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)	-39.4 (3.3)	-35.4 (3.1)
Adjusted mean (SE)[1]	-40.6 (3.1)	-36.0 (3.2)
95% confidence interval[1]	-46.6, -34.5	-42.4, -29.6
CS1002 vs. simple linctus		
Adjusted VAS mean difference (SE)[1]	-4.6 (4.4)	
95% confidence interval[1]	-13.2, 4.1	
p-value[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)	-38.4 (3.1)	-32.8 (3.1)
Adjusted mean (SE)[1]	-39.2 (3.0)	-33.7 (3.2)
95% confidence interval[1]	-45.2, -33.2	-39.9, -27.4
CS1002 vs. simple linctus		
Adjusted VAS mean difference (SE)[1]	-5.6 (4.2)	
95% confidence interval[1]	-13.9, 2.8	
p-value[1]	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

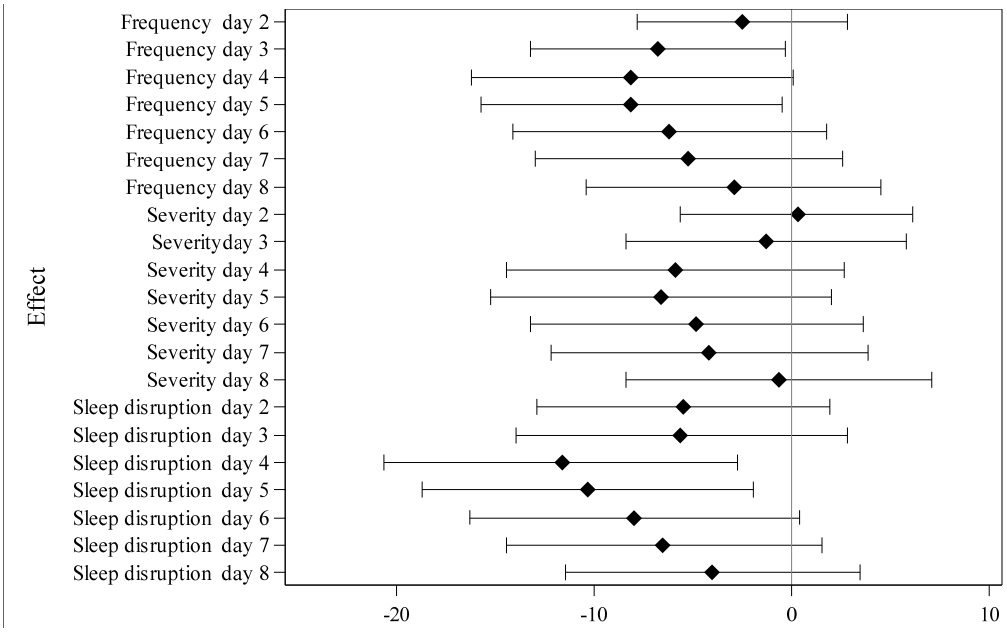
In the second analysis of the randomised set, missing cough VAS data at Day 4 was imputed, with baseline observations carried forward (BOCF). Analysis using this approach showed similar findings to the primary endpoint analysis (see Supplementary File Table 3), with the ANCOVA analysis demonstrating 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)	-37.5 (3.1)	-31.2 (3.1)
Adjusted mean (SE)[1]	-38.1 (3.0)	-31.5 (3.1)
95% confidence interval[1]	-44.1, -32.1	-37.7, -25.4
CS1002 vs. simple linctus		
Adjusted VAS mean difference (SE)[1]	-6.5 (4.2)	
95% confidence interval[1]	-14.9, 1.8	
p-value[1]	0.1229	

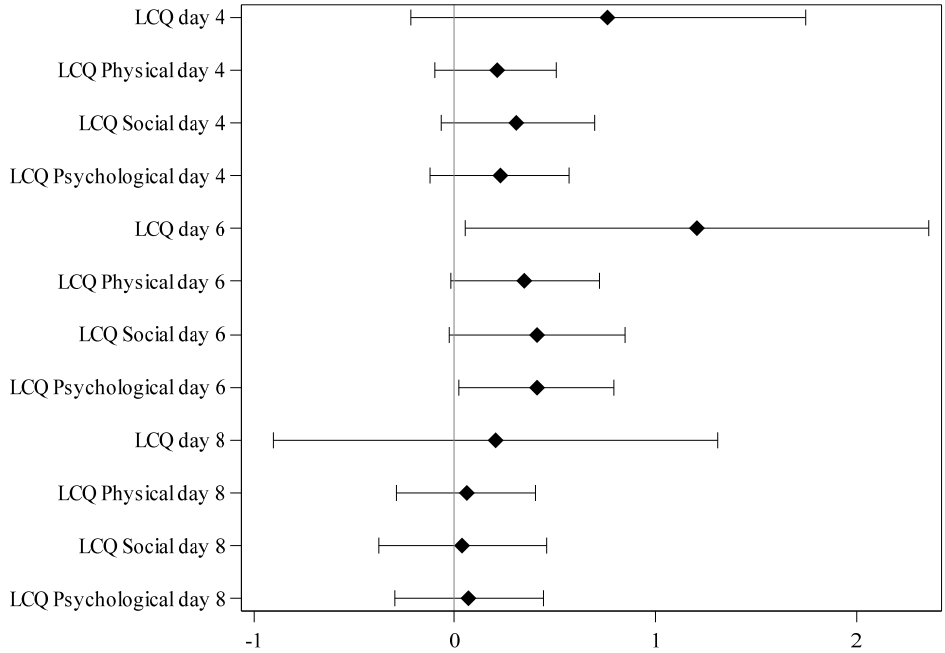
Note: Cough severity VAS scores range from 0 (no cough) to 100 (worst cough ever)
Negative values indicate a reduction in cough severity from baseline
[1] ANCOVA analysis on baseline observation carried forward data including treatment, day, pooled centre and baseline cough severity terms

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



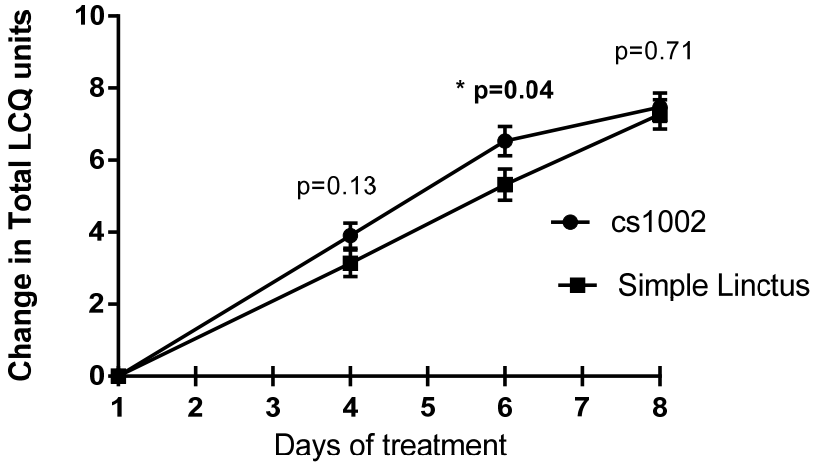
Estimates and 95% CI: Negative values favour CS1002 and positive values favour Simple Linctus.
Based on ITT population

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