes in the risk benefit assessment, the consent form should be reviewed and updated if necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

10.3 Independent Ethics Committees (IEC)

This protocol and any accompanying material provided to the subject (such as subject information sheets or descriptions of the study used to obtain informed consent) as well as any advertising or compensation given to the subject, will be submitted by the investigator to an Independent Ethics Committee. Approval from the committee must be obtained before starting the study, and should be documented in a letter to the investigator specifying the date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of the Independent Ethics Committee approval must also be submitted by the investigator to the Committee in accordance with local procedures and regulatory requirements.

10.4 Financial Disclosure

The investigator(s) will provide the Sponsor with sufficient accurate financial information by completing a Financial Disclosure Form to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The investigator is responsible to promptly update any information provided to the Sponsor if relevant changes occur in the course of the investigation and for 1 year following the completion of the study (last subject, last visit).

11. CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between an appropriate representative of the sponsor and the investigator. Protocol modifications must be prepared by a representative of the sponsor and initially reviewed and approved by the Medical Manager and Biostatistician.

All protocol modifications must be submitted to the appropriate Independent Ethics Committee for information and approval in accordance with local requirements, and to Regulatory Agencies

if required. Approval must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g. change in monitor(s), change of telephone number(s).

12. CONDITIONS FOR TERMINATING THE STUDY

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures to be put in place on an individual study basis after review and consultation. In terminating the study, the sponsor and the investigator will ensure that adequate consideration is given to the protection of the subject's interests.

13. STUDY DOCUMENTATION, CRFS AND RECORD KEEPING

13.1 Investigator Files/Retention of Documents

Records and documents pertaining to the conduct of this study, including eCRFs, PRO data, Informed Consent Forms, clinical or hospital charts, laboratory test results, and medication records, must be retained by the principal Investigator after completion or discontinuation of the study, or for the length of time required by the sponsor, relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

13.2 Source Documents and Background Data

Study monitors will perform ongoing data review including source document verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorised centre personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which subject data are recorded and documented for the first time. They include, but are not limited to, subject reported outcomes, evaluation checklists, copies of transcriptions that are certified after verification as being accurate and complete, subject files and records kept at pharmacies.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 13.1.

To facilitate source data verification, the Investigators and institutions must provide Infirst+ HEALTHCARE or their designee access to applicable source documents and reports from study related monitoring, Sponsor audits, and IRB/EC review.

13.3 Case Report Forms or Electronic Case Report Forms

For each subject enrolled, an Electronic Case Report Form must be completed by the Investigator or an authorized delegate from the centre staff.

All Data will be held in compliance with all appropriate EU and FDA Statutes, Directives and Guidelines.

13.4 Confidentiality of study Documents and Subject Records

Data collected during this study may be used to support the development, registration or marketing of cs1002. InFirst+ HEALTHCARE will control all data collected during the study, and will abide by the EU Directive on Data Privacy concerning the processing and use of patients' personal data. For the purpose of data privacy legislation, InFirst HEALTHCARE will be the data controller.

After patients have consented to take part in the study their medical records and the data collected during the study will be reviewed by InFirst HEALTHCARE and/or its representatives. These records and data may, in addition, be reviewed by the following: independent auditors who validate the data on behalf of InFirst HEALTHCARE; third parties with whom InFirst HEALTHCARE may develop, register or market cs1002 national or local regulatory authorities and the IRB(s)/IEC(s) which gave their approval for this study to proceed.

Although patients will be known by a unique number, their initials and date of birth may also be collected and used to assist InFirst+ HEALTHCARE to verify the accuracy of the data. The results of this study containing the unique number, initials, date of birth and relevant medical information including ethnicity may be recorded and transferred to and used in other countries

throughout the world, which may not afford the same level of protection that applies within the EU. The purpose of any such transfer would be to support regulatory submissions made by InFirst HEALTHCARE in order to market cs1002 in other countries.

13.5 Audit / Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the UK Medicines and Healthcare products Regulatory Agency (MHRA), InFirst HEALTHCARE or its representatives, interested commercial parties and the IRB/IEC for each study site.

14. INDEMNITY / LIABILITY AND INSURANCE

Infirst+ HEALTHCARE will adhere to the recommendations of the Association of British Pharmaceutical Industry (ABPI) Guidelines. If appropriate, a copy of the Indemnity document will be supplied to the Investigator before study initiation. Infirst+ HEALTHCARE will ensure that suitable insurance cover is in place prior to the start of the study. An insurance certificate shall be supplied to the monitoring CRO.

15. CLINICAL STUDY REPORT (CSR)

A clinical study report will be written and distributed to Health Authorities and Independent Ethics Committee as required by applicable regulatory requirements.

16. PUBLICATION POLICY

All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by Infirst+ HEALTHCARE, in advance of submission. The review is aimed at protecting Infirst+ HEALTHCARE's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results or other information, generated or created in relation to the study shall be set out in the agreement between each Investigator and the CRO/ Infirst+ HEALTHCARE.

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18. APPENDICES

18.1 Appendix 1 Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Recommendations guiding physicians
in biomedical research involving human subjects
Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected. Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8 In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible

to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE
(Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

18.2 Appendix 2 Leicester Cough Questionnaire for Acute Cough (LCQ-acute)

This Questionnaire must only be used for reference only and not photocopied for subject use.

This questionnaire is designed to assess the impact of cough on various aspects of your life. Read each question carefully and answer by CIRCLING the response that best applies to you. Please answer ALL questions, as honestly as you can.

1. In the last 24-hours, have you had chest or stomach pains as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

2. In the last 24-hours, have you been bothered by sputum (phlegm) production when you cough?

1	2	3	4	5	6	7
Every time	Most times	Several times	Some times	Occasionally	Rarely	Never

3. In the last 24-hours, have you been tired because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

4. In the last 24-hours, have felt in control of your cough?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time

5. How often during the last 24-hours have you felt embarrassed by your coughing?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

6. In the last 24-hours, my cough has made me feel anxious

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

7. In the last 24-hours, my cough has interfered with my job, or other daily tasks

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

8. In the last 24-hours, I felt that my cough interfered with the overall enjoyment of my life

1	2	3	4	5	6	7

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

9. In the last 2 weeks, exposure to paints or fumes has made me cough

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

10. In the last 24-hours, has your cough disturbed your sleep?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

11. In the last 24-hours, how many times have you had coughing bouts?

1	2	3	4	5	6	7
All the time (continuously)	Most times of during the day	Several times during the day	Some times during the day	Occasionally through the day	Rarely	None

12. In the last 24-hours, my cough has made me feel frustrated

1	2	3	4	5	6	7
All of the time	Most of	A good bit	Some of	A little of the	Hardly any	None of

	the time	of the time	the time	time	of the time	the time

13. In the last 24-hours, my cough has made me feel fed up

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

14. In the last 24-hours, have you suffered from a hoarse voice as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

15. In the last 24-hours, have you had a lot of energy?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time

16. In the last 24-hours, have you worried that your cough may indicate a serious illness?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

17. In the last 24-hours, have you been concerned that other people think something is wrong with you, because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

18. In the last 24-hours, my cough has interrupted conversation or telephone calls

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

19. In the last 24-hours, I feel that my cough has annoyed my partner, family or friends

1	2	3	4	5	6	7
Every time I cough	Most times when I cough	Several times when I cough	Some times when I cough	Occasionally when I cough	Rarely	Never

Thank you for completing this questionnaire.

LCQ Scoring

1. Domains (questions):

Physical: 1,2,3,9,10,11,14,15

Psychological 4,5,6,12,13,16,17

Social: 7,8,18,19

2. Domain Scores: total score from items in domain / number of items in domain (range 1–7)

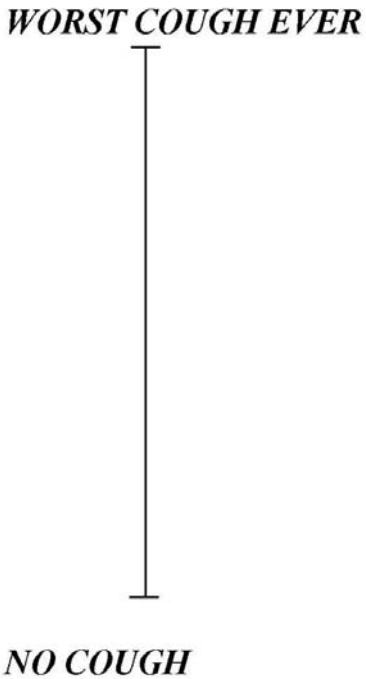
3. Total Scores: Addition of domain scores (range 3–21)

18.3 Appendix 3 Cough Severity Visual Analogue Scale

This Visual Analogue Scale must only be used for reference only and not photocopied for subject use.

Cough Severity Visual Analogue Scale

Please put a cross on the line to indicate the severity of your cough in the past 24-hours.



18.4 Appendix 4 Cough Frequency Visual Analogue Scale

This Visual Analogue Scale must only be used for reference only and not photocopied for subject use.

Cough Frequency Visual Analogue Scale

Please put a cross on the line to indicate how often you coughed in the past 24-hours.

COUGHED CONSTANTLY

NEVER COUGHED

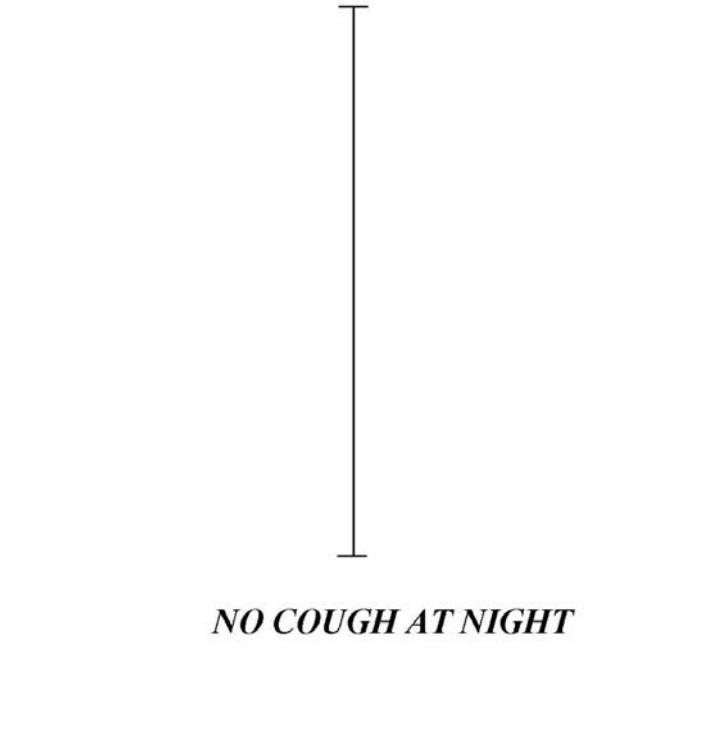
18.5 Appendix 5 Cough Sleep Disruption Visual Analogue Scale

This Visual Analogue Scale must only be used for reference only and not photocopied for subject use.

Cough Sleep Disruption Visual Analogue Scale

Please put a cross on the line to indicate how much your cough disrupted your sleep in the past 24-hours.

COUGH DISRUPTED MY SLEEP ALL NIGHT



NO COUGH AT NIGHT

Clinical Study Protocol IFH-2014-004

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Yes
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Page 2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Pages 5 and 6
	2b	Specific objectives or hypotheses	Page 6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Page 8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	4a	Eligibility criteria for participants	Page 7
	4b	Settings and locations where the data were collected	Page 7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Pages 8 and 9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Pages 9 and 10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	Page 10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Page 8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Page 8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Page 8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Pages 8 and 22

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Page 9
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Pages 10 and 11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Page 28
	13b	For each group, losses and exclusions after randomisation, together with reasons	Page 28
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Page 7
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Page 12
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Page 14
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Pages 13, 14 and 15
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Pages 13, 14 and 15
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Pages 15 and 16
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Page 19
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Page 17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Pages 17, 18, 19 and 20
Other information			
Registration	23	Registration number and name of trial registry	Page 3
Protocol	24	Where the full trial protocol can be accessed, if available	Page 3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Page 21

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

THE ROCOCO STUDY: A REAL WORLD EVALUATION OF AN OVER THE COUNTER MEDICINE IN ACUTE COUGH (A MULTICENTRE, RANDOMISED, CONTROLLED STUDY)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014112.R2
Article Type:	Research
Date Submitted by the Author:	17-Nov-2016
Complete List of Authors:	Birring, Surinder; King's College London, Division of Asthma, Allergy and Lung Biology Brew, John; Infirst Healthcare Ltd Kilbourn, Tony; Infirst Healthcare Ltd Edwards, Viv; Infirst Healthcare Ltd Wilson, Rosamund; Spica Consultants Ltd Morice, Alyn; University of Hull, Dermatology
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	General practice / Family practice, Respiratory medicine
Keywords:	Controlled clinical trial, Cough, Demulcent, Diphenhydramine, Simple Linctus

JOURNAL: BMJ OPEN

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THE ROCOCO STUDY: A **R**EAL WORLD EVALUATION OF AN **O**VER THE **CO**UNTER MEDICINE IN ACUTE **CO**UGH (A MULTICENTRE, RANDOMISED, CONTROLLED STUDY)

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ABSTRACT

OBJECTIVES: To investigate the efficacy and safety of CS1002, an over-the-counter cough treatment containing diphenhydramine, ammonium chloride and levomenthol in a cocoa-based demulcent.

DESIGN: A multicentre, randomised, parallel group, controlled, single-blinded study in subjects with acute upper respiratory tract infection-associated cough.

SETTING: 4 GP surgeries and 14 pharmacies in the UK.

PARTICIPANTS: Subjects aged ≥18 years who self-referred to a general practitioner or pharmacist with acute cough of <7 days' duration. Subject inclusion criterion was cough severity ≥60mm on a 0-100mm visual analogue scale (VAS). Exclusion criteria included current smokers or history of smoking within the past 12 months (including e-cigarettes). 163 subjects were randomised to the study (mean subject age 38 years, 57% females).

INTERVENTIONS: Subjects were randomised to CS1002 (Unicough) or Simple Linctus (SL), a widely used cough treatment, and treatment duration was 7 days or until resolution of cough.

MAIN OUTCOME MEASURES: The primary analysis was intention-to-treat (157 subjects) and comprised cough severity assessed using a VAS after 3 days' treatment (pre-specified primary endpoint at Day 4). Cough frequency, sleep disruption, health status (Leicester Cough Questionnaire [LCQ-acute]) and cough resolution were also assessed.

RESULTS: At Day 4 (primary endpoint), the adjusted mean difference [95% confidence interval] in cough severity VAS between CS1002 and SL was -5.9mm [-14.4,2.7], p=0.18. At the end of the study (Day 7) the mean difference in cough severity VAS was -4.2mm [-12.2,3.9], p=0.31. CS1002 was associated with a greater reduction in cough sleep disruption (mean difference -11.6mm [-20.6,-2.7], p=0.01) and cough frequency (mean difference -8.1mm [-16.2,0.1], p=0.05) compared to SL. There was greater improvement in LCQ-acute

quality of life scores with CS1002 compared to SL: mean difference [95% CI] 1.2 [0.05,2.36], p=0.04 after 5 days' treatment. More subjects prematurely stopped treatment due to cough improvement in the CS1002 group (24.4%) compared to SL (10.7%; p=0.02). Adverse events were comparable between CS1002 (20.5%) and SL (27.6%) and largely related to the study indication. Six subjects (7%) in the CS1002 group reduced the dose of medication due to drowsiness/tiredness, which subsequently resolved. These events were not reported by subjects as AEs.

CONCLUSIONS: Although the primary endpoint was not achieved, CS1002 was associated with greater reductions in cough frequency, sleep disruption and improved health status compared to SL.

ABSTRACT WORD COUNT: 288 Words

TRIAL REGISTRATION: EudraCT number 2014-004255-31 protocol publically available at https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-004255-31/GB. The protocol was submitted to the MHRA in December 2014 prior to commencing the study (see attached MHRA approval letter containing the EudraCT number prior to commencing the study) but the MHRA were late in posting the study protocol into the EudraCT/clinical trials register database. No amendments were made to the protocol.

ARTICLE SUMMARY

Strengths and limitations of this study

- A recent Cochrane systematic review of cough medicines found no good evidence for or against the effectiveness of OTC medications in acute cough. .
- This is one of the largest multiple dosing, multi-centre, randomised, controlled trials in subjects with cough to date, and the first to recruit subjects seeking cough medicines at pharmacies and is therefore more likely to represent the broader population with acute cough due to upper respiratory tract infection.
- Subjects were unselected for the category of cough, and included a broad range of subjects with self-reported dry, chesty and tickly cough.
- The study was single-blinded because an active control, Simple Linctus, was used as the comparator but it is possible that there may have been greater differences in efficacy outcome measures if an inactive placebo had been used.
- Our findings highlight the challenges of evaluating cough medicines in a rapidly improving condition and will facilitate the design of future studies of acute cough.

INTRODUCTION

Approximately 1 in 5 people in the United Kingdom (UK) suffer an acute cough over the winter [1] and it is one of the most common reasons for consulting a general practitioner (GP), at a cost to the National Health Service (NHS) of approximately £2 billion per year.[2-4] Although most acute coughs improve spontaneously, many patients use over-the-counter (OTC) medicines. In 2014, £98.7 million was spent in the UK on OTC cough treatments.[5] OTC cough medicines include antitussives, expectorants, mucolytics, antihistamines, decongestants, and numerous drug combinations.[6] There is a lack of data supporting the efficacy of OTC medicines in the treatment of acute cough associated with upper respiratory tract infection (URTI). In 2012, a Cochrane systematic review concluded there was no strong evidence for or against their effectiveness.[6] Methodological flaws in clinical trial design, paucity of placebo-controlled trials, use of un-validated outcome measures, and inefficacy of medicines were some of the reasons for the poor evidence base.

CS1002 is an OTC cough medicine that contains 3 active ingredients: diphenhydramine, levomenthol, and ammonium chloride in a cocoa-based demulcent preparation. Diphenhydramine is an antihistamine that has been reported to reduce the heightened cough reflex sensitivity in subjects with cough associated with an URTI.[7] Menthol and eucalyptus have been used for many centuries for treating coughs and colds.[8] Menthol is obtained from mint oils, mainly peppermint, or made synthetically from coal tar. It has a pungent odour that provides a cooling and soothing effect in the mouth and throat and is often used to relieve congestion.[8] Menthol has also been reported to inhibit cough reflex sensitivity compared to placebo.[9] Ammonium chloride is an acid-forming salt that is thought to exert an expectorant effect by loosening sputum.[10] The effectiveness and mode of action of ammonium chloride remains controversial.[10] The cocoa-based demulcent preparation used

in CS1002 is more viscous than most available OTC cough medicines. Demulcents are thought to reduce cough and cold symptoms because of a soothing effect on the mucus membrane.[11] The aim of this study was to investigate the efficacy of CS1002, an OTC cough medicine for cough associated with URTI, in a randomised controlled trial.

METHODS

Study Design

This multicentre, randomised, parallel group, controlled, single-blinded study was conducted in 4 GP surgeries and 14 pharmacies in the UK between 30 December 2014 and 9 May 2015. The control was a widely used simple linctus (SL) medicine available for acute cough in the UK. The investigators were blinded to the nature of the investigational product by using identical sealed packaging for both medicines. Subjects self-administered their assigned medication outside the pharmacy or GP surgery.

Subjects

Subjects aged ≥18 years who self-referred themselves to a GP or pharmacist with an acute cough of less than 7 days' duration were recruited. Subject inclusion criterion was a severity of at least 60mm on a 0 to 100mm visual analogue scale (VAS). Subject exclusion criteria were (i) subjects with a chronic cough, (ii) current or history of smoking within the past 12 months (including e-cigarettes), (iii) subjects with any relevant hospital stay of >2 days within a 6-month period, (iv) use of any cough or cold treatment for the current cough episode, including antibiotics, (v) productive cough with excessive secretion, (vi) use of angiotensin converting enzyme (ACE) inhibitor medication.

Subject Involvement

Subjects were not involved in the design or conduct of this study.

Ethics and Trial Registration

The protocol was approved by the North West - Greater Manchester South Research Ethics Committee (Reference: 14/NW/1424). The trial protocol was registered prior to commencing

the study in the publically available EudraCT database (Reference: 2014-004255-31) and no protocol amendments were made subsequently. All participants provided written informed consent.

Randomisation

All subjects considered eligible for study participation and who signed a consent form were given a unique randomisation number based on a pre-defined computer-generated randomisation scheme corresponding to a sealed medication pack that contained either CS1002 (2x150mL) or SL (2x150mL). Subjects were allocated treatment using a block randomisation with a block size of 4.

Study Medication

Subjects were randomised to one of the following treatments:

- CS1002 (Unicough): diphenhydramine 14mg/5mL, levomenthol 1.1mg/5mL and ammonium chloride 135mg/5mL in a cocoa-based demulcent preparation.
- SL: citric acid monohydrate 125mg/5mL in a syrup base.

Interventions

The subjects were approached, screened, consented and randomised during their initial consultation with their GP or the pharmacist. Subjects took their study medication orally 4 times daily (5mL in the morning, 5mL at lunchtime, 10mL at teatime, and 10mL at bedtime) for up to 7 days. Subjects were instructed to take the medication regularly until the cough resolved.

Methods of Evaluation

Subjects completed their assessments and compliance with medication in a daily diary. Each subject received a tamper-evident unidentifiable patient pack which was only opened on leaving the site. On completion, the pack was returned in a resealed and unidentifiable state. An independent data management organisation was utilised for data entry and to manage adverse event (AE) reporting. The investigators were blinded to the assignment of treatment and to the outcome assessments. The schedule of study visits is presented in Figure 1. The subjects were asked to complete assessments at baseline (Day 1) and then at the same time of day from Day 2 to Day 8. The study evaluated the efficacy of the study medications by assessing various aspects of acute cough.[12] Cough severity, frequency, and impact on sleep disruption in the previous 24 hours were assessed using a VAS. Health related quality of life (HRQoL) was assessed using the Leicester Cough Questionnaire for acute cough (LCQ-acute).[3,13] The LCQ is a valid and reliable health status measure of acute cough in adults and is responsive to change. It comprises 19 items divided into 3 domains (physical, psychological and social) and uses a 7-point Likert response scale. A higher score indicates a better health status. The LCQ is designed for self-administration and takes less than 5 minutes to complete.[3,14]

Primary Efficacy Endpoint

The primary efficacy endpoint was change from baseline to Day 4 (i.e. after 3 complete days of treatment) in cough severity on a 100mm VAS (ranging from 0=no cough to 100=worst cough ever).

Secondary Efficacy Endpoints

The following pre-specified endpoints were evaluated: (i) change from baseline in cough severity VAS at Days 6 and 8, (ii) change from baseline in cough frequency and cough sleep disruption VAS at Days 4, 6 and 8, (iii) time to resolution of cough symptoms, defined as the day at which cough severity VAS <17mm (the threshold considered to be of minimal severity and the minimally important difference [MID] in acute cough),[12] (iv) change from baseline in LCQ-acute score at Days 4, 6 and 8.

Safety Monitoring

Subjects were advised to reduce the dose of medication if they experienced drowsiness, and to document this in their daily diary. If drowsiness persisted, they were advised to discontinue the medication. Subjects were advised to contact their doctor or a 24-hour help line if they felt unwell. Safety was assessed in terms of the frequency and severity of AEs occurring during the study and this was recorded by the investigator.

Statistical Analysis and Sample Size

The sample size calculation was based on a difference in the change in cough severity VAS of 17mm between subjects treated with CS1002 and SL. Evaluation of the VAS in acute cough has suggested that the MID is 17mm.[12] It was estimated that approximately 180 subjects would be required to achieve a power of 90% to detect a difference between the treatment groups of 17mm, with a standard deviation of 35mm.[12]

The primary analysis was conducted on the intention-to-treat (ITT) population, comprising all randomised subjects who were treated with at least one dose of study medication and provided a baseline and at least one on-treatment assessment of cough severity. No

imputation was used for missing data (i.e. only observed data was used). A mixed model for repeated measures (MMRM) analysis was used to compare the effect of study treatments on cough parameters from baseline. The model included effects for treatment group, day, pooled centre, baseline cough severity, and treatment-by-day and baseline-by-day cough severity interaction terms. Residual plots and a normality test were used to assess normality. The results were also repeated for the per-protocol set (PPS), defined as subjects in the ITT population who did not have an important protocol violation. A sensitivity analysis was also conducted to assess the robustness of the primary efficacy results to the method of handling missing data, using a last observation carried forward (LOCF) approach and a baseline observation carried forward (BOCF) approach for subjects with no on-treatment data. Parametric data was presented as mean and either standard deviation (SD), standard error of the mean (SEM), or 95% confidence intervals (95% CI). Statistical significance was defined as $p \leq 0.05$. The proportions of subjects with cough resolution were compared using a stratified (by centre) Cochran-Mantel-Haenszel test. Time-to-event analysis using a Cox proportional hazards model stratified by centre was used to estimate a hazard ratio.

RESULTS

Subjects

A total of 163 subjects were randomised into the study at 4 GP sites and 14 pharmacy sites. The reasons for screening failures are shown in Figure 2. The ITT population comprised 157 subjects (82 CS1002, 75 SL), and the PPS comprised 142 subjects (75 CS1002, 67 SL) (Figure 2). The baseline characteristics of both treatment groups were well-matched (Table 1). The mean age of the subjects was 38 years, 57% of subjects were female, and 62% of subjects were white (34% Asian and 4% black). The groups were well-matched for the proportion of subjects describing the characteristics of their cough as dry (CS1002 50%; SL 52%), chesty (CS1002 29%; SL 31%) or tickly (CS1002 21%; SL 17%).

Table 1: Subject Demographic and Baseline Characteristics

	CS1002 n (%) N=82	**Simple linctus n (%) N=75**
Gender [N (%)]		
Male	34 (42)	34 (45)
Female	48 (59)	41 (55)
Age [years]		
Mean (SD)	38.5 (17.3)	38.2 (16.6)
Median (range)	31.5 (18, 75)	34.0 (18, 86)
Type of referral [N (%)]		
GP	30 (37)	27 (36)
Pharmacist	52 (63)	48 (64)
Smoking status [N (%)]		
Never smoked	64 (78)	54 (72)
Ex-smoker	18 (22)	21 (28)
Cough characteristics, mean (SD)		
Cough duration [days]	3.0 (1.5)	3.1 (1.6)
Cough severity VAS (mm)	80.4 (10.1)	81.6 (9.9)
Cough frequency VAS (mm)	79.5 (16.1)	76.7 (15.5)
Cough sleep disruption VAS (mm)	75.5 (23.2)	64.6 (29.2)
LCQ-acute scores, mean (SD)		
Total score	10.8 (3.5)	11.4 (3.2)
Physical score	3.7 (1.2)	4.1 (1.1)
Psychological score	3.7 (1.2)	3.9 (1.1)
Social score	3.4 (1.4)	3.5 (1.3)

LCQ = Leicester Cough Questionnaire; VAS = visual analogue scale (using a scale of 0-100 mm)
Based on ITT population

Exposure

Subjects took CS1002 medication for a mean (SD) of 6.2 (2.1) days and SL medication for 6.6 (1.8) days. The mean number of doses of study medication were 22.2 (8.7) for the CS1002 group and 23.7 (8.3) in the SL group. The maximum number of medication doses possible during the study was 28. The weight of the bottles of treatment returned at the end of study was planned to be used to estimate compliance, excluding doses not taken due to early termination from the study due to recovery. The weight of medicine broadly agreed with self-reported consumption stated by subjects receiving CS1002, with a mean (SD) of 94% (17%) vs. 94% (18%) for subjects receiving SL.

Primary Efficacy Endpoint

There was a clinically meaningful improvement in cough severity VAS at Day 4 in both groups (Table 2, Figure 3). The magnitude of the reduction in cough severity score was greater in the CS1002 group compared to the SL group but was not statistically significant; mean (95% CI) difference of 5.9mm (-14.4, 2.7), p=0.18. The PPS and ITT sensitivity analyses with imputations were also consistent with this finding (see Supplementary File).

Secondary Efficacy Endpoints

Cough Severity: There was a progressive decrease in cough severity VAS over the study, with the CS1002 group reporting a greater reduction compared to the SL group between Days 3 to 7 (Figure 3). The between group changes in cough severity VAS did not achieve

statistical significance (mean (95% CI) difference of 4.2mm (-12.2, 3.9), p=0.31 at Day 7) (Table 2 and Figure 3).

Cough Frequency: There was a greater reduction in cough frequency VAS with CS1002 compared to SL at all time points (Figure 4). At Day 4, there was an 8.1mm (95% CI: -16.2, 0.1) greater reduction in cough frequency VAS for CS1002 compared to SL (p=0.05) (Table 2 and Figure 4).

Cough Resolution: By Day 4, 29.3% of subjects in the CS1002 group had achieved cough resolution compared with 17.3% in the SL group (p=0.08) (Table 2). There was no significant difference between the treatment groups regarding median time taken to achieve cough resolution (CS1002 6.5 days, SL 7.0 days, hazard ratio 1.300, p=0.20, Figure 5). In a post-hoc analysis, 20 subjects (24.4%) in the CS1002 group and 10 (10.7%) in SL group stopped treatment by Day 4 due to improvement in cough (p=0.02).

Sleep Disruption: There was a greater reduction in sleep disruption with CS1002 compared to SL at all time points (Figure 6). At Day 4, the magnitude of reduction in cough sleep disruption score was greater for the CS1002 group than for the SL group, mean difference of 11.6mm (95% CCI: -20.6,-2.7), p=0.01 (Figure 6 and Table 2). A summary of all VAS results is provided in Supplementary File Figure 1.

Table 2: Analysis of Key Efficacy Parameters at Day 4

Key Efficacy Assessments	CS1002	Simple linctus
Number of subjects	82	75
Cough severity		
Baseline value (mean±SD)	80.4 (10.1)	81.6 (9.9)
Change from baseline to Day 4: Mean (95% CI)	-38.9 (-45.2,-33.2)	-32.8 (-39.6,-27.0)
Adjusted mean difference (95% CI)	-5.9 (-14.4,2.7)	
p-value	**p=0.18**	
Cough frequency		
Baseline value (mean±SD)	79.5 (16.1)	76.7 (15.5)
Change from baseline to Day 4: Mean (95% CI)	-40.7 (-46.0,-34.6)	-32.1 (-38.1,-26.4)
Adjusted mean difference (95% CI)	-8.1 (-16.2,0.1)	
p-value	**p=0.05**	
Cough resolution		
Day 4 value (n, %)	24 (29.3%)	13 (17.3)
Difference (%)	12%	
p-value	**p=0.08**	
Sleep disruption		
Baseline value (mean±SD)	75.5 (23.2)	64.6 (29.2)
Change from baseline to Day 4; Mean (95% CI)	-42.8 (-46.9,-34.4)	-26.3 (-35.5,-22.6)
Adjusted mean difference (95% CI)	-11.6 (-20.6,-2.7)	
p-value	**p=0.01**	

NB. Negative values indicate a reduction in cough symptoms
Based on ITT population. Adjusted mean difference = difference in between group differences

Health-Related Quality of Life: LCQ-acute total scores increased over time for both treatment groups, indicating an improvement in HRQoL. At Day 6, the magnitude of the improvement was significantly greater in the CS1002 group compared to the SL group (mean difference 1.21 (95% CCI: 0.05, 2.36), p=0.04) (see Supplementary File Figures 2 and 3).

Adverse Events (AEs)

AEs were reported for 17 subjects (20.5%) in the CS1002 group and 21 subjects (27.6%) in the SL group during the study (Table 3). The AEs were generally indicative of the study indication or likely to be associated with URTI, with the majority being mild or moderate

severity. Events classified as severe were only seen in the SL treatment group, and comprised cough, sneezing and joint swelling (all occurring in 1 subject each). No SAEs or deaths were reported. There were no AEs of drowsiness reported during the study. Six subjects (7%) in the CS1002 group and no subjects in the SL group reported in their diary that they reduced the dose of medication due to drowsiness/tiredness. These events were not reported by the subjects as AE. Following the reduction of the dose of medication there were no further reports of drowsiness or tiredness.

Table 3: Adverse Events

AEs, n (%)	CS1002 N=83 Total N (%)	Simple linctus N=79 Total N (%)
Number of subjects with an AE	17 (20.5)	21 (27.6)
Nervous system disorders	7 (8.4)	10 (13.2)
Headache	5 (6.0)	9 (11.8)
Dizziness	1 (1.2)	2 (2.6)
Respiratory, thoracic and mediastinal disorders	8 (9.6)	9 (11.8)
Oropharyngeal pain	2 (2.4)	4 (5.3)
Cough	2 (2.4)	3 (3.9)
Productive cough	3 (3.6)	1 (1.3)
Dyspnoea	0 (0.0)	2 (2.6)
Gastrointestinal disorders	5 (6.0)	2 (2.6)
Diarrhoea	3 (3.6)	0 (0.0)
Abdominal pain upper	2 (2.4)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	5 (6.6)
Pain	0 (0.0)	3 (3.9)
Pyrexia	0 (0.0)	2 (2.6)
Infections and infestations	1 (1.2)	2 (2.6)
Lower respiratory tract infection	0 (0.0)	2 (2.6)

Treated set population. AEs reported for >1 subject.

DISCUSSION

This multicentre, randomised study compared the efficacy and safety of two OTC cough mixtures: CS1002 containing diphenhydramine, ammonium-chloride and levomenthol in a cocoa-based demulcent preparation versus SL containing citric acid monohydrate. This is one of the largest multiple dosing, randomised controlled trials in subjects with URTI-associated cough to date, and the first to recruit subjects seeking cough medicines at pharmacies. The study did not achieve a significant reduction in primary end-point cough severity after 3 days of treatment, but there were greater reductions in cough frequency and sleep disruption and resolution of cough in subjects receiving CS1002 compared to SL.

Our trial represents a significant advance in the study of URTI-associated cough for a number of reasons. A Cochrane systematic review of cough medicines concluded that there was no evidence for or against cough medicines for URTI-associated cough.[6] Previous trials of cough medicines have been hampered by the recruitment of small numbers of subjects, the recruitment of subjects not representative of URTI-associated cough, uncontrolled study design and the use of un-validated endpoints. We conducted a randomised clinical trial that included validated cough outcome measures. Our primary outcome measure, the VAS, is widely used in studies of cough.[15] We recruited subjects with an URTI-associated cough who were otherwise healthy and seeking an antitussive medicine. Our subjects were unselected for the category of cough, and included a broad range of subjects with self-reported dry, chesty and tickly cough. We conducted a large study, recruiting subjects from 18 sites. This is the first study to recruit subjects presenting to pharmacies, and therefore the study population is more likely to resemble the broader population seeking cough medicines. There were few subjects that dropped out of the trial, and therefore our data completeness was good. The efficacy of the interventions was evaluated with widely used and validated

end-points of cough severity VAS and LCQ-acute HRQoL questionnaires.[15,16] We conducted a controlled trial and the comparator was a widely used OTC treatment. SL, which costs less than many OTC medicines to purchase but like most cough medicines, it lacks a strong evidence base. Its efficacy has not been compared to natural recovery, placebo, or to other cough medicines. The rate of reduction of cough severity VAS associated with SL in our study does appear to be greater than that reported for natural recovery.[12] The mechanism of action of SL is poorly understood, but is thought to be related to a demulcent effect and the hyper-salivation resulting from the sugary taste.[11]

There was a clinically significant reduction in primary end-point cough severity VAS at Day 4 in both groups. However, CS1002 did not achieve the primary end-point of a greater reduction in cough severity at Day 4 compared to SL. There were, however, greater reductions in secondary endpoints of sleep disruption and cough frequency, and improvements in HRQoL associated with CS1002 compared to SL. There was also a trend favouring greater resolution of cough at Day 4 with CS1002 compared to SL, with a near doubling of the proportion of subjects whose cough had resolved. This was supported by a post-hoc analysis that found a significantly greater number of subjects had discontinued their medication due to resolution of cough by Day 4 (CS1002, 24.4% vs. SL, 10.7%: p=0.02). The MID for cough outcome measures of frequency VAS, sleep disruption VAS and cough resolution have not been reported in URTI-associated cough, and this should be studied in future to facilitate the clinical interpretation of data. CS1002 was well tolerated, and there were few significant adverse events, including drowsiness. Drowsiness was managed with dose reduction, and no subjects discontinued the medication because of this symptom. Subjects were compliant with both medications, and this was verified by counting the doses of medication returned at the end of the study. The mechanism of action of CS1002 is poorly

understood. There are a number of possibilities, which include a reduction in cough reflex sensitivity,[7] promotion of more restful sleep, and a demulcent action. CS1002 contains a cocoa-flavoured demulcent that is more viscous than most available OTC cough medicines, and this may potentially promote palatability.

There are a number of important limitations with our study. We did not utilise a placebo comparator, and the study was not double-blinded. The limitations of a single-blinded study were reduced by informing the subjects that they were going to receive a cough medicine, but not the characteristics of the medicine. The investigators were blinded to the study because both medicines were contained in identical packaging, and subjects were instructed to commence their medication outside the pharmacy or GP clinic. We used SL as the comparator since this is a widely used cough treatment. It is possible that there may have been greater differences in efficacy outcome measures if we had used an inactive placebo. Another option for comparator that should be considered in future studies is the demulcent used in CS1002. It is likely that there was also significant natural recovery in our study. Our data highlights the difficulty in evaluating cough medicines in a rapidly resolving condition. We don't know whether the cough at study entry was worsening or improving and this could have impacted on our findings. We were short of our recruitment target of 180 subjects; we recruited 163 subjects. This was due to a delay in the start of the study, and consequently a reduced time window for recruitment during the cough and cold winter season. We think it is unlikely that the slight under-recruitment of subjects would have altered our study conclusions. The reasons for screen failures were not recorded for many patients, particularly at busy pharmacy sites. The reasons were, however, recorded for 2,238 subjects and suggest that a large number of subjects approached had duration of cough greater than 7 days. It is possible that the discontinuation of medication could have reflected lack of efficacy as well as

recovery. We didn't investigate the cause of the acute cough, and future studies should possibly assess viruses, pertussis and bacterial causes. We did not assess cough with objective outcome measures, such as cough frequency monitoring.[16] Recently, there have been significant advances in cough monitoring technology, and this should be possible in future studies.[17]

In conclusion, the OTC cough medicine CS1002 did not achieve a significant reduction in the primary endpoint cough severity, but it was associated with a greater reduction in cough frequency and sleep disruption, and increased resolution of cough leading to early discontinuation of medication and improved HRQoL compared to comparator SL. Further studies should investigate the impact of natural recovery and placebo on cough outcome measures to facilitate the optimal study protocol in URTI-associated cough.

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AUTHORS' CONTRIBUTIONS

SB = Surinder Birring; JB = John Brew; TK = Tony Kilbourn; VE = Viv Edwards; RW = Rosamund Wilson; AM = Alyn Morice

Conception/design of work: SB, JB, TK, VE, RW, AM

Data analysis: RW, VE, JB

Data interpretation: all authors

Drafting manuscript: SB with input from JB, TK, VE, RW and AM. Help was also provided by Debbie Jordan, a professional medical writer.

Review and approval of manuscript: all authors

COMPETING INTERESTS

Surinder Birring has received personal fees from Infirst Healthcare during the conduct of the study for advisory work. Alyn Morice has received personal fees from Infirst Healthcare during the conduct of the study for advisory work. John Brew, Viv Edwards, and Tony Kilbourn are employees of Infirst Healthcare Ltd. Rosamund Wilson is a statistical consultant to Infirst Healthcare.

DATA SHARING STATEMENT

No additional data are available.

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FIGURE LEGENDS

Figure 1: Study Design

Figure 2: Trial CONSORT Flow Diagram

Figure 3: Change in Cough Severity over Time

Figure 4: Change in Cough Frequency over Time

Figure 5: Resolution of Cough: Cumulative Percentage of Subjects

Figure 6: Change in Cough Sleep Disruption over Time

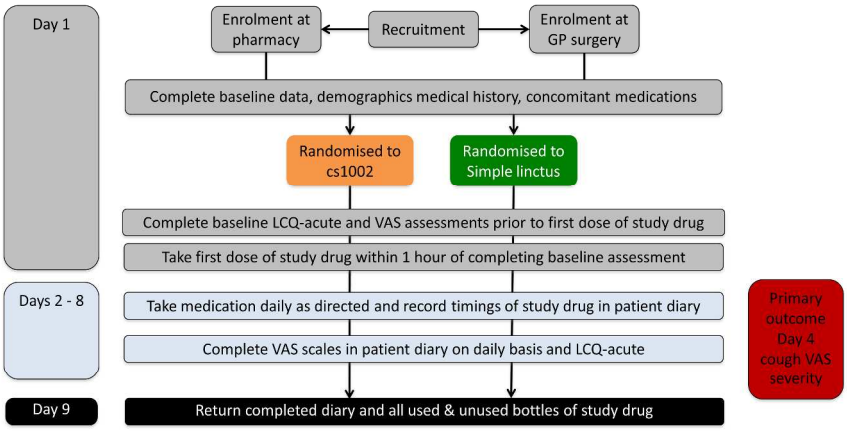


Figure 1: Study Design

338x190mm (300 x 300 DPI)

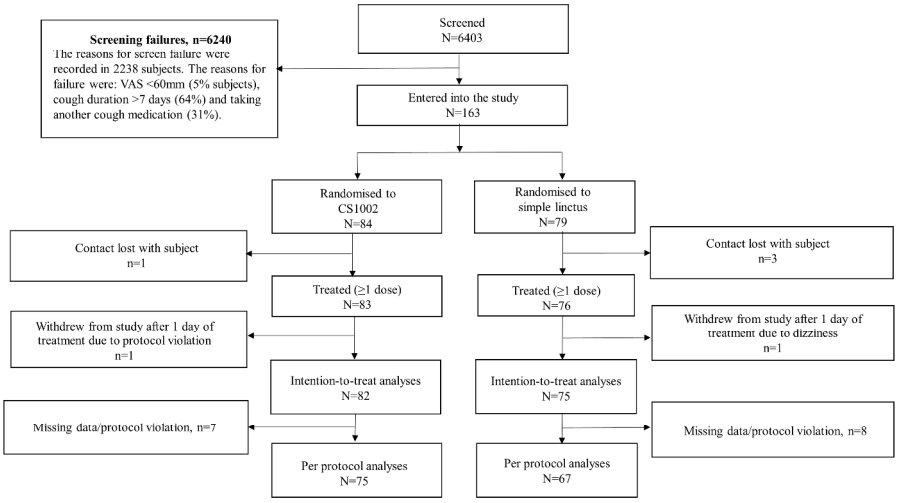
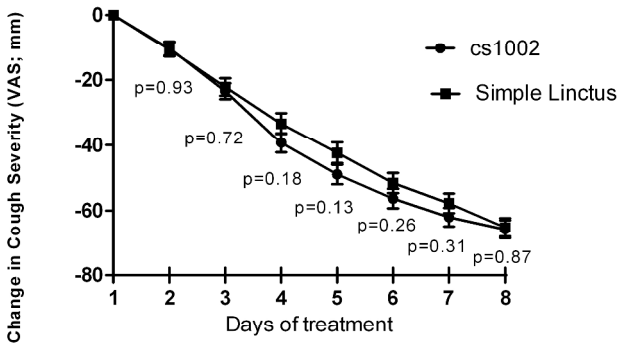


Figure 2: Trial CONSORT Flow Diagram

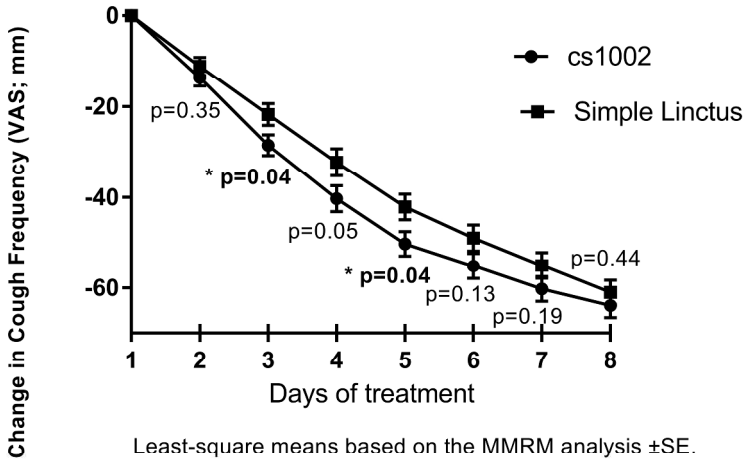
338x190mm (300 x 300 DPI)



Based on ITT population
Cough severity assessed using a 100 mm visual analogue scale (VAS)

Figure 3: Change in Cough Severity over Time

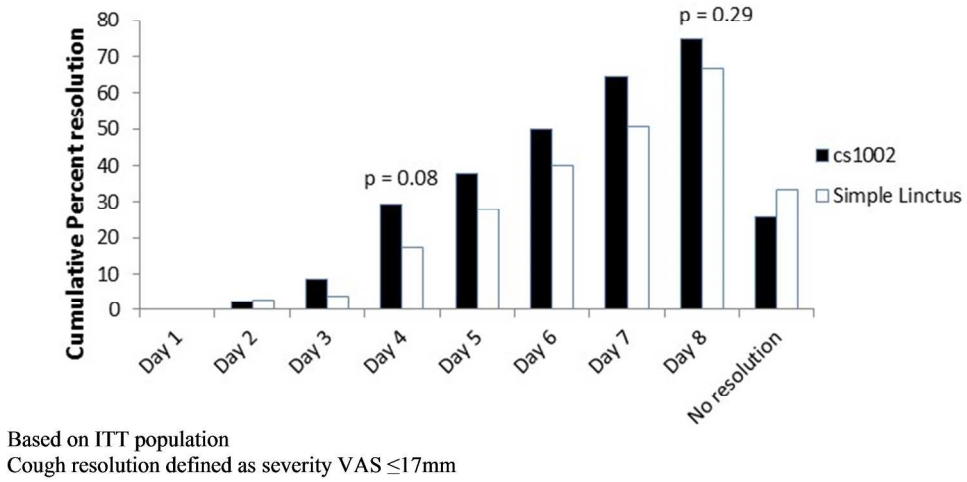
338x190mm (300 x 300 DPI)



Based on ITT population
Cough frequency assessed using a 100 mm visual analogue scale (VAS)

Figure 4: Change in Cough Frequency over Time

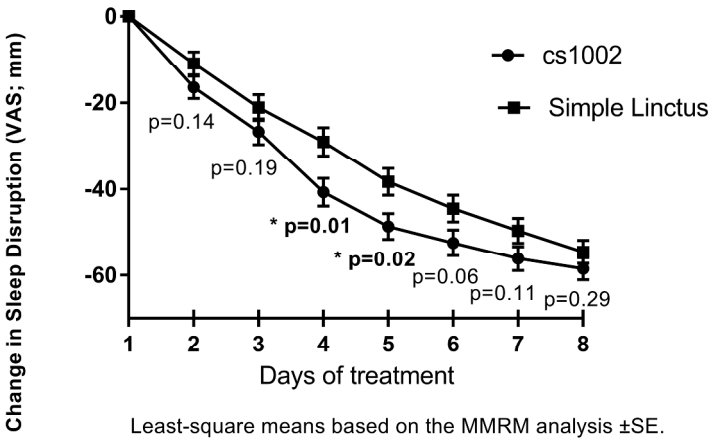
338x190mm (300 x 300 DPI)



Based on ITT population
Cough resolution defined as severity VAS ≤17mm

Figure 5: Resolution of Cough: Cumulative Percentage of Subjects

338x190mm (300 x 300 DPI)



Least-square means based on the MMRM analysis ±SE.

Based on ITT population
Sleep disruption assessed using a 100 mm visual analogue scale (VAS)

Figure 6: Change in Cough Sleep Disruption over Time

338x190mm (300 x 300 DPI)

Supplementary File

Per-protocol Analysis

A supportive analysis of the primary endpoint of the comparison of change in cough severity for CS1002 versus simple linctus from baseline to Day 4 of the study was conducted using the per-protocol set (PPS), as summarised in Supplementary File Table 1. Analysis using the PPS showed similar findings to the primary endpoint analysis, with the 4.6 mm difference in change in cough severity score between groups, not achieving statistical significance (p=0.30).

Supplementary File Table 1: Change in cough severity VAS at Day 4 (Per-Protocol Set)

	CS1002	simple linctus
Number of subjects	75	67
Baseline cough severity VAS, mm Mean (SD)	80.3 (10.0)	81.2 (9.5)
Change in VAS from baseline to Day 4 Mean (SE) Adjusted mean (SE)[1] 95% confidence interval[1]	 -39.4 (3.3) -40.6 (3.1) -46.6, -34.5	 -35.4 (3.1) -36.0 (3.2) -42.4, -29.6
CS1002 vs. simple linctus Adjusted VAS mean difference (SE)[1] 95% confidence interval[1] p-value[1]	 -4.6 (4.4) -13.2, 4.1 0.3009	

Note: Cough severity VAS scores range from 0 (no cough) to 100 (worst cough ever)
Negative values indicate a reduction in cough severity from baseline
[1] ANCOVA analysis on observed data including treatment, day, pooled centre and baseline cough severity terms along with treatment-by-day and baseline-by-day interaction terms

Sensitivity Analysis

Two sensitivity analyses were performed with imputations for missing data. In the first analysis, a last observation carried forward (LOCF) approach for missing data was used in the intention-to-treat (ITT) population. For this analysis if the Day 4 cough severity score was missing (the last on-treatment assessment of cough), the severity prior to Day 4 was carried forward. Analysis using this approach showed similar findings to the primary endpoint analysis (see Supplementary File Table 2), with the analysis of covariance (ANCOVA) demonstrating mean changes in cough severity of -39.2 mm (95% CIs -45.2, -33.2) for CS1002 and -33.7 mm (95% CIs -39.9, -27.4) for simple linctus. The 5.6 mm difference in change in cough severity score between the groups did not achieve statistical significance (p=0.19).

Supplementary File Table 2: Sensitivity analysis of change in cough severity at Day 4 (Last Observation Carried Forward, ITT Population)

	CS1002	simple linctus
Number of subjects	82	75
Baseline cough severity VAS, mm Mean (SD)	80.4 (10.1)	81.6 (9.9)
Change in VAS from baseline to Day 4 Mean (SE) Adjusted mean (SE)[1] 95% confidence interval[1]	-38.4 (3.1) -39.2 (3.0) -45.2, -33.2	-32.8 (3.1) -33.7 (3.2) -39.9, -27.4
CS1002 vs. simple linctus Adjusted VAS mean difference (SE)[1] 95% confidence interval[1] p-value[1]	-5.6 (4.2) -13.9, 2.8 0.1904	

Note: Cough severity VAS scores range from 0 (no cough) to 100 (worst cough ever)
Negative values indicate a reduction in cough severity from baseline
[1] ANCOVA analysis on LOCF data including treatment, day, pooled centre and baseline cough severity terms

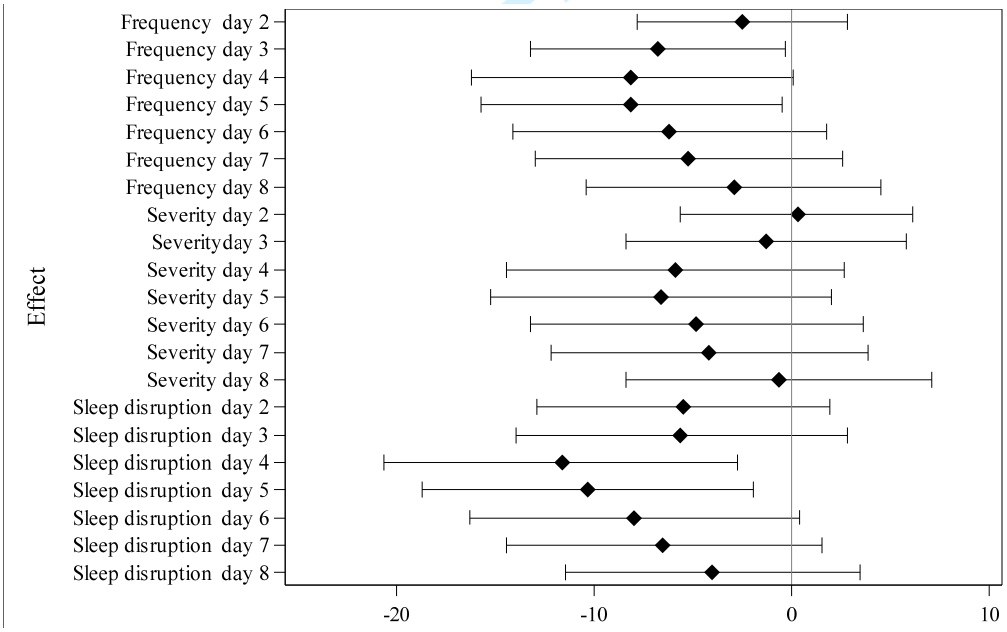
In the second analysis of the randomised set, missing cough VAS data at Day 4 was imputed, with baseline observations carried forward (BOCF). Analysis using this approach showed similar findings to the primary endpoint analysis (see Supplementary File Table 3), with the ANCOVA analysis demonstrating mean changes in cough severity of -38.1 (95% CIs -44.1, -32.1) for CS1002 and -31.5 (95% CIs -37.7, -25.4) for simple linctus. The 6.5 mm difference in change in cough severity score between the treatment groups did not achieve statistical significance (p=0.12).

Supplementary File Table 3: Sensitivity analysis of change in cough severity at Day 4 (Baseline Observation Carried Forward, ITT Population)

	CS1002	simple linctus
Number of subjects	84	79
Baseline cough severity VAS, mm Mean (SD)	80.5 (10.1)	81.5 (10.2)
Change in VAS from baseline to Day 4 Mean (SE) Adjusted mean (SE)[1] 95% confidence interval[1]	-37.5 (3.1) -38.1 (3.0) -44.1, -32.1	-31.2 (3.1) -31.5 (3.1) -37.7, -25.4
CS1002 vs. simple linctus Adjusted VAS mean difference (SE)[1] 95% confidence interval[1] p-value[1]	-6.5 (4.2) -14.9, 1.8 0.1229	

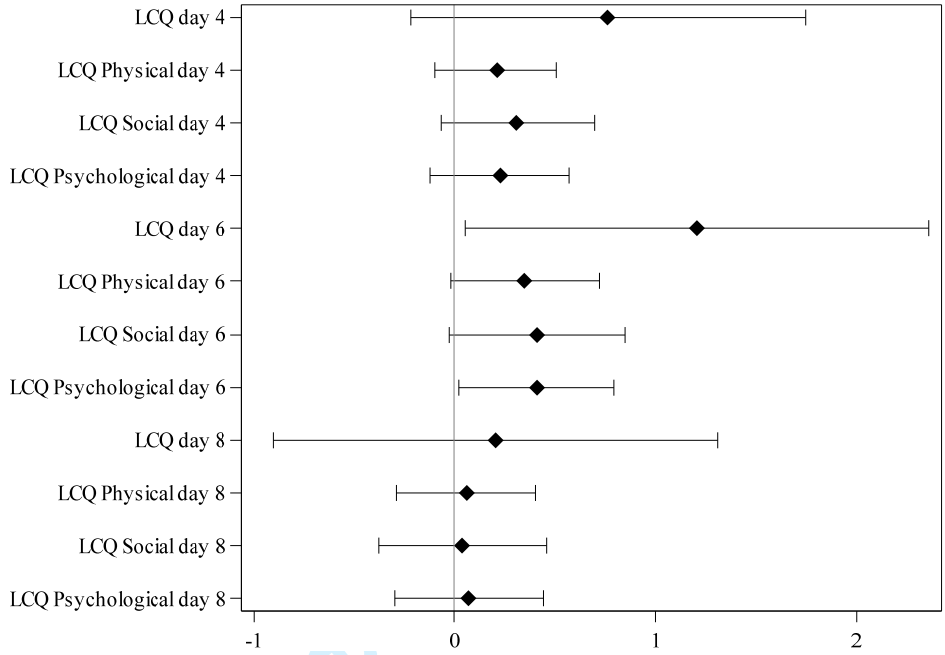
Note: Cough severity VAS scores range from 0 (no cough) to 100 (worst cough ever)
Negative values indicate a reduction in cough severity from baseline
[1] ANCOVA analysis on baseline observation carried forward data including treatment, day, pooled centre and baseline cough severity terms

Supplementary File Figure 1: Forest plot of cough frequency, cough severity and cough sleep disruption VAS scores (Days 2 – 8)



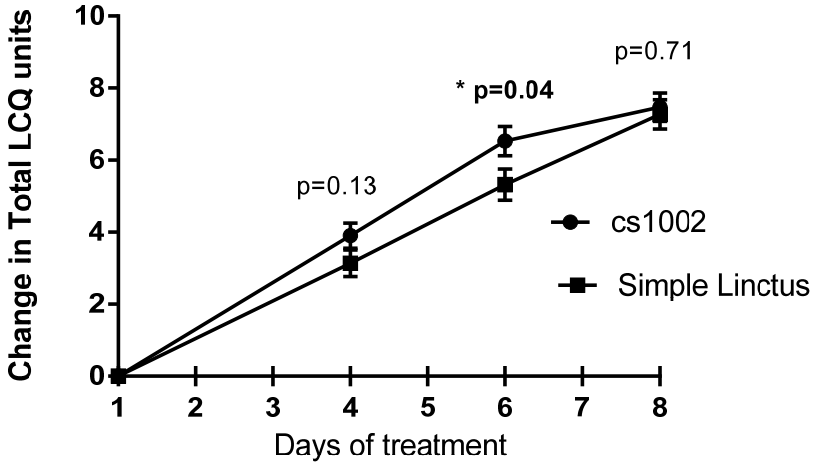
Estimates and 95% CI: Negative values favour CS1002 and positive values favour Simple Linctus.
Based on ITT population

Supplementary File Figure 2: Forest Plot of HRQoL (LCQ) Scores



Estimates and 95% CI: Positive values favour CS1002 and negative values favour Simple Linctus.
ITT population

Supplementary File Figure 3: Change in total LCQ (quality of life) score over time



Least-square means based on the MMRM analysis ±SE.

Based on ITT population
LCQ = Leicester Cough Questionnaire

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Yes
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Page 2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Pages 5 and 6
	2b	Specific objectives or hypotheses	Page 6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Page 8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	4a	Eligibility criteria for participants	Page 7
	4b	Settings and locations where the data were collected	Page 7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Pages 8 and 9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Pages 9 and 10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	Page 10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Page 8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Page 8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Page 8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Pages 8 and 22

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Page 9
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Pages 10 and 11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Page 28
	13b	For each group, losses and exclusions after randomisation, together with reasons	Page 28
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Page 7
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Page 12
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Page 14
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Pages 13, 14 and 15
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Pages 13, 14 and 15
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Pages 15 and 16
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Page 19
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Page 17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Pages 17, 18, 19 and 20
Other information			
Registration	23	Registration number and name of trial registry	Page 3
Protocol	24	Where the full trial protocol can be accessed, if available	Page 3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Page 21

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.