Reckitt Benckiser Healthcare International Limited

1 STUDY REPORT TITLE PAGE

EudraCT Number:	2010-020985-94
Study Number:	TH 1010
Protocol Title:	A randomised, double blind, placebo-controlled, parallel group, single dose study of the efficacy of a flavoured variant of Strepsils Throat Lozenge in the relief of dry and irritated sore throat due to upper respiratory tract infection or environmental factors.
Study Phase:	III
Date First Patient Enrolled:	02 November 2010
Date Last Patient Completed:	01 March 2011
Report Date:	05 August 2011
Chief Investigator:	Dr Alan G Wade, CPS Research, West of Scotland Science Park, Glasgow, G20 0XQ, United Kingdom
Study Conduct Statement:	This study was conducted in accordance with ICH Good Clinical Practice and the ethical principles contained within the Declaration of Helsinki (South Africa, 1996), as referenced in EU Directive 2001/20/EC. Documents defined by ICH GCP as "essential documents" will be archived in the RB company archive in Hull, UK.

Reviewed and Agreed by:

Clinical Project Manager:

Mr Zuhaib Baig BSc(Hons)
Reckitt Benckiser Healthcare UK Ltd
Date

Statistician:

Michael A Goulder 04-JAN-12

Mr Michael Goulder BSc(Hons)
Worldwide Clinical Trials
Date

Report Author:

Dr Rosemary Collier PhD
For CPS Research
20/12/11
Date

Chief Investigator:

Dr Alan G Wade MBChB FRCA
CPS Research
29/12/11
Date

Reviewed and Approved by:

R&D Manager - Clinical (Healthcare) in the EU:		**Global Medical Director:**	
Sue Aspley 06 Jan 12		6 January 2012	
Dr Sue Aspley BSc (Hons), PhD Reckitt Benckiser Healthcare UK Ltd	Date	Dr Phil Berry MB ChB, MPH Reckitt Benckiser Healthcare UK Ltd	Date

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Study Sponsor: Reckitt Benckiser Healthcare, UK Ltd, Dansom Lane, Hull HU87DS

2 SYNOPSIS

Name of Sponsor/ Company: Reckitt Benckiser Healthcare International Ltd.	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority use only)**
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Title of Trial: A randomised, double blind, placebo-controlled, parallel group, single dose study of the efficacy of a flavoured variant of Strepsils Throat Lozenge in the relief of dry and irritated sore throat due to upper respiratory tract infection or environmental factors.

Investigator(s): Dr Alan G Wade

Trial Site(s): Single centre at CPS Research, Glasgow, United Kingdom

Publication (reference): None

Studied Period: 4 months **Date first patient enrolled:** 2 November 2010 **Date last patient completed:** 1 March 2011	**Phase of Development:** III

Objectives: The primary objective of this study was to determine the analgesic properties of an experimental formulation of Strepsils lozenge in patients with a dry and irritated sore throat due to upper respiratory tract infection (URTI) or environmental factors. The analgesic properties were assessed by comparing sore throat relief and throat soreness in patients treated with the Strepsils lozenge and patients treated with a placebo lozenge. In addition to the analgesic endpoints, functional measures of throat dryness and throat irritation were also assessed.

The secondary objective of this study was to determine consumer acceptability of the product via responses to a consumer questionnaire.

Methodology: This was a randomised, double blind, parallel group, single dose study comparing the efficacy of an experimental formulation of Strepsils lozenge with placebo.

Subjective rating scales for throat soreness, throat dryness, throat irritation (11-point scale) and sore throat relief (7-point scale) were used to assess efficacy. Throat soreness, throat dryness and throat irritation were assessed at screening, 0 (pre-dose) and 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes after dosing. Sore throat relief was assessed at all post-dose time points. A consumer questionnaire was completed at 0 (pre-dose), 1, 5, 20, 60 and 180 minutes after dosing to assess consumer acceptability and the treatment was rated at the end of the 3-hour assessment period.

Adverse events were assessed at 0 (pre-dose), 180 minutes and up to 24 hours post-dose. A patient diary was used to capture adverse event and concomitant medication information from 3 hours to up to 24 hours post-dose.

Number of Patients: **Planned:** 200 (100 in each treatment group)
Analysed: 203 (Full analysis set); 195 (Per-protocol)

Diagnosis and Main Criteria for Inclusion: Male and female patients aged between 16 and 75 years of age with a sore throat due to URTI or environmental factors, of onset within 4 days of presenting were eligible for study entry. Patients had to have confirmed objective findings of a sore throat as assessed by scoring at least 3 points on the expanded Tonsillopharyngitis Assessment (TPA). They also had to have a sore throat, a dry throat and a scratchy, tickly or itchy throat as shown by scoring at least 6 on the throat soreness scale, 3 or less on a throat dryness scale and 5 or less on a throat irritation scale (all ordinal 0-10 scales).

Patients with conditions, or who had taken medications, that could interfere with the assessment of sore throat analgesic activity or those with an allergy or intolerance to the study medication or any of the other constituents were excluded.

Test Product: Experimental flavoured throat lozenge containing 2, 4–dichlorobenzyl alcohol

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(1.2 mg) and amylmetacresol (0.6 mg), single oral dose, batch number 02172164, expiry date 9 March 2011

Patients were instructed to suck the lozenge slowly, moving it around the mouth until dissolved and not to chew or crunch it.

Duration of Treatment: Single dose (one lozenge)

Reference Therapy: Placebo: a single shape matched, non-medicated, sugar free throat lozenge, single oral dose, batch number 01945196, expiry date 9 March 2011

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the area under the curve (AUC) for the change from baseline in severity of throat soreness on swallowing (using the 11-point throat soreness scale) to 2 hours.

Secondary variables included:

The change from baseline in severity of throat soreness, throat dryness, throat irritation and sore throat relief at all time points up to 3 hours post-dose

The AUCs for the change from baseline to 3 hours in severity of throat soreness and the changes from baseline to 2 and 3 hours for throat dryness and throat irritation (using the respective 11-point scales) and sore throat relief (using the 7-point scale)

Time to onset of moderate pain relief, overall treatment rating and consumer acceptability by responses to the questions from the consumer questionnaire

Safety: The overall proportion of patients with adverse events (AEs) and serious adverse events (SAEs) was assessed in the clinic and up to 24-hour post-dose using a patient diary.

Statistical Methods:

All efficacy variables were analysed using the full analysis dataset, which consisted of all patients who were randomised to the study and took study medication. The primary analysis and secondary analysis of the AUC from 0 to 2 hours for sore throat relief were repeated using a per-protocol set.

The primary efficacy variable was analysed using Analysis of Covariance (ANCOVA) with the baseline severity of throat soreness as a covariate and a factor for treatment group.

The secondary AUC, changes from baseline and overall treatment rating variables were analysed using ANCOVA with baseline severity of throat soreness as a covariate and a factor for treatment group. Covariates for throat dryness and throat irritation were also added to the model for analyses of these variables. The time to onset of moderate pain relief was compared between treatment groups using the Cox-proportional Hazards model. Consumer questionnaire responses were analysed using a logistic regression model (binary data) or ANCOVA (non-binary data).

Safety data were analysed using the safety set which included all patients who took study medication. The proportion of patients reporting treatment emergent adverse events was compared between treatment groups using the chi-square test.

Treatment group differences were presented with 95% confidence intervals. All AUC analyses were based on actual timings and were calculated using the trapezoidal rule.

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Name of Finished Product:	Volume:	
Name of Active Ingredient(s): 1.2 mg 2,4-dichlorobenzyl alcohol, 0.6 mg amylmetacresol	Page:	

SUMMARY & CONCLUSIONS

PATIENTS:

A total of 203 patients (101 test, 102 placebo) were randomised into the study and were treated with study medication. All 203 patients completed the study. The patients (107 males, 96 females) had a mean age of 34 years (range 16-67) and were mainly Caucasian (198, 98%). Their mean duration of sore throat was 2.2 days; 92% of patients had a sore throat due to URTI and 8% due environmental factors (as assessed by a study nurse).

The treatment groups were well-balanced for the demographic characteristics. The TPA score, and the pre-dose ratings for throat soreness, throat irritation, throat dryness were generally comparable between the two treatment groups. However, there was an imbalance in the proportion of patients describing their throats as swollen and inflamed (8% test, 20% placebo).

EFFICACY RESULTS:

The results for the primary efficacy variable and other AUC variables for throat soreness, sore throat relief, throat dryness and throat irritation are summarised in Table 1. The per-protocol analyses of the primary variable and AUC from 0 to 2 hours for sore throat relief gave similar results to those of the full analysis set.

TABLE 1 **Summary statistics for AUCs from 0 to 2 and 0 to 3 hours for analgesic and functional ratings – full analysis set**

Variable	Test (n=101)	Placebo (n=102)	Treatment difference	
	LS mean [a]	LS mean [a]	LSD mean difference for test – placebo (95% CI)	p-value
$AUC_{0\text{-}2h}$ for the change from baseline in throat soreness	-1.50	-1.53	0.04 (-0.34, 0.42)[b]	0.85
$AUC_{0\text{-}3h}$ for the change from baseline in throat soreness	-1.47	-1.55	0.07 (-0.32, 0.47)[b]	0.72
$AUC_{0\text{-}2h}$ for sore throat relief	2.78	2.42	0.36 (0.09, 0.63)[c]	0.0102
$AUC_{0\text{-}3h}$ for sore throat relief	2.77	2.43	0.34 (0.05, 0.63)[c]	0.02
$AUC_{0\text{-}2h}$ for the change from baseline in throat dryness [d]	1.87	1.75	0.12 (-0.27, 0.50)[c]	0.55
$AUC_{0\text{-}3h}$ for the change from baseline in throat dryness [d]	1.74	1.65	0.09 (-0.31, 0.48)[c]	0.66
$AUC_{0\text{-}2h}$ for the change from baseline in throat irritation [e]	1.55	1.27	0.28 (-0.08, 0.65)[c]	0.13
$AUC_{0\text{-}3h}$ for the change from baseline in throat irritation [e]	1.48	1.24	0.25 (-0.14, 0.63)[c]	0.21

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b A negative difference favours test lozenge.
c A positive difference favours test lozenge
d Estimated from ANCOVA model with factor for treatment and covariates for baseline throat soreness and baseline throat dryness
e Estimated from ANCOVA model with factor for treatment and covariates for baseline throat soreness and baseline throat irritation

Throat soreness measured on an 11-point scale where 0 = Not sore, 10 = Very sore
Sore throat relief measured on a 7-point scale where 1 = No relief, 2 = Slight relief, 3 = Mild relief, 4 = Moderate relief, 5 = Considerable relief, 6 = Almost complete relief, 7 = Complete relief
Throat dryness measured on an 11-point scale 0 = Completely dry, 10 = Completely moist
Throat irritation measured on an 11-point scale 0 = Completely scratchy, tickly or itchy 10 = Not at all scratchy, tickly or itchy

Key secondary efficacy variable data are summarised in Tables 2 and 3. There was significantly greater sore throat relief achieved in the test treatment group compared with

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placebo from 1 to 75 minutes post-dose, but not thereafter.

TABLE 2 **Mean ± sd changes in throat soreness from baseline and mean (± sd) sore throat relief over 3 hours post-dose**

	Throat soreness			Sore throat relief		
Minutes post-dose	Test (n)	Placebo (n)	T vs. P	Test (n)	Placebo (n)	T vs. P
0	7.12±1.44 (101)	7.13±0.99 (102)	ns			
1	-0.40±1.63 (101)	-0.40±1.27 (102)	ns	1.90±0.97 (101)	1.48±0.79 (102)	***
5	-1.37±1.92 (101)	-1.28±1.77 (101)	ns	2.52±1.04 (101)	2.00±0.88 (102)	***
10	-1.53±1.91 (101)	-1.63±1.87 (102)	ns	2.78±1.20 (101)	2.37±0.98 (102)	**
15	-1.45±1.87 (101)	-1.58±1.85 (102)	ns	2.85±1.13 (101)	2.47±1.03 (102)	*
30	-1.50±1.85 (101)	-1.49±1.66 (102)	ns	2.83±1.10 (101)	2.51±1.03 (102)	*
45	-1.65±2.09 (101)	-1.39±1.76 (102)	ns	2.88±1.19 (101)	2.46±1.05 (102)	**
60	-1.47±1.99 (101)	-1.49±1.68 (102)	ns	2.87±1.25 (101)	2.47±1.08 (102)	*
75	-1.59±1.90 (101)	-1.70±1.75 (101)	ns	2.79±1.21 (101)	2.46±1.09 (101)	*
90	-1.52±2.06 (101)	-1.74±1.85 (102)	ns	2.80±1.22 (101)	2.51±1.21 (102)	ns
105	-1.50±2.01 (101)	-1.60±1.79 (102)	ns	2.78±1.20 (101)	2.46±1.18 (102)	ns
120	-1.51±2.11 (101)	-1.66±1.82 (102)	ns	2.75±1.27 (101)	2.45±1.29 (102)	ns
135	-1.46±2.16 (101)	-1.53±1.85 (102)	ns	2.70±1.28 (101)	2.45±1.23 (102)	ns
150	-1.39±1.98 (101)	-1.64±1.83 (102)	ns	2.67±1.27 (101)	2.39±1.22 (102)	ns
165	-1.44±2.05 (100)	-1.63±2.08 (102)	ns	2.76±1.33 (100)	2.43±1.33 (101)	ns
180	-1.38±2.16 (101)	-1.39±1.90 (102)	ns	2.81±1.29 (101)	2.46±1.28 (102)	ns

ns	Test lozenge (T) vs. placebo (P) comparison not statistically significant
*	Test lozenge (T) vs. placebo (P) comparison statistically significant at 5% level
**	Test lozenge (T) vs. placebo (P) comparison statistically significant at 1% level
***	Test free lozenge (T) vs. placebo (P) comparison statistically significant at 0.1% level

Throat soreness measured on an 11-point scale where 0 = Not sore, 10 = Very sore

Sore throat relief measured on a 7-point scale where 1 = No relief, 2 = Slight relief, 3 = Mild relief, 4 = Moderate relief, 5 = Considerable relief, 6 = Almost complete relief, 7 = Complete relief

There was no significant difference between treatments in the time to onset of moderate pain relief.

The changes from baseline in throat dryness, as assessed on the 11-point throat dryness scale showed that the test treatment group had significantly greater moistening than the placebo group at 1 and 5 minutes post-dose, but later differences were not significant. There was a significant improvement in throat irritation at 1, 5 and 10 minutes post-dose in the test group compared with placebo. Peak improvements in throat dryness and throat irritation were achieved with test lozenge at 5 and 10 minutes post-dose, respectively.

The throat dryness element of the consumer questionnaire supported the findings from the subjective rating scale. The responses showed that the speed of onset of a moistening/mouth watering sensation was significantly faster in the test lozenge group (n=101) than in the placebo group (n=101; Odds ratio 2.53, 95% CI 1.53 to 4.18, p=0.0003). At 1 and 5 minutes post-dose, patients in the test group had a significantly greater degree of throat hydration than those in the placebo group ($p<0.01$; $p<0.05$ respectively).

At 3 hours post-dose, patients treated with the test lozenge had a significantly greater degree of mouth watering/moistening effect (p=0.0002) and a greater degree of coating of the throat compared to placebo (p=0.03). There were also significant differences between the treatments in the moistening (p=0.011) and lubricating effects (p=0.007), with an effect felt deeper down the throat after taking the test lozenge than the placebo lozenge at 3 hours post-dose.

Patients rated test lozenges more highly as a treatment for sore throat than placebo lozenges at 3 hours post-dose (Table 3). Patients also began to feel more like their best overall at 1 hour

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Name of Active Ingredient(s): 1.2 mg 2,4-dichlorobenzyl alcohol, 0.6 mg amylmetacresol	Page:	

with a significant difference between treatments (p=0.002) in favour of the test lozenge.

TABLE 3 Summary statistics for treatment ratings – full analysis set

Variable	Test (n=101)	Placebo (n=102)	Treatment difference	
	LS mean[a]	LS mean[a]	LSD mean difference for test – placebo (95% CI)[b]	p-value
Overall treatment rating at 3 hours	5.00	4.21	0.79 (0.01, 1.58)	0.049
Rating as a treatment for dry/irritated sore throat	5.03	4.29	0.74 (-0.03, 1.51)	0.06

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b A positive difference favours test lozenge
Measured on an 11-point scale where 0 = Poor, 10 = Excellent

SAFETY RESULTS:

In the test lozenge group, 10 (10%) patients reported 11 treatment emergent AEs and in the placebo group, 8 (8%) patients reported 11 AEs. There was no statistically significant difference between treatments in the proportion of patients reporting events (p=0.61). All treatment emergent events were of mild severity, except one that was of moderate severity. All of the AEs were classified as not or unlikely to be related to the study medication. Headache was the most commonly reported treatment emergent AE in both treatment groups; 6 (6%) patients reported 7 headaches in the test lozenge group and 5 (5%) reported 5 events in the placebo group. There were no SAEs or discontinuations due to AE in this study.

CONCLUSION:

The experimental formulation lozenge provides fast and effective pain relief for patients with a dry and irritated sore throat due to URTI or environmental factors. Following a single dose, pain relief is evident after 1 minute with peak analgesic effect occurring at 45 minutes and superior pain relief over 3 hours compared with placebo lozenges. The test lozenges also provide rapid improvements in throat dryness and throat irritation, with peak effects at 5 and 10 minutes after intake.

The lozenges are well accepted by consumers. They have moistening and lubricating effects, which are felt deep down in the throat and are rated as a better treatment for sore throat than placebo lozenges 3 hours after intake.

The test lozenges are well tolerated and there are no apparent safety concerns regarding their use.

Date of the report: 05 August 2011

3 TABLE OF CONTENTS

1	STUDY REPORT TITLE PAGE	1
2	SYNOPSIS	3
3	TABLE OF CONTENTS	8
3.1	List of Tables and Figures Contained in the Body of the Report	10
3.2	List of Appendices	13
4	LIST OF ABBREVIATIONS AND DEFINITION OF TERMS	15
5	ETHICS	17
5.1	Independent Ethics Committee (IEC) or Institutional Review Board (IRB)	17
5.2	Ethical Conduct of the Study	17
5.3	Patient Information and Consent	17
6	INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE	18
7	INTRODUCTION	18
8	STUDY OBJECTIVES	19
9	INVESTIGATIONAL PLAN	19
9.1	Overall Study Design and Plan – Description	19
9.2	Discussion of Study Design, Including the Choice of Control Groups	22
9.3	Selection of Study Population	23
9.3.1	Inclusion Criteria	23
9.3.2	Exclusion Criteria	23
9.3.3	Removal of Patients from Therapy or Assessment	25
9.4	Treatments	25
9.4.1	Treatments Administered	25
9.4.2	Identity of Investigational Product(s)	26
9.4.3	Method of Assigning Patients to Treatment Groups	26
9.4.4	Selection of Doses in the Study	26
9.4.5	Selection of Timing of Dose for Each Patient	26
9.4.6	Blinding	27
9.4.7	Prior and Concomitant Therapy	27
9.4.8	Treatment Compliance	28
9.5	Efficacy and Safety Variables	28
9.5.1	Efficacy and Safety Measurements Assessed and Flowchart	28

9.5.2	Appropriateness of Measurements	34
9.5.3	Primary Efficacy Variable(s)	35
9.5.4	Drug Concentration Measurements	36
9.6	Data Quality Assurance	36
9.7	Statistical Methods Planned in the Protocol and Determination of Sample Size	37
9.7.1	Statistical and Analytical Plans	37
9.7.1.1	Efficacy	37
9.7.1.2	Safety	39
9.7.2	Determination of Sample Size	40
9.8	Changes in the Conduct of the Study or Planned Analysis	40
9.8.1	Changes in the Conduct of the Study	40
9.8.2	Changes in the Planned Statistical Analysis of the Study	40
10	STUDY PATIENTS	41
10.1	Disposition of Patients	41
10.2	Protocol Deviations	41
11	EFFICACY EVALUATION	42
11.1	Data Sets Analysed	42
11.2	Demographic and Other Baseline Characteristics	43
11.2.1	Demographic and Baseline Data	43
11.2.2	Baseline Disease Characteristics	44
11.2.3	Medical History	44
11.2.4	Pre-dose Efficacy Data	45
11.2.5	Concomitant Medication	46
11.3	Measurements of Treatment Compliance	46
11.4	Efficacy results	46
11.4.1	Analysis of Efficacy	46
11.4.1.1	Primary Endpoint	46
11.4.1.2	Secondary Endpoints	47
11.4.2	Analytical Issues	67
11.4.2.1	Adjustments for Covariates	68
11.4.2.2	Handling of Dropouts or Missing Data	68
11.4.2.3	Interim Analyses and Data Monitoring	69
11.4.2.4	Multi-site Studies	69

11.4.2.5 Multiple Comparison/Multiplicity 69
11.4.2.6 Use of an "Efficacy Subset" of Patients 69
11.4.2.7 Active-Control Studies Intended to Show Equivalence 70
11.4.2.8 Examination of Subgroups 70
11.4.3 Tabulation of Individual Response Data 70
11.4.4 Drug Dose, Drug Concentration and Relationships to Response 70
11.4.5 Drug-Drug and Drug-Disease Interactions 71
11.4.6 By-Patient Displays 71
11.4.7 Efficacy Conclusions 71
12 SAFETY EVALUATION 75
12.1 Extent of Exposure 75
12.2 Adverse Events (AEs) 75
12.2.1 Brief Summary of Events 75
12.2.2 Display of Adverse Events 75
12.2.3 Analysis of Adverse Events 76
12.3 Deaths, Other Serious Adverse Events (SAEs) and other Significant Adverse Events 76
12.4 Clinical Laboratory Evaluation 76
12.5 Vital Signs, Physical Findings and other Observations Related to Safety 76
12.6 Safety Conclusions 76
13 DISCUSSION AND OVERALL CONCLUSIONS 77
13.1 Discussion 77
13.2 Conclusion 79
14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT 81
15 REFERENCE LIST 87

3.1 List of Tables and Figures Contained in the Body of the Report

Table 9.1.1 Flowchart of Study Procedures 21
Table 9.5.1 Flowchart of Efficacy and Safety Assessments 29
Table 9.5.2 Rating Systems used to Determine Adverse Event Severity and Relationship to Study Medication 34
Figure 10.1.1: Disposition of Patients 41

Table 10.2.1 Number (%) of patients with major protocol deviation 42
Table 11.1.1 Number (%) of patients analysed in each dataset 43
Table 11.2.1 Demographic characteristics – Full analysis set 44
Table 11.2.2 Baseline sore throat characteristics – Full analysis set 44
Table 11.2.3 Pre-dose efficacy variables (mean ± sd /% of patients) – Full analysis set 45
Table 11.4.1 Primary Efficacy Endpoint: AUC from baseline to 2 hours post-dose for the change from baseline in throat soreness 47
Table 11.4.2 AUC from baseline to 3 hours post-dose for the change from baseline in throat soreness – Full analysis set 47
Table 11.4.3 Mean ± sd (n) for change from baseline in throat soreness at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose – Full analysis set 48
Figure 11.4.1 Mean change from baseline in throat soreness from 1 to 180 minutes post first dose – Full analysis set 49
Table 11.4.4 AUC from baseline to 2 hours post-dose for sore throat relief (TOTPAR) 50
Table 11.4.5 AUC from baseline to 3 hours post-dose for sore throat relief (TOTPAR) – Full analysis set 50
Table 11.4.6 Mean ± sd (n) for sore throat relief at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose – Full analysis set 51
Figure 11.4.2 Mean sore throat relief from 1 to 180 minutes post first dose – Full analysis set 52
Table 11.4.7 AUC from baseline to 2 and 3 hours post-dose for the change from baseline in throat dryness – Full analysis set 53
Table 11.4.8 Mean ± sd (n) for change from baseline in throat dryness at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose – Full analysis set 54
Figure 11.4.3 Mean change from baseline in throat dryness from 1 to 180 minutes post first dose – Full analysis set 54
Table 11.4.9 AUC from baseline to 2 and 3 hours post-dose for the change from baseline in throat irritation – Full analysis set 55
Table 11.4.10 Mean ± sd (n) for change from baseline in throat irritation at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose – Full analysis set 56
Figure 11.4.4 Mean change from baseline in throat irritation from 1 to 180 minutes post first dose – Full analysis set 56
Table 11.4.11 Overall treatment rating at 3 hours – Full analysis set 57

Table 11.4.12 Change from pre-dose to 3 hours post-dose for the functional impairment scale (each component and overall total score) – Full analysis set 58

Table 11.4.13 Speed of onset of moistening/mouth-watering sensation – Full analysis set 59

Table 11.4.14 Mean ± sd (n) for degree of hydration of throat at 1, 5, 20 and 60 minutes – Full analysis set 59

Table 11.4.15 Consumer questionnaire: How deep down within the throat was hydration felt 5 minutes after dosing – Full analysis set 60

Table 11.4.16 Consumer questionnaire: Degree of lubrication of throat at 20 minutes and 2 hours post-dose – Full analysis set 60

Table 11.4.17 Consumer questionnaire: Change from baseline in how bothering the throat discomfort was at 20 minutes and 2 and 3 hours post-dose – Full analysis set 61

Table 11.4.18 Consumer questionnaire: Change from baseline in how much the patient felt like their best overall at 1 and 3 hours post-dose – Full analysis set 62

Table 11.4.19 Consumer questionnaire: Change from baseline in degree of happiness in relation to their throat at 1 and 3 hours post-dose – Full analysis set 62

Table 11.4.20 Consumer questionnaire: Whether patient felt any better than before they took the lozenge at 3 hours post-dose – Full analysis set 63

Table 11.4.21 Consumer questionnaire: Whether patient felt less distracted than before they took the lozenge at 3 hours post-dose – Full analysis set 63

Table 11.4.22 Consumer questionnaire: Whether patient felt less frustrated than before they took the lozenge at 3 hours post-dose – Full analysis set 63

Table 11.4.23 Consumer questionnaire: Whether patient felt happier than before they took the lozenge at 3 hours post-dose – Full analysis set 64

Table 11.4.24 Patient rating of lozenge as a treatment for dry/irritated sore throat – Full analysis set 64

Table 11.4.25 Patient assessment of degree of coating of lozenge at 3 hours post-dose – Full analysis set 65

Table 11.4.26 Patient assessment of degree of watering/moistening of lozenge at 3 hours post-dose – Full analysis set 65

Table 11.4.27 Consumer questionnaire: How deep down within the throat was relief felt 3 hours post-dose – Full analysis set 66

Table 11.4.28 Consumer questionnaire: How deep down within the throat was moistening felt at 3 hours post-dose – Full analysis set 66

Table 11.4.29 Consumer questionnaire: How deep down within the throat was lubrication felt at 3 hours post-dose – Full analysis set.....67
Table 11.4.30 Consumer questionnaire: Whether throat felt as moist as normal at 3 hours post-dose – Full analysis set.....67
Table 11.4.31 Missing data.....69
Table 11.4.32 Efficacy objectives, variables and conclusions.....72
Table 12.2.1 Severity and relationship of treatment emergent adverse events to therapy.....76

3.2 List of Appendices

16 APPENDIX

16.1 STUDY INFORMATION

16.1.1 Protocol and Protocol amendments

16.1.2 Sample case report form (unique pages only)

16.1.3 List of IECs or IRBs

16.1.4 List and description of Investigators and other important participants in the study

16.1.5 Signature of principal or chief/coordinating Investigator(s)

16.1.6 Listing of subjects receiving test drug(s) from specific batches, where more than one batch was used

All subjects in this study received study medication from one batch, so this appendix is not present.

16.1.7 Randomisation scheme and codes (subject identification and treatment assigned)

16.1.8 Audit certificates

No audits related to this study were conducted, so this appendix is not present.

16.1.9 Documentation of statistical methods

16.1.10 Documentation of inter-laboratory standardisation methods and Quality assurance procedures if used

16.1.11 Publications based on the study

None of the data from this study has been published, so this appendix is not present.

16.1.12 Important publications referenced in the report

None of the publications referenced in the report is appended.

16.2 SUBJECT DATA LISTINGS

16.2.1 Discontinued Subjects

No subjects discontinued the study, so this appendix is not present.

16.2.2 Protocol Deviations

There were no Protocol deviations in this study, so this appendix is not present.

16.2.3 Subjects Excluded from the Efficacy Analysis

No subjects were excluded from the efficacy analysis, so this appendix is not present.

16.2.4 Demographic data

16.2.5 Compliance and/or drug concentration data

Compliance and drug concentration data were not collected in this study, so this appendix is not present.

16.2.6 Individual efficacy response data

16.2.7 Adverse event listings (each subject)

16.2.8 Listing of individual laboratory measurements by subject

No laboratory measurements were performed in the study, so this appendix is not present.

16.3 CASE REPORT FORMS

CRFs for deaths, other serious adverse events and withdrawals for adverse events. No subjects died, experienced serious adverse events or withdrew because of adverse events, so no CRFs are appended.

Other CRFs submitted. No other CRFs are appended.

16.4 INDIVIDUAL SUBJECT DATA LISTINGS (US ARCHIVAL LISTINGS)

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Abbreviation in Full
AE	Adverse Event
AMC	Amylmetacresol BP
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
ATC	Anatomic Therapeutic Class
AUC	Area under the curve
AE	Adverse event
CRF	Case Report Form
CSP	Clinical Study Protocol
CV	Curriculum vitae
DCBA	2,4-Dichlorobenzyl alcohol
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IMSU	Investigational Material Supplies Unit
IRB	Institutional Review Board
LS	Least square
MedDRA	Medical Dictionary for Regulatory Authorities
NA	Not applicable
RB	Reckitt Benckiser
RBHI	Reckitt Benckiser Healthcare International
R&D	Research and Development
SAE	Serious adverse event
SPID	Sum of the pain intensity difference
TOTPAR	Total pain relief (sum of the pain relief scores)
TPA	Tonsillopharyngitis Assessment
UK	United Kingdom (of Great Britain and Northern Ireland)
UNK	Unknown
URTI	Upper Respiratory Tract Infection
US	United States (of America)

Abbreviation	Abbreviation in Full
WHO	World Health Organisation

5 ETHICS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The name and full address of the IEC consulted are provided in Appendix 16.1.3.

The Clinical Study Protocol (CSP), together with the participant information and consent documents and study specific advertisements for recruiting patients were initially reviewed on 7 September 2010. The IEC gave a favourable ethical opinion subject to conditions, which included changes to the participant information sheet. The participant information and consent documents were reviewed and approved by the Fife and Forth Valley Research Ethics Committee on 24 September 2010.

5.2 Ethical Conduct of the Study

This study was conducted in accordance with the Declaration of Helsinki (South Africa, 1996), as referenced in EU Directive 2001/20/EC. It complied with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

5.3 Patient Information and Consent

Copies of a representative participant information sheet and a blank consent form (version 2 dated 14 September 2010) are provided in Appendix 16.1.3.

Patients who were considered by the Investigator to be suitable for entry into the study were given the opportunity to read the participant information sheet and consent form, and to ask questions. If they were happy with, and understood the information, they were asked to sign the consent form. The Investigator or research nurse also signed the form. The patient was given a copy of the information sheet and signed consent form. No protocol-related procedures were performed prior to the patient signing the consent form.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Appendix 16.1.4 contains a table listing the names and affiliations of the individuals whose participation materially affected the conduct of the study, together with their roles. The curriculum vitae (CV) of the Chief Investigator, Dr A Wade and the Principal Investigator, Dr G Crawford are also included in the Appendix.

The study was carried out at CPS Research in Glasgow under the guidance of the Chief and Principal Investigator. Some study related activities were delegated to suitably qualified site personnel.

Test and placebo lozenges were manufactured by Reckitt Benckiser (RB; Nottingham, UK). The study drug supplies were packed and shipped to CPS Research in Glasgow by the Investigational Medicinal Supplies Unit (IMSU), RB (Hull, UK). Monitoring and project management were performed by personnel at Reckitt Benckiser Healthcare International (RBHI; Slough, UK). RBHI was also responsible for the expedited reporting of any serious adverse events (SAEs) occurring during the study to the relevant Regulatory Authorities.

Data management and the statistical analyses were performed by Worldwide Clinical Trials (Nottingham, UK) and report writing by CPS Research.

7 INTRODUCTION

The study was conducted to support the launch of a new formulation of Strepsils throat lozenges globally. The formulation of this lozenge was designed to produce an extreme mouth-watering effect by the addition of 2.1% tartaric acid.

Strepsils throat lozenges contain the active antimicrobial ingredients amylmetacresol BP (0.6 mg) and 2,4-dichlorobenzyl alcohol (1.2 mg) (AMC/DCBA) and come in a variety of flavours. They are indicated for the symptomatic relief of mouth and throat infections and are the leading brand for sore throat relief in many markets around the world. The efficacy of existing Strepsils lozenge variants has been established in previous studies[1,2,3,4,5,6].

This study examined the effect of a new flavoured, sugar free variant of Strepsils throat lozenge compared with a non-medicated, sugar free placebo throat lozenge in patients with a dry and irritated sore throat over a period of 3 hours. Efficacy was assessed by patient–reported outcomes using rating scales for throat soreness, sore throat relief, and novel scales for throat irritation and throat dryness.

The assessment ratings relating to analgesia i.e. throat soreness and sore throat relief are accepted, validated analgesic assessment methodologies and have been used in clinical studies with other medications[7,8,9,10,11]. The throat moistening/lubricating sensation provided by the test lozenge in patients with a dry and irritated throat was also of interest and hence throat dryness and throat irritation were assessed. The 11-point categorical rating scale (completely dry – completely

moist) used to quantify throat dryness has been used successfully in previous in-house consumer studies. In order to quantify throat irritation, patients described the scratchy, itchy or tickly nature of their sore throat on an 11-point categorical scale (completely scratchy, itchy or tickly – not at all scratchy, itchy or tickly). Scratchy, itchy and tickly are specific words that consumers in previous market research have used to describe an irritated sore throat. Additional data regarding consumer acceptability of the product and its mouth lubricating ability were obtained using a consumer questionnaire. In order to explore fully the effects of the test lozenge on throat irritation and dryness, the inclusion criteria for this study differed from previous studies on Strepsils lozenge by the selection only of subjects who reported a dry and irritated throat at screening either due to upper respiratory tract infection (URTI) or environmental factors.

8 STUDY OBJECTIVES

The primary objective of this study was to determine the analgesic properties of an experimental formulation of Strepsils lozenge in patients with a dry and irritated sore throat due to URTI or environmental factors. The analgesic properties were assessed by comparing sore throat relief and throat soreness in patients treated with the test lozenge and patients treated with a placebo lozenge. In addition to the analgesic endpoints, functional measures of throat dryness and throat irritation were also assessed.

The secondary objective of this study was to determine consumer acceptability of the product via responses to a consumer questionnaire (Appendix III of the CSP, Appendix 16.1.1).

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan – Description

The study Protocol is included as Appendix 16.1.1. The case report form (CRF) is included as Appendix 16.1.2.

This was a single centre, randomised, double-blind, parallel-group, placebo-controlled, single dose study of the efficacy of a test lozenge in the relief of dry and irritated sore throat due to URTI or environmental factors.

The study comprised 3 study periods: pre-study screening, treatment period and a telephone follow-up.

Patients were recruited into the study after responding to study specific advertisements. Pre-screening of patients responding to advertising was conducted by telephone using a standardised script before patients. Patients who were successfully pre-screened and consented to take part in the study were given an appointment to attend the investigational site, CPS Research premises.

Eligible patients who satisfied the inclusion and exclusion criteria were randomised to receive either a test or placebo lozenge, according to their assigned randomisation number. Baseline assessments were performed before patients were administered

the study medication. Patients completed the 3-hour assessments under supervision in a designated area within the investigational site. No food, drink, additional medication/throat lozenges or smoking were permitted. On completion of the 3-hour assessments, patients left the investigational site with a diary card to record adverse events (AEs) and concomitant medications for up to 24 hours post-dose.

Between 1 and 3 days post-dose, a trained representative of the investigational site followed up the patients by telephone to capture any AEs and concomitant medications recorded in the diary. Data from the patient diary were transcribed into the CRF by a member of the CPS Research team. Any ongoing AEs were to be followed up as described in Section 13.1.6 of the CSP (Appendix 16.1.1). The patient was also requested to post the diary cards back to CPS Research.

No invasive procedures e.g. blood samples, were required for the study.

It was planned that 200 patients (100 in each treatment group) would be recruited to ensure that 170 patients (85 in each treatment group) provided data for the primary endpoint (the area under the change from baseline curve (AUC) in severity of throat soreness, from 0 to 2 hours).

A flowchart of study procedures is given in Table 9.1.1.

Table 9.1.1 Flowchart of Study Procedures

Study Period	Pre-Study Screen	Treatment period (Day 1)		Follow–up
Assessment times	N/A	0 min (pre-dose)[a]	1 to 180 min post-dose, as specified)	1-3 days post-dose
Informed Consent	X			
Demographics	X			
Medical History	X			
Concomitant Medication	X			X (up to 24 hours post-dose, diary)
Washout (if required)	X			
Females: Pregnancy, fertility, contraceptives precaution questions	X			X (pregnancy only)
Tonsillopharyngitis (TPA) Score	X			
Sore throat symptom categorisation and emotional impact assessment	X	X[b]		
Eligibility	X			
Diary cards given out and patients instructed on use		X		
Randomisation		X		
Time of First Dose		X		
Throat Soreness	X	X	X[c]	
Sore Throat Relief			X[c]	
Throat dryness	X	X	X[c]	
Throat irritation	X	X	X[c]	
Treatment Rating			X (180 min)	
Consumer Questionnaire		X	X (1, 5, 20, 60, 120, 180 min)	
Adverse Events (AEs)		X	X (180 min)	X (up to 24 hours post-dose, diary)
Telephone call to patient for review of AE and Concomitant Medication Diary				X

a Baseline assessments were made no more than 1 minute before the first dose.

b Included in the Consumer Questionnaire questions at pre-dose

c Assessments at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose

9.2 Discussion of Study Design, Including the Choice of Control Groups

The assessment methods for throat soreness and sore throat relief used in this study are accepted and validated analgesic methodologies based on the Sore Throat Pain Model described in the literature by Schachtel[10,12,13]. They have been previously used in other studies with Strepsils lozenges (BH5013, TH0705 and TH0817)[2,3,4] and in studies investigating the analgesic properties of a sore throat lozenge containing the non-steroidal anti inflammatory drug, flurbiprofen[8,9,11].

In order to discriminate between test and placebo treatment, it was important to include patients with a sufficient degree of throat soreness at baseline. Therefore, to be eligible for study entry, patients had to have a throat soreness score of 6 or more as scored on the Throat Soreness Scale. In addition to this subjective measure of throat soreness, patients had to undergo an objective tonsillopharyngitis assessment (TPA). The TPA has been used in sore throat studies by Schachtel[12,13] and in Strepsils lozenge studies[2,4]. This assessment ensured that patients had some objective sign of a sore throat and that only patients with acute tonsillopharyngitis were recruited into the study. The TPA consisted of assessments of 7 pertinent features of tonsillopharyngitis: oral temperature, size of tonsils, oropharyngeal colour, number of oropharyngeal enanthems, and size, number and tenderness of the anterior cervical lymph nodes. The TPA provided a score ranging from 0 to 21 points. A minimum score of 3 points was required to confirm the presence of tonsillopharyngitis and permit entry into the study.

In contrast to previous studies with Strepsils lozenge, the current study aimed to recruit people with sore throat due either to URTI or environmental factors (dry air etc.,) and who had significant levels of throat irritation and dryness at study entry.

A throat lozenge format has a number of key advantages for treating sore throat and can contribute to relief of sore throat by having a soothing, demulcent effect. In order to control for the contribution of the throat lozenge formulation to the efficacy of the active throat lozenges, a non-medicated, sugar free throat placebo lozenge was used as a control. This placebo control was the same size and shape as the test lozenge and provided the appropriate control when given using a third party blinding method to allow for a slight difference in appearance.

Although no previous studies had been conducted focussing on subjects with a dry and irritated throat, it was deemed acceptable to use a previous efficacy study (TH0817) comparing Strepsils Cool and Warm Lozenges with a non-medicated, sugar based placebo lozenge as the basis for estimating the appropriate sample size to ensure adequate statistical power for the current study. TH0817 demonstrated that Strepsils Cool and Warm Lozenges provided a significantly greater reduction in throat soreness than placebo, as shown by the difference in the AUC for severity of throat soreness from 0 to 2 hours.

9.3 Selection of Study Population

Patients with a dry and irritated sore throat due to a URTI or environmental factors were recruited into the study using study specific advertising. Patients responding to advertisements underwent an initial screening by telephone according to a pre-determined script (Patient recruitment pre-screening questionnaire, Appendix IV of the CSP, Appendix 16.1.1).

9.3.1 Inclusion Criteria

Only patients to whom all of the following conditions applied were included:

1) Age: ≥16 to ≤75.

2) Both male and female patients were included.

3) Primary diagnosis: Patients with dry and irritated sore throat of onset within the past 4 days (i.e. ≤4 days) due to URTI or environmental factors.

4) Objective findings that confirmed the presence of tonsillopharyngitis (≥3 points on the expanded 21-point TPA).

5) Patients who had a sore throat (≥6) on the Throat Soreness Scale at baseline. They were instructed by the study nurse to swallow and circle the number on the scale that showed how your sore throat is when you swallow. Ratings on this 0-10 ordinal scale were marked with 0= Not sore (besides '0' rating) and 10=Very sore (beside '10).

6) Patients who had a dry throat (≤3) on the throat dryness scale at baseline. They were instructed by the study nurse to swallow and circle the number on the scale that showed how your dry/moist your throat is when you swallow. Ratings on this 0-10 ordinal scale will be marked with 0= completely dry (besides '0' rating) and 10= completely moist (beside '10).

7) Patients who had a scratchy, tickly or itchy throat (≤5) on the throat irritation scale at baseline. They were instructed by the study nurse to swallow and circle the number on the scale that showed how scratchy, tickly or itchy your throat is when you swallow. Ratings on this 0-10 ordinal scale were marked with 0= completely scratchy, tickly or itchy (besides '0' rating) and 10= not at all scratchy, tickly or itchy (beside '10).

8) Patients who had given written informed consent.

9.3.2 Exclusion Criteria

Patients to whom any of the following conditions applied were excluded:

1) Any previous history of allergy or known intolerance to the study drug or the formulation constituents, AMC, DCBA, tartaric acid, isomalt, maltitol, water, flavourings, sweeteners (acesulfame) and colourings (copper chlorophyllin).

2) Those whose sore throat had been present for more than 4 days

3) Those who had evidence of mouth breathing

4) Those who had evidence of severe coughing

5) Those who had any disease that could compromise breathing e.g. bronchopneumonia

6) Those who had taken any medicated confectionary, throat pastille, spray, or any product with demulcent properties such as boiled sweets in the previous 2 hours.

7) Those who had used any sore throat medication containing a local anaesthetic within the past 4 hours

8) Those who had used any analgesic, antipyretic or 'cold' medication (e.g. decongestant, antihistamine, antitussive or throat lozenge) within the previous 8 hours

9) Those who had used a longer acting or slow release analgesic during the previous 24 hours e.g. piroxicam and naproxen

10) Those who had taken antibiotics during the previous 14 days

11) Those with any painful condition that might distract attention from sore throat pain e.g. mouth ulcers etc.

12) Those with a history of severe renal impairment

13) Those with a history of severe hepatic impairment

14) Those with a history of alcohol abuse or stating that they regularly consumed alcohol in excess of the recommended amounts (excessive alcohol >21 units per week for females and >28 units per week for males)

15) Those unable to refrain from smoking during their stay in the investigative site

16) Women of childbearing potential, who reported they were pregnant or lactating, seeking pregnancy or failing to take adequate contraceptive precautions, (i.e. an oral or injectable contraceptive, an approved hormonal implant or topical patch or an intrauterine device. Adequate contraception also included abstinence, barrier contraception and partner vasectomy. A woman of child bearing potential was defined as any female who is less than 2 years postmenopausal or has not undergone a hysterectomy or surgical sterilisation, e.g. bilateral tubal ligation, bilateral ovariectomy (oophorectomy).

17) Those previously randomised into the study

18) Those who had participated in a clinical trial in the previous 30 days. Thirty days were calculated from time of last dosing in the prior trial to time of anticipated dosing in this trial.

19) Those unable in the opinion of the investigator to comply fully with the study requirements, e.g. such as those who could not comprehend or correctly use the pain rating scales.

9.3.3 Removal of Patients from Therapy or Assessment

The investigator could withdraw the patient from the study at any time. Reasons for removing a patient from the study included, but were not limited to:

- AEs that in the judgement of the Investigator could cause severe or permanent harm (significant clinical deterioration is an AE)
- Violation of the study protocol
- In the Investigator's judgement, it was in the patient's best interest
- Patient declined further study participation

The reason for withdrawal was documented as one of the following: AE, lack of efficacy, withdrawal of consent, lost to follow up, protocol violation, death/SAE or other reason. The Investigator made reasonable attempts to contact patients who were lost to follow up to record the information from their adverse event/concomitant medication diary; a minimum of 2 documented telephone calls or a letter was considered reasonable.

If a patient was withdrawn prematurely from the study, the following assessments were carried out:

- AEs
- The clinical assessments detailed in section 11.2.3.1 (follow up visit) of the CSP (Appendix 16.1.1) and any others that were deemed appropriate for the clinical care of the patient.
- Review of the patient diary.

9.4 Treatments

9.4.1 Treatments Administered

Patients were randomly allocated to receive one of the following two treatments as a single oral dose between November 2010 and February 2011:

i) Sugar free test lozenge containing 1.2mg DCBA and 0.6mg AMC

ii) Non-medicated, sugar free placebo lozenge

Each patient was provided with the throat lozenge at the investigational site with instructions given to suck on the lozenge slowly and to move the lozenge around the

mouth, until it had dissolved in the mouth. The patient was also instructed not to chew or crunch the lozenge, as this would affect the effectiveness of the lozenge.

An independent member of the investigational site staff supervised administration of the study treatment, by watching the patients put the lozenge in their mouths.

Blinding was maintained as patients were asked to close their eyes prior to being given the lozenge until the lozenge was in the mouth (see Section 9.4.6).

9.4.2 Identity of Investigational Product(s)

The identities of the medications supplied in the study were:

i) Sugar free test lozenge containing 1.2mg DCBA and 0.6mg AMC; batch number 02172164, expiry date 9 March 2011

ii) Non-medicated sugar free placebo lozenges; batch number 01945196, expiry date 9 March 2011

The sugar free test lozenges and the non-medicated, sugar free placebo lozenges were manufactured, primary packed, secondary packed and labelled to Good Manufacturing Practice (GMP) standards by RB, Nottingham, NG90 2DB.

All drug supplies were packed into patient packs and labelled to GMP standards by the IMSU, Reckitt Benckiser Healthcare UK Ltd, Dansom Lane, Hull, HU8 7DS. Details of the packaging and labelling are given in Sections 12.4 and 12.5 of the CSP (Appendix 16.1.1). The blinded drug supplies were shipped directly from the IMSU to the investigational site.

Investigational products were stored below 25°C.

9.4.3 Method of Assigning Patients to Treatment Groups

The randomisation code is presented in Appendix 16.1.7. Randomisation was generated for 300 patients in blocks of six.

Drug supplies were packed and labelled by the IMSU, according to a computer generated randomisation schedule provided by the RB statistician who was not conducting the analysis of the study.

At screening, patients were allocated a unique patient (screening) number. On randomisation, patients were allocated a randomisation number in numerical sequence. Issue of the study drug in this sequence ensured randomisation.

9.4.4 Selection of Doses in the Study

The dose and route of administration selected in this study represent the normal usage of non-prescription unit doses for Strepsils Throat lozenges.

9.4.5 Selection of Timing of Dose for Each Patient

This was a single dose study.

Patients were not allowed any food, drink, additional medication/throat lozenges or smoking within 3 hours of receiving the study medication. Specific instructions given to patients about how to take the lozenge are described in Section 9.4.1.

9.4.6 Blinding

The RB statistician and the IMSU held a master randomisation list. IMSU supplied CPS Research with the randomisation code for each patient as a code break envelope.

The code was only to be broken for an individual patient in an emergency such as an SAE that required knowledge of which study drug was taken in order to provide appropriate treatment. If the code for a patient was broken, the Investigator was to withdraw the patient from the study, document the details of the event in the patient's CRF and promptly inform the RB Clinical Project Manager.

The study monitor checked the randomisation code break envelopes on a regular basis at monitoring visits. All codes, whether sealed or opened, were returned to RB at the end of the study.

A third party blinding method was employed due to slight differences in the appearance of the test and placebo lozenges. This was to ensure that the study drug and placebo were indistinguishable to the patient. Each patient was asked to close his/her eyes prior to being given a single throat lozenge by an independent member of the investigational staff who was not involved in the study assessments. The independent member of the investigational site staff watched each patient put the throat lozenge into their mouth. Once the throat lozenge had been put in the mouth, the patient was allowed to open his/her eyes.

RB broke the code for all patients only after all data queries had been answered and the database had been locked.

The code for the analysis was broken on 15 April 2011, only after all data queries had been answered and the database had been locked.

In the event, the randomisation code was not broken for any patients during the study.

9.4.7 Prior and Concomitant Therapy

Concomitant therapies are defined as prescribed medications, physical therapy, and over-the-counter preparations, including herbal preparations licensed for medicinal use, other than study medication and supplementary medication that the patient received during the course of the study.

The Investigator recorded any medications given in the treatment of adverse events on the concomitant medication page in the patient's case report form. Any medication taken by the patient during the course of the study was also to be recorded on this form.

Any changes in concomitant therapy during the study were documented, including cessation of therapy, initiation of therapy and dose changes.

Use of the following treatments was not permitted unless the specified washout period had elapsed before the baseline assessment:

- Sore throat medication containing a local anaesthetic in the 4 hours before dosing (i.e. before the dosing day): Washout period of 4 hours
- Medicated confectionary, throat pastille, spray or any product with demulcent properties such as boiled sweets in the 2 hours before dosing: Washout period of 2 hours
- Analgesic, antipyretic or 'cold' medication (e.g. decongestant, antihistamine, antitussive, or throat lozenge) in the 8 hours before dosing: Washout period of 8 hours
- Longer acting or slow release analgesic e.g. piroxicam and naproxen, in the 24 hours before dosing (i.e. before first dosing day): Washout period of 24 hours
- Use of antibiotic in the 14 days before enrolment into the study (i.e. before dosing

A washout period of up to 24 hours before the baseline assessment allowed patients who had taken any of the prohibited therapies listed above, except for antibiotics, to be considered for entry.

9.4.8 Treatment Compliance

An independent member of the site staff watched each patient's consumption of the single dose of study medication to ensure treatment compliance.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flowchart

The schedule of efficacy and safety assessments for this study is summarised in Table 9.5.1.

Table 9.5.1 Flowchart of Efficacy and Safety Assessments

Study Period	Pre-Study Screen	Treatment period (Day 1)		Telephone Follow–up (1-3 days post-dose)
Assessment times		0 min (pre-dose)[a]	1 to 180 min post-dose, as specified)	
Efficacy assessments				
Throat Soreness	X	X	X [b]	
Sore Throat Relief			X [b]	
Throat dryness	X	X	X [b]	
Throat irritation	X	X	X [b]	
Treatment Rating			X (180 min)	
Consumer Questionnaire		X	X (1, 5, 20, 60, 120, 180 min)	
Safety assessments				
Adverse Events (AEs)		X	X (180 min)	X (up to 24 hours post-dose, diary)
Concomitant Medication	X			X (up to 24 hours post-dose, diary)
Females: Pregnancy, fertility, contraceptives precaution questions	X			X (pregnancy only)

a Baseline assessments were made no more than 1 minute before the first dose.

b Assessments at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose

All efficacy assessments were patient-reported outcomes. The recording of AE/concomitant medication from 3 hours post-dose to up to 24 hours was also a patient-reported outcome. Other assessments were conducted by the Investigator or a delegated individual qualified by education and experience to perform the delegated task(s). A study nurse assessed whether the sore throat was due to a URTI or environmental factors.

Demographic information: Sex, race categorised as Caucasian, Asian, Afro-Caribbean or other, date of birth and smoking/alcohol use were collected at screening.

Medical history: A medical history was taken at screening.

Females only: At the screening visit, female patients were asked if they might be pregnant, if they were lactating or seeking pregnancy, if they were taking adequate contraceptive precautions, if they had at least 2 years post-menopausal, if they had been sterilised or had had a hysterectomy. During the 1-3 day post-dose telephone

call, female patients were asked again if they might be pregnant and site staff transcribed the response into the CRF.

Concomitant medication: Concomitant medication taken by the patient in the 14 days prior to study entry was recorded at screening along with any changes in medication use during the study period. Patients recorded use of all medications taken up to 24 hours post-dose in a patient diary, including the date, time and reason for taking the medication. After the 1-3 day post-dose telephone call, site staff answered the question 'Have there been any changes in the patient's medication (other than study medication) since their last visit?' in the CRF and transcribed any concomitant medication details.

Tonsillopharyngitis assessment (TPA): Oral temperature, size of tonsils, oropharyngeal colour, number of oropharyngeal enanthems, and size, number and tenderness of the anterior cervical lymph nodes were scored on a 0-3 range at screening. The total TPA score ranged from 0 to 21 points. A minimum score of 3 points was required to confirm the presence of tonsillopharyngitis and permit entry into the study.

Sore throat symptom categorisation and emotional impact assessment: Patients were asked to select one response to each of the three questions at screening and 0 minutes (pre-dose). Two questions concerned description of the sore throat ('how would you describe your sore throat' and 'which phrase best describes your throat now when you swallow') and one concerned feelings ('which description best fits how your sore throat makes you feel').

Throat soreness: Patients completed the throat soreness assessment at screening, 0 minutes (pre-dose), 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose. Patients were asked to 'swallow and circle the number on the scale that shows how sore your throat is when you swallow'. Ratings on the 0 to 10 ordinal scale were marked with 0= 'not sore' and 10= 'very sore' (Appendix I of the CSP, Appendix 16.1.1).

Sore throat relief: Patients completed the throat dryness assessment at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose. Patients were instructed by the study nurse to 'tick the phrase that best describes the relief of your sore throat now'. Scores were collected on a 7-point categorical scale ('no relief', 'slight relief', 'mild relief', 'moderate relief', 'considerable relief', 'almost complete relief', 'complete relief').

Throat dryness: Patients completed the throat dryness assessment at screening, 0 minutes (pre-dose), 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose. Patients were asked to 'swallow and circle the number on the scale that shows how dry your throat is when you swallow'. Ratings on the 0 to 10 ordinal scale were marked with 0= 'completely dry' and 10= 'completely moist'.

Throat irritation: Patients completed the throat irritation assessment at screening, 0 minutes (pre-dose), 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180

minutes post-dose. Patients were asked to 'swallow and circle the number on the scale that shows how scratchy, tickly or itchy your throat is when you swallow'. Ratings on the 0 to 10 ordinal scale were marked with 0= 'completely scratchy, tickly or itchy' and '10= 'not at all scratchy, tickly or itchy'.

Consumer Questionnaire: Patients completed the consumer questions at 0 minutes (pre-dose), 1, 5, 20, 60, 120 and 180 minutes post-dose. The questionnaire covered a range of questions completed at different times, including the following:

- The functional impairment scale, which assessed the extent to which the sore throat affected four daily activities (talking, swallowing, concentrating and reading), was completed at 0 minutes (pre-dose) and 180 minutes. The responses were rated on a 0 to 10 categorical scale with 0= 'would not interfere at all' and 10= 'would completely interfere' and were combined to give a total score ranging from 0 to 40.

- 'How bothering do you find your throat discomfort' was asked at 0 minutes (pre-dose) and 20, 120 and 180 minutes post-dose. The response was rated on a 0 to 10 ordinal scale marked with 0= 'not bothering' and 10= 'extremely bothering'.

- How much do you feel like your best overall' was asked at 0 minutes (pre-dose) and 60, and 180 minutes post-dose. The response was rated on a 0 to 10 ordinal scale marked with 0= 'I feel at my very worst' and 10= 'I feel at my very best'.

- 'How happy are you, in relation to your throat' was asked at 0 minutes (pre-dose) and 60, and 180 minutes post-dose. The response was rated on a 0 to 10 ordinal scale marked with 0= 'Very unhappy with my throat' and 10= 'Very happy with my throat'.

- 'How hydrated does your throat feel' was asked at 1, 5, 20 and 60 minutes post-dose. The response was rated on a 0 to 10 ordinal scale marked with 0= 'no hydration' and 10= 'very hydrated'.

- 'How lubricated does your throat feel' was asked at 20 and 120 minutes post-dose. The response was rated on a 0 to 10 ordinal scale marked with 0= 'no lubrication' and 10= 'very lubricated'.

- 'Please describe the type of sensation you experienced' was asked at 1 minute post-dose and the patient selected one of five possible responses (mouth-watering sensation, moisture sensation, hydrating sensation, lubricating sensation, no sensation).

- 'How quickly did you feel the moistening/mouth-watering sensation' was asked at 1 minute post-dose and the patient selected one of six possible responses

('Instantly as soon as I started to suck' 'Started after 1 to 5 seconds', 'Started after 6 to 10 seconds', 'Started after 11 to 20 seconds', 'Started after more than 20 seconds' 'No lubricating/mouth-watering sensation')

- 'How deep down within the throat was the hydration felt' was asked at 5 minutes post-dose. The response was rated on a 0 to 10 ordinal scale marked 0= 'Not at all deep in the throat' and 10= 'Very deep in the throat'.

At 180 minutes post-dose, the patients were asked the following questions in the consumer questionnaire:

- Do you feel any better than before you took the lozenge? (yes, no).
- Do you feel less distracted than before you took the lozenge? (yes, no).
- Do you feel less frustrated than before you took the lozenge? (yes, no).
- Do you feel happier than before you took the lozenge? (yes, no).
- 'How would you rate this lozenge as a treatment for dry/irritated sore throat' on a 0 to 10 ordinal scale marked with 0= 'Poor' and 10= 'Excellent'.
- 'How much do you think the lozenge coated your throat' on a 0 to 10 ordinal scale marked with 0= 'No coating' and 10= 'Throat completely coated'.
- 'How mouth watering/moistening is this lozenge' on a 0 to 10 ordinal scale marked with 0= 'Not mouth watering/moistening' and 10= 'Very mouth watering/moistening'.
- 'How deep down within the throat was the relief felt' on a 0 to 10 ordinal scale marked with 0= 'Not at all deep in the throat' 10= 'Very deep in the throat'.
- 'How deep down within the throat do you think this lozenge moistened the throat' on a 0 to 10 ordinal scale marked with 0= 'Not at all deep in the throat', 10= 'Very deep in the throat'.
- 'How deep down within the throat was the lubrication felt' on a 0 to 10 ordinal scale marked with 0= 'Not at all deep in the throat', 10= 'Very deep in the throat'.
- 'Does your throat feel as moist as normal' on a 0 to 10 ordinal scale marked with 0= 'Feels much less moist than normal', 10= 'Feels at least as moist as normal'.

Overall Treatment Rating: At 180 minutes post-dose, patients were asked to provide an overall treatment rating for the lozenge ('How would you rate this lozenge

as a treatment for sore throat?'). Patients selected a number from 0 (indicating poor) to 10 (indicating excellent) on an 11-point ordinal scale.

Patients remained quiet and isolated, in a designated area within the investigational site, during dosing and throughout the 3-hour in-clinic evaluation, under constant supervision by the clinic staff. This helped to avoid any discussion between patients regarding their allocated medication.

A study nurse instructed the patients on how to complete the self-assessment forms and the consumer questionnaire. Patients were asked to swallow the lozenge and then complete the four throat rating scales at each time point within a period of 90 seconds. When completing the assessments, patients were provided with their pre-dose assessment scores but were not allowed access to their other scores. To ensure accurate completion of the assessments, a study nurse supervised the patients during the 3-hour evaluation. A study nurse ensured that the time schedule and the restrictions were adhered to throughout the assessment period and prompted patients at each of the assessment time points.

Full details of the throat and consumer questionnaire assessments are given in Appendices I and III of the CSP, Appendix 16.1.1.

Adverse Events: All AEs reported spontaneously by the patient or in response to questioning or observation by the Investigator and/or supervising study nurse were recorded in the CRF. The Investigator and/or supervising study nurse asked the patients if they had experienced any symptoms or complaints (other than symptoms of a sore throat) at pre-dose and 3 hours post-dose at the end of the in-clinic assessment period. Patients recorded any AEs up to 24 hours post-dose in a patient diary, including the time that the AE started, reason/nature of the AE, time that the AE ended and action taken. After the 1-3 day post-dose telephone call, site staff answered the question 'Has the patient experienced any signs or symptoms since their last visit' in the CRF and transcribed any AE details.

The severity of AEs and relationship of the study medication to the AE were determined by the Investigator. The definitions used for rating the severity and relationship to study medication are given in Table 9.5.2, but medical experience and judgement were also used in the assessment of severity.

Table 9.5.2 Rating Systems used to Determine Adverse Event Severity and Relationship to Study Medication

Variable	Category	Definition
Severity	Mild	The AE did not limit usual activities; the subject may have experienced slight discomfort.
	Moderate	The AE resulted in some limitation of usual activities; the subject may have experienced significant discomfort.
	Severe	The AE resulted in an inability to carry out usual activities; the subject may have experienced intolerable discomfort or pain.
Relationship to study medication	Definite	An AE that followed an anticipated response to the study medication; and that was confirmed by both improvement upon stopping the study medication (dechallenge), and reappearance of the reaction on repeated exposure (rechallenge)
	Probable	An AE that followed a reasonable temporal sequence from administration of the study medication, that was an anticipated response to the study medication; and that could not have been reasonably explained by the known characteristics of the subject's clinical state or concomitant therapy
	Possible	An AE that followed a reasonable temporal sequence from administration of the study medicines; that might have been an anticipated response to the study medication; but that could have been produced by the subject's clinical state or concomitant therapy.
	Unlikely	An AE that did not follow an anticipated response to the study medication; which may have been attributable to other than the study medication and that was more likely to have been produced by the subject's clinical state or concomitant therapy.
	None	An AE that was known beyond all reasonable doubt to be caused by the subject's state or concomitant therapy.

9.5.2 Appropriateness of Measurements

The assessments of analgesic efficacy were made using standard, published and reliable methodologies. Subjective rating scales included ordinal and categorical scales. Throat soreness, pain relief, throat dryness and throat irritation over the 3-hour period were analysed using the area under the curve (AUC) rather than using the sum of the pain intensity difference (SPID) or sum of the pain relief scores (TOTPAR). The AUC analyses were based on actual rather than scheduled timings and allowed for the uneven time interval between assessments.

Safety was assessed by standard AE reporting methodologies.

9.5.3 Primary Efficacy Variable(s)

The primary efficacy endpoint for this study was the AUC for the change in baseline in severity of throat soreness, from 0 to 2 hours.

This was derived from the change in baseline scores from 0 to 2 hours and was calculated using the trapezoidal rule.

The secondary efficacy endpoints for this study were:

- AUC from baseline to 3 hours for the change in baseline in the severity of throat soreness
- Change from baseline in severity of throat soreness (using the 11-point throat soreness scale) at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose
- AUC from baseline to 2 hours post-dose for sore throat relief
- AUC from baseline to 3 hours post-dose for sore throat relief
- Sore throat relief at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose
- AUC from baseline to 2 hours for the change from baseline in throat dryness
- AUC from baseline to 3 hours for the change from baseline in throat dryness
- Change from baseline in throat dryness (using the 11-point throat dryness scale) at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose
- AUC from baseline to 2 hours for the change from baseline in throat irritation
- AUC from baseline to 3 hours for the change from baseline in throat irritation
- Change from baseline in throat irritation (using the 11-point throat irritation scale) at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose
- Onset of analgesia defined as time to first reporting 'moderate pain relief' (which is the midpoint on the 7-point sore throat relief scale).
- Overall treatment rating at 3 hours
- Responses to the questions from the consumer questionnaire

9.5.4 Drug Concentration Measurements

Drug concentrations were not measured in this study.

9.6 Data Quality Assurance

Quality of study data was assured through source data verification and monitoring of the investigational site as detailed in Section 15 of the CSP (Appendix 16.1.1) and use of data management procedures. The quality assurance and internal quality control procedures of Reckitt Benckiser, CPS and Worldwide Clinical Trials also provide reassurance that the clinical study programme was carried out in accordance with GCP guidelines.

All data were entered onto the Worldwide Clinical Trials NODES computer database by a member of the Data Management Section and then verified by repeat data entry by a further Section member.

Before database lock on 15 April 2011, a database audit was performed which had three components.

Audit component 1: Consistency checking and query generation

Twenty patients were selected to undergo full consistency checking where an error would be failure to issue a query when current procedure calls for data enquiry to be raised, or another failure to appropriately respond to a consistency check. A total of one query was missed on one of the 20 cases. This was for confirmation the patient took medication in the 14 days prior to screening and if so a request for the site to provide the concomitant medication record.

Audit component 2: Transcription and annotation procedures

Twenty patients were selected for full assessment where errors could be either transcription or other failures with respect to standard procedures for annotating working copies. No errors were found.

Audit component 3: Critical data fields

The critical fields were checked for 100% of cases. Any errors found were corrected. The fields determined by the Study Statistician and Clinical Project Leader were all AE information, randomisation number, date and time of taking the lozenge, time of assessment, throat soreness and pain relief data from pre-dose to 120 minutes post-dose. All observed errors were corrected.

The findings of the audit indicated that data entry procedures have been followed carefully. No errors were found and no remedial actions were considered necessary.

Audit certificates are included in Appendix 16.1.8.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

The statistical analysis was conducted by Worldwide Clinical Trials on behalf of RBHI. A copy of the final statistical analysis plan is presented as Appendix 16.1.9.

All statistical tests performed were 2-tailed with significance determined by reference to the 5% significance level, unless otherwise stated. The null hypothesis at all times was the equality of the treatments being compared. All comparisons between the treatments were reported with 95% confidence intervals for the difference. For each statistical test, an observed significance level was quoted. Where this value was less than 0.05, 0.01 or 0.001, attention was drawn to the fact using the conventional "*", "**" or "***" annotation, respectively.

Normality assumptions were evaluated by an examination of the residual plots and the Shapiro-Wilk test of normality. Depending on the degree of departure from these assumptions, an alternate non-parametric approach could have been used for supportive purposes.

For any given variable, baseline was taken as the latest recorded assessment available prior to dosing with the study throat lozenge. All tabulations involving change from baseline data only included patients with cohort data i.e. with data at baseline and at follow-up.

All the AUC analyses were based on actual rather than scheduled timings and were calculated using the trapezoidal rule. If the actual time was not recorded, the scheduled time was used instead. For ease of interpretation, the AUC value obtained was divided by the total time that the scale was assessed for reporting purposes.

For all non-AUC analyses, missing data were not replaced.

In the case where a patient recorded more than one score for any particular efficacy measure, the worst of the recorded scores was used for analysis purposes.

The comparability of treatment groups with respect to patient demographics and baseline characteristics was assessed in a descriptive manner, but no formal statistical testing was performed.

All calculations and figures were produced using SAS Version 9.2[14].

Concomitant medications ongoing at randomisation were coded using the ATC level 2 categories from the WHO Dictionary Enhanced 3.10 Version.

9.7.1 Statistical and Analytical Plans

9.7.1.1 Efficacy

Two study populations, the full analysis set and the per-protocol analysis set, were used to analyse efficacy in this study, as described in Section 11.1.

Primary Endpoint

The primary efficacy endpoint was analysed by analysis of covariance (ANCOVA) with baseline throat soreness severity as a covariate and a factor for treatment group. Least squares (LS) adjusted mean values for each treatment group were presented, together with the difference in least squares means. The 95% confidence interval for the difference in least square means was estimated using the mean square error from the ANCOVA.

Secondary Endpoints

All secondary endpoints and the supportive analyses were considered as descriptive evidence of efficacy and were analysed without any procedures to account for multiple comparisons.

The following variables were analysed using the same ANCOVA model as for the primary endpoint:

- AUC for the change from baseline in severity of throat soreness, from 0 to 3 hours
- The change from baseline in severity of throat soreness (using the 11-point throat soreness scale) at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose
- AUC from baseline to 2 hours post-dose for sore throat relief (TOTPAR)
- AUC from baseline to 3 hours post-dose for sore throat relief (TOTPAR)
- Sore throat relief at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose
- Overall treatment rating at 3 hours post-dose

The AUC for the change from baseline in throat dryness at 2 and 3 hours post-dose and the change from baseline in throat dryness at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose were analysed by ANCOVA with a factor for treatment group and covariates for the baseline value for throat dryness and baseline throat soreness severity.

The AUC for change from baseline in throat irritation at 2 and 3 hours post-dose and the change from baseline in throat dryness at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose were analysed by ANCOVA with a factor for treatment group and covariates for the baseline value for throat irritation and baseline throat soreness severity.

The time taken for patients to first report at least moderate sore throat relief (i.e. onset of analgesia) was compared between treatment groups using a Cox proportional hazards model with a factor for treatment group and a covariate for

baseline throat soreness severity. Patients not reporting at least moderate sore throat relief were censored at the time of their last recorded follow-up assessment.

The change from pre-dose to 3 hours post-dose in the functional impairment scale (each component and overall total score) were analysed by ANCOVA with a factor for treatment group and covariates for the baseline throat soreness and the relevant baseline functional impairment score.

For the consumer questionnaire, questions with binary responses were analysed using a logistic regression model with a factor for treatment group and a covariate for baseline throat soreness severity. Questions on non-numeric ordinal scales were analysed using a proportional odds model [15] using PROC LOGISTIC in SAS with a factor for treatment group and a covariate for baseline throat soreness severity. Questions on numeric ordinal scales were analysed using the same ANCOVA model as the primary efficacy endpoint, except for the following three questions: 'How much do you feel like your best overall?'; 'How happy are you, in relation to your throat?' and 'How bothering do you find your throat discomfort now?' These were analysed by ANCOVA with a factor for treatment group and covariates for the baseline throat soreness and the relevant baseline score for the specific question. Questions where the patients could select multiple responses were tabulated but were not formally analysed.

Exploratory Analysis

Analyses of the primary efficacy endpoint were performed by key baseline characteristics. For each subgroup, the main effect and treatment-by-subgroup interaction terms were added to the standard model used in the primary endpoint analysis. Key variables of interest were baseline throat soreness severity (≤median, >median), baseline throat dryness (≤median, >median), baseline throat irritation (≤median, >median), cause of sore throat (URTI/environmental factors), age at study entry (≤median, >median), gender and total score from the TPA at baseline (≤median, >median. These models were used to estimate treatment comparisons within the subgroups that correspond with the sub-grouping factor. For the investigation of baseline throat soreness severity subgroup effect, the model fitted was analysis of variance (ANOVA) rather than ANCOVA as baseline throat soreness severity was considered a two-level factor rather than as a continuous covariate.

9.7.1.2 Safety

The safety set, which included all randomised patients who took the study medication, was used to analyse safety. The safety set was analysed as treated.

Safety and tolerability were assessed in terms of the overall proportion of patients with AEs and SAEs.

Extent of Exposure

Extent of exposure was described by whether the patient took the trial medication.

Adverse Events (AEs)

All treatment emergent AEs were listed and tabulated by treatment, severity, relationship to therapy and primary system organ class according to MedDRA Version 13.1. In counting the number of events reported, continuous events, i.e. those reported more than once and which did not cease, were counted only once; non-continuous adverse events reported several times by the same patient were counted as multiple events. Events present immediately prior to the dose of study medication that did not worsen in severity, were not included. Events with start dates during follow-up (i.e. more than 24 hours after dosing) were not considered treatment emergent and were listed separately in Appendix 16.2.7.

Differences between treatment groups in the proportion of patients reporting treatment emergent adverse events were compared using the chi-square test.

Withdrawals

The number of patients who withdrew from the study was presented. The timings and reasons for withdrawal were summarised by treatment if appropriate.

Concomitant Medications

Concomitant medications commencing during the study were coded using the ATC level 2 categories from the WHO Dictionary Enhanced 3.10 Version.

9.7.2 Determination of Sample Size

In a previous study conducted with Strepsils Original Lozenges[4], the difference in the mean AUC for the change from baseline in the severity of throat soreness (using the 11-point Throat Soreness Scale) from 0-2 hours between Strepsils Original lozenge and placebo for patients with a TPA ≥3 was 0.8 with a standard deviation of 1.6. Assuming that the variability for the same variable for the test lozenge was of a similar magnitude as for Strepsils lozenge in the previous study, and assuming that the differences in patient population would not have an impact, 85 patients per group would have provided 90% power to detect a difference of 0.8 in the mean AUC between the test product and placebo using a 2 sample t-test at the 5% significance level. In order to account for dropouts, a total of 200 patients were recruited into the study (100 patients per group). The actual variability observed during the study was 1.37 (root mean square error from the ANCOVA model of the full analysis set) which was lower than predicted and suggests that the study was more than adequately powered.

9.8 Changes in the Conduct of the Study or Planned Analysis

9.8.1 Changes in the Conduct of the Study

No changes were made in the conduct of the study

9.8.2 Changes in the Planned Statistical Analysis of the Study

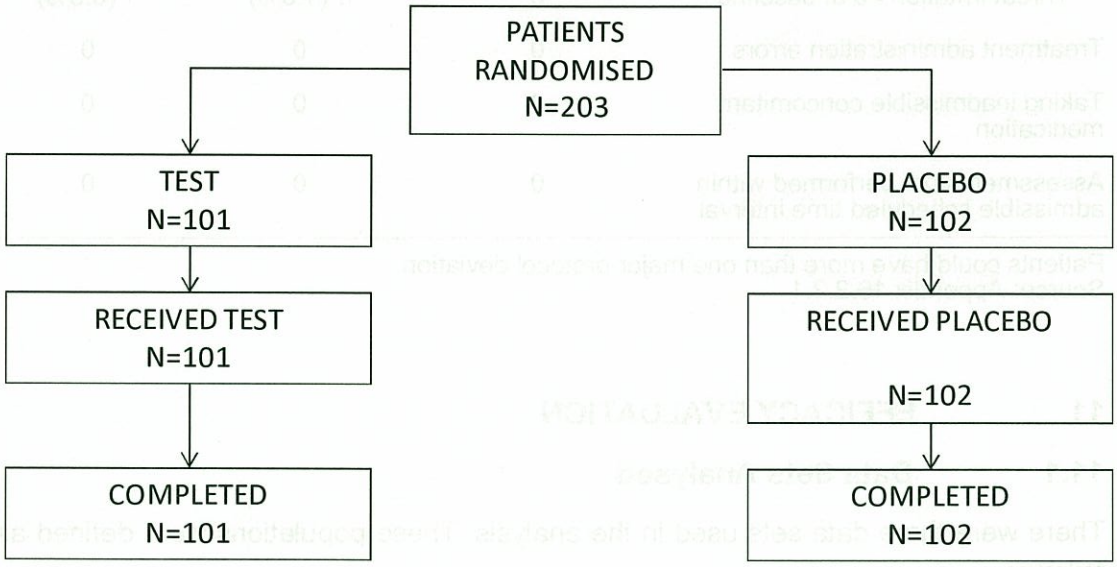
No changes were made in the planned statistical analyses.

10 STUDY PATIENTS

10.1 Disposition of Patients

A total of 203 patients were randomised into the study between 2 November 2010 and 26 February 2011. One hundred and one (101) patients received the test lozenge and 102 patients received a placebo throat lozenge. All 203 patients completed the study (Figure 10.1.1).

Figure 10.1.1: Disposition of Patients



Data source: Table 14.1.1

10.2 Protocol Deviations

The number (%) of patients with a major protocol deviation is summarised in Table 10.2.1. A listing of individual patients who deviated from the protocol is presented in Appendix 16.2.2.

Overall, eight patients entered the study despite not satisfying the entry criteria. Patient number 44 (placebo) had inadmissible baseline scores for throat irritation and throat dryness. Six patients (numbers 001, 028, 032 and 040 – test; numbers 021 and 031 - placebo) had throat soreness scores of less than six at baseline, which were inadmissible by the protocol. A further patient number 003 (placebo) had an inadmissible throat dryness at baseline. All these eight patients were excluded from the per-protocol dataset.

There were no treatment administration errors and no patients were taking inadmissible concomitant medication. No assessments were performed outside the admissible scheduled timings.

Table 10.2.1 Number (%) of patients with major protocol deviation

	Test (N=101)	Placebo (N=102)	Total (N=203)
Did not satisfy entry criteria	4 (4.0%)	4 (3.9%)	8 (3.9%)
Throat soreness <6 at baseline	4 (4.0%)	2 (2.0%)	6 (3.0%)
Throat dryness >3 at baseline	0	2 (2.0%)	2 (1.0%)
Throat irritation >5 at baseline	0	1 (1.0%)	1 (0.5%)
Treatment administration errors	0	0	0
Taking inadmissible concomitant medication	0	0	0
Assessments not performed within admissible scheduled time interval	0	0	0

Patients could have more than one major protocol deviation
Source: Appendix 16.2.2.1

11 EFFICACY EVALUATION

11.1 Data Sets Analysed

There were three data sets used in the analysis. These populations were defined as follows:

The **safety set,** which included all patients who take the study medication. The safety set was analysed as treated.

The analysis of efficacy data used two datasets:

The **full analysis set**, which consisted of all patients who were randomised to the study and took the study medication. Any patients with treatment administration errors were analysed according to the treatment to which they were randomised. This was the primary efficacy analysis population. For this study, the full analysis set and the safety set were identical.

The **per-protocol** set, which was a subset of the full analysis set and consisted of all patients who satisfied all of the inclusion/exclusion criteria, who correctly received the treatment to which they were randomised, and who successfully completed the treatment period up to the 2 hour assessment.

All protocol deviations were assessed and documented on a case-by-case basis prior to the database lock, and any incidence of deviations considered having a serious impact on the efficacy results led to the relevant patient being excluded from the analysis set. Major protocol deviations included:

- Treatment administration errors

- Taking inadmissible concomitant medication (within the first 2 hours post-dosing or inadequate washout prior to randomisation)
- Inadmissible starting times of the follow-up assessments within the first 2 hours post dosing
    - 1, 5, 10 and 15 minute assessments not performed within ±1 minute of the scheduled times
    - 30, 45, 60, 75, 90, 105 and 120 minute assessments not performed within ±5 minutes of the scheduled times

The per-protocol analysis set was only used to assess the primary efficacy endpoint (the AUC from baseline in severity of throat soreness, from 0 to 2 hours) and the AUC from baseline to 2 hours in sore throat relief.

The number (%) of patients included in the datasets is summarised in Table 11.1.1.

Table 11.1.1 Number (%) of patients analysed in each dataset

Variable	Test	Placebo	Total
Safety analysis set	101 (100%)	102 (100%)	203 (100%)
Full analysis set	101 (100%)	102 (100%)	203 (100%)
Per-protocol analysis set	97 (96%)	98 (96%)	195 (96%)

Source: Appendix 16.2.3.1

Appendix 16.2.3 contains a tabular listing of all patients excluded from the efficacy analysis and reasons for exclusion.

The strategy for the inclusion/exclusion criteria for each of the data sets analysed was included in the statistical analysis plan for the study and finalised following discussions of evaluability held after the database had been locked and prior to the blind being broken.

11.2 Demographic and Other Baseline Characteristics

11.2.1 Demographic and Baseline Data

A summary of patient demographics is presented in Tables 14.1.2 to 14.1.5. Summary statistics and frequency distributions are presented both overall and by treatment group. In general, the treatment groups were well balanced for the demographic variables.

The demographic characteristics are summarised in Table 11.2.1. Overall, the age ranged from 16 to 67 years, with a mean age of 34.3 years and 107 (53%) patients were male. The majority of patients, namely 198 (98%) were Caucasian. A total of 161 (79%) patients drank alcohol, 76 (37%) were current smokers and 30 (15%)

were former smokers. Table 14.1.2 presents full summary statistics of demographic variables; the treatments were balanced with respect to all variables.

Table 11.2.1 Demographic characteristics – Full analysis set

Variable	Test	Placebo	Overall
Number of patients	101	102	203
Age (yr) (Mean ± sd)	34.3±14.0	34.3±13.2	34.3±13.6
Gender (% male)	51.5%	53.9%	52.7%
Race (% Caucasian)	98.0%	97.1%	97.5%
Alcohol drinker (%)	83.2%	75.5%	79.3%
Current smoker (%)	34.7%	40.2%	37.4%

Source: Table 14.1.2

11.2.2 Baseline Disease Characteristics

The baseline disease characteristics are summarised in Table 11.2.2. Mean duration of URTI was 2.2 days and mean duration of sore throat was 2.2 days. A total of 186 (92%) patients had cause of sore throat recorded as due to URTI and the remaining 17 (8%) patients had a sore throat due to environmental factors (Table 14.1.2).

The mean total score from the TPA at screening was 6.28 with a range of 3 to 15. Throat soreness was measured on an 11-point scale at screening where 0 = not sore and 10 = very sore and the patient had to score at least 6 to be eligible for entry; the mean score was 7.16 (Table 14.1.5).

The treatments were balanced with respect to all variables.

Table 11.2.2 Baseline sore throat characteristics – Full analysis set

Variable	Test	Placebo	Overall
Number of patients	101	102	203
Duration of URTI (days) (Mean ± sd)	2.2±1.0	2.2±1.0	2.2±1.0
Duration of sore throat (days) (Mean ± sd)	2.1±0.8	2.2±0.8	2.2±0.8
Cause of sore throat			
URTI (%)	92.1%	91.2%	91.6%
Environmental factors (%)	7.9%	8.8%	8.4%
Tonsillopharyngitis assessment (Mean ± sd)	6.05±2.41	6.50±2.96	6.28±2.71
Throat soreness (Mean ± sd)[a]	7.20±1.07	7.12±0.82	7.16±0.95

a Assessment of throat soreness on an 11-point scale (0 = Not Sore and 10 = Very Sore)

Source: Tables 14.1.2 and 14.1.5

11.2.3 Medical History

A total of 40 (20%) patients reported a previous medical condition (Table 14.1.3) and 86 (42%) patients reported an ongoing medical condition of which 21 (10%) patients had conditions within the gastrointestinal system and 20 (10%) had conditions of the musculoskeletal system (Table 14.1.4). There was some imbalance between the two treatment groups in the types of ongoing condition.

11.2.4 Pre-dose Efficacy Data

Table 14.1.6 presents a summary of the mean values of the efficacy variables recorded immediately before dosing. Table 11.2.3 below summarises these data. With respect to the functional impairment scale, of the four activities referenced, the sore throat was most affecting swallowing (mean score 6.81) and talking (mean score 5.67). The mean score for throat soreness was 7.12 with six patients having scores less than six, which violated the protocol inclusion criteria. Mean throat dryness was 2.26 with two patients having scores of greater than three which was inadmissible by the protocol. Mean throat irritation score was 2.41 with one patient having a score of seven which violated the protocol inclusion criteria. The majority of patients, 157 (77%) had dry and scratchy throat, 28 (14%) patients had swollen and inflamed throats. There was an imbalance between treatment groups in the proportion of patients with swollen and inflamed throats, namely 20% in the placebo and only 8% in the Test lozenge group; all other efficacy variables were balanced between treatment groups.

Table 11.2.3 Pre-dose efficacy variables (mean ± sd /% of patients) – Full analysis set

Variable	Test	Placebo	Overall
Functional Impairment Scale (How sore throat affected) *Each activity measured on an 11-point scale where 0 = Would not interfere at all, 10 = Would completely interfere*			
Number of patients	101	102	203
Talking	5.74±2.35	5.59±2.41	5.67±2.37
Swallowing	6.90±1.95	6.73±1.92	6.81±1.93
Concentrating	5.05±2.52	4.36±2.83	4.70±2.70
Reading	3.39±2.69	2.83±2.96	3.11±2.83
Total score (0 to 40)	21.1±7.4	19.5±7.9	20.3±7.7
Assessment of throat soreness on an 11-point scale (0 = Not Sore and 10 = Very Sore)	7.12±1.44 (101)	7.13±0.99 (102)	7.12±1.23 (203)
Assessment of throat dryness on an 11-point scale (0 = Completely dry and 10 = Completely moist)	2.24±0.83 (101)	2.27±1.01 (102)	2.26±0.92 (203)
Assessment of throat irritation on an 11-point scale (0 = Completely scratchy, tickly or itchy and 10 = Not at all scratchy, tickly)	2.40±1.10 (101)	2.42±1.21 (102)	2.41±1.15 (203)
How dry or moist the patient throat felt normally on an 11-point scale (0 = Completely dry and 10 = Completely moist)	7.06±2.54 (101)	6.89±2.78 (102)	6.98±2.66 (203)
How bothering did the patient find his/her throat discomfort on an 11-point scale (0 = Not bothering and 10 = Extremely bothering)	7.39±1.64 (101)	7.12±1.184 (102)	7.25±1.74 (203)
Description of throat			
Dry and scratchy (%)	80 (79.2%)	77 (75.5%)	157 (77.3%)
Sharp and stabbing pain (%)	13 (12.9%)	5 (4.9%)	18 (8.9%)
Swollen and inflamed (%)	8 (7.9%)	20 (19.6%)	28 (13.8%)

Source: Table 14.1.6

Individual patient demographic and baseline data are presented in Appendix 16.2.4.

11.2.5 Concomitant Medication

Details of concomitant medication ongoing at time of randomisation are presented in Table 14.1.7, 67 (33%) patients reported the use of at least one concomitant medication. In terms of WHO ATC level 2 categories, the most commonly reported category was sex hormones and modulators of the genital system with 27 (13%) patients reporting. No patients were taking inadmissible concomitant medication.

11.3 Measurements of Treatment Compliance

All patients took their study medication dose under supervision at the investigational site.

11.4 Efficacy results

11.4.1 Analysis of Efficacy

11.4.1.1 Primary Endpoint

The primary endpoint was the AUC for the change from baseline in severity of throat soreness, from 0 to 2 hours. Table 11.4.1 presents details of the AUC for the change from baseline to 2 hours post-dose in throat soreness.

Using the full analysis set (n=203), there was no evidence of any difference between the two treatment groups (p=0.85). The LS mean reductions were –1.50 (test) and –1.53 (placebo). The term for baseline throat soreness was highly statistically significant in the ANCOVA model (p<0.0001; Table 14.2.1.1).

For the equivalent per-protocol analysis (n=195), the results mirrored the full analysis set with the LS means reductions estimated from the model were –1.62 and –1.60 for test and placebo lozenges respectively (treatment p-value = 0.90; Table 14.2.1.2).

Table 11.4.1 Primary Efficacy Endpoint: AUC from baseline to 2 hours post-dose for the change from baseline in throat soreness

	Test		Placebo
FULL ANALYSIS SET			
N	101		102
Mean±sd	-1.49±1.67		-1.53±1.43
LS mean[a]	-1.50		-1.53
Difference between LS means[b]		0.04	
Se		0.19	
95% CI		-0.34, 0.42	
p-value for treatment[a]		0.85	
PER-PROTOCOL SET			
N	97		98
Mean±sd	-1.65±1.50		-1.57±1.43
LS mean[a]	-1.62		-1.60
Difference between LS means[b]		-0.03	
Se		0.20	
95% CI		-0.42,0.37	
p-value for treatment[a]		0.90	

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b Test lozenge minus placebo. A negative difference favours test lozenge.
Source: Tables 14.2.1.1 and 14.2.1.2

Throat soreness measured on an 11-point scale where 0 = Not sore, 10 = Very sore

11.4.1.2 Secondary Endpoints

AUC for the Change from Baseline to 3 hours in Throat Soreness

Table 11.4.2 presents details of the AUC for the change from baseline to 3 hours post-dose in throat soreness for the full analysis set. There was no evidence of any difference between the two treatment groups (p=0.72). The LS mean reductions were -1.47 (test lozenge) and –1.55 (placebo). The term for baseline throat soreness was highly statistically significant in the ANCOVA model (p<0.0001). Further details are given in Table 14.2.2.

Table 11.4.2 AUC from baseline to 3 hours post-dose for the change from baseline in throat soreness – Full analysis set

	Test		Placebo
N	101		102
Mean±sd	-1.47±1.69		-1.55±1.45
LS mean[a]	-1.47		-1.55
Difference between LS means[b]		0.07	
Se		0.20	
95% CI		-0.32, 0.47	
p-value for treatment[a]		0.72	

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b Test lozenge minus placebo. A negative difference favours test lozenge.
Source: Table 14.2.2

Throat soreness measured on an 11-point scale where 0 = Not sore, 10 = Very sore

Change from Baseline in Throat Soreness

Table 11.4.3 presents details of change in throat soreness at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose. For all these

assessments, there was no statistically significant differences between the treatment groups and there was little difference between the two treatments in the mean changes from baseline as can be seen in Figure 11.4.1 below. Maximum reductions following administration of the test lozenge were achieved at 45 minutes post-dose. Full summary statistics are presented in Tables 14.2.3 to 14.2.17.

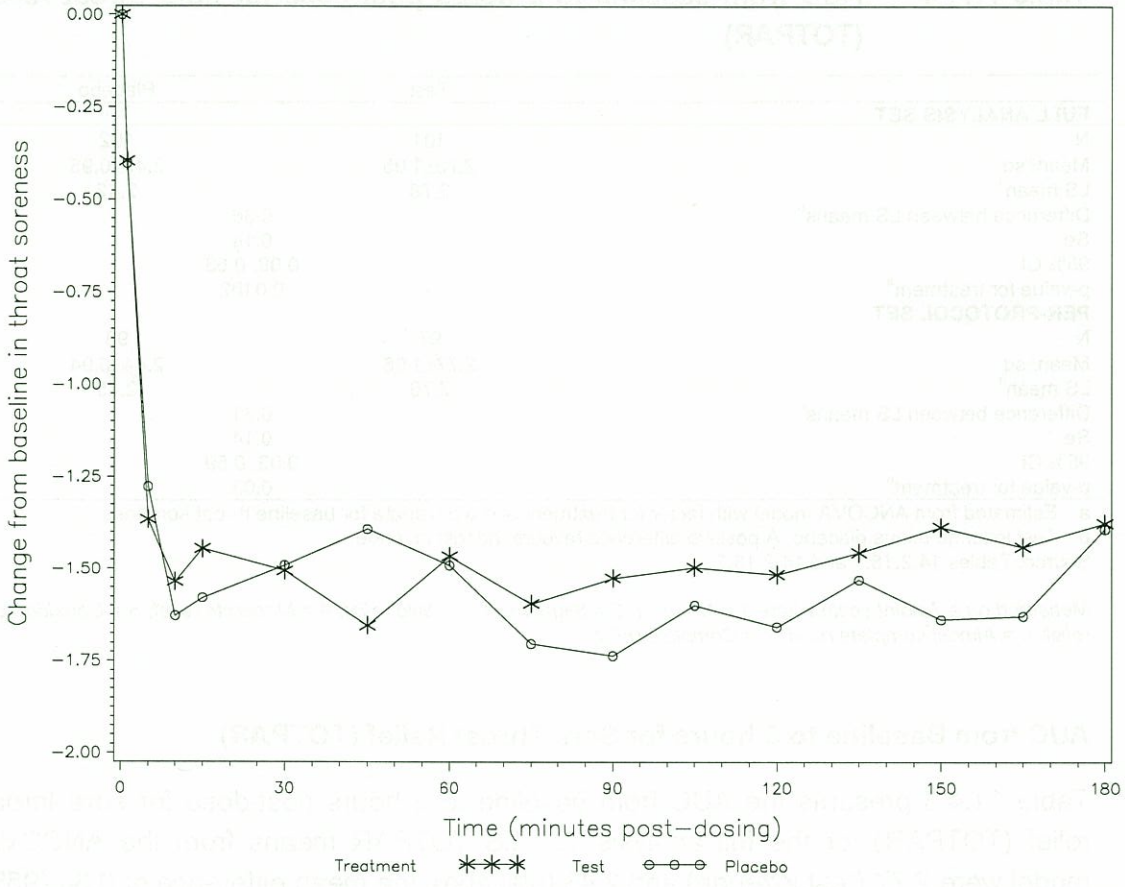
Table 11.4.3 Mean ± sd (n) for change from baseline in throat soreness at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose – Full analysis set

Minutes post-dose	Test	Placebo
Baseline	7.12±1.44 (101)	7.13±0.99 (102)
1	-0.40±1.63 (101)	-0.40±1.27 (102)
5	-1.37±1.92 (101)	-1.28±1.77 (101)
10	-1.53±1.91 (101)	-1.63±1.87 (102)
15	-1.45±1.87 (101)	-1.58±1.85 (102)
30	-1.50±1.85 (101)	-1.49±1.66 (102)
45	-1.65±2.09 (101)	-1.39±1.76 (102)
60	-1.47±1.99 (101)	-1.49±1.68 (102)
75	-1.59±1.90 (101)	-1.70±1.75 (101)
90	-1.52±2.06 (101)	-1.74±1.85 (102)
105	-1.50±2.01 (101)	-1.60±1.79 (102)
120	-1.51±2.11 (101)	-1.66±1.82 (102)
135	-1.46±2.16 (101)	-1.53±1.85 (102)
150	-1.39±1.98 (101)	-1.64±1.83 (102)
165	-1.44±2.05 (100)	-1.63±2.08 (102)
180	-1.38±2.16 (101)	-1.39±1.90 (102)

Source: Tables 14.2.3 to 14.2.17

Throat soreness measured on an 11-point scale where 0 = Not sore, 10 = Very sore

Figure 11.4.1 Mean change from baseline in throat soreness from 1 to 180 minutes post first dose – Full analysis set



Throat soreness measured on an 11-point scale where 0 = Not sore, 10 = Very sore

AUC from Baseline to 2 hours for Sore Throat Relief (TOTPAR)

Table 11.4.4 presents the AUC from baseline to 2 hours post-dose for sore throat relief (TOTPAR) for the full analysis and per-protocol sets.

For the full analysis set, LS TOTPAR means from the ANCOVA model were 2.78 (test lozenge) and 2.42 (placebo); the mean difference of 0.36 (95% CI 0.09, 0.63) was statistically significantly (p=0.0102) in favour of the test lozenge. The term for baseline throat soreness severity (p=0.03) were also statistically significant (Table 14.2.18.1). The equivalent per-protocol analysis had identical statistical conclusions. The LS means were 2.76 and 2.45 for the test lozenge and placebo respectively (Table 14.2.18.2).

Table 11.4.4 AUC from baseline to 2 hours post-dose for sore throat relief (TOTPAR)

	Test		Placebo
FULL ANALYSIS SET			
N	101		102
Mean±sd	2.78±1.05		2.42±0.95
LS mean[a]	2.78		2.42
Difference between LS means[b]		0.36	
Se		0.14	
95% CI		0.09, 0.63	
p-value for treatment[a]		0.0102	
PER-PROTOCOL SET			
N	97		98
Mean±sd	2.77±1.06		2.44±0.94
LS mean[a]	2.76		2.45
Difference between LS means[b]		0.31	
Se		0.14	
95% CI		0.03, 0.59	
p-value for treatment[a]		0.03	

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b Test lozenge minus placebo. A positive difference favours the test lozenge.
Source: Tables 14.2.18.1 and 14.2.18.2

Measured on a 7-point scale where 1 = No relief, 2 = Slight relief, 3 = Mild relief, 4 = Moderate relief, 5 = Considerable relief, 6 = Almost complete relief, 7 = Complete relief

AUC from Baseline to 3 hours for Sore Throat Relief (TOTPAR)

Table 11.4.5 presents the AUC from baseline to 3 hours post-dose for sore throat relief (TOTPAR) for the full analysis set. LS TOTPAR means from the ANCOVA model were 2.77 (test lozenge) and 2.43 (placebo); the mean difference of 0.34 (95% CI 0.05, 0.63) was statistically significantly (p=0.02) in favour of the test lozenge. The term for baseline throat soreness severity was not statistically significant (p=0.07; Table 14.2.18.1).

Table 11.4.5 AUC from baseline to 3 hours post-dose for sore throat relief (TOTPAR) – Full analysis set

	Test		Placebo
N	101		102
Mean±sd	2.77±1.08		2.43±1.00
LS mean[a]	2.77		2.43
Difference between LS means[b]		0.34	
Se		0.15	
95% CI		0.05, 0.63	
p-value for treatment[a]		0.02	

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b Test lozenge minus placebo. A positive difference favours test lozenge.
Source: Tables 14.2.19

Measured on a 7-point scale where 1 = No relief, 2 = Slight relief, 3 = Mild relief, 4 = Moderate relief, 5 = Considerable relief, 6 = Almost complete relief, 7 = Complete relief

Change in Sore Throat Relief

Table 11.4.6 presents details of sore throat relief at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose. For all these assessments, mean sore throat relief was greater for the test lozenge, with differences versus

placebo being statistically significant from one to 75 minutes inclusive as can be seen in Figure 11.4.2 below. Maximum relief following administration of the test lozenge was achieved at 45 minutes post-dose. Full summary statistics are presented in Tables 14.2.20 to 14.2.34.

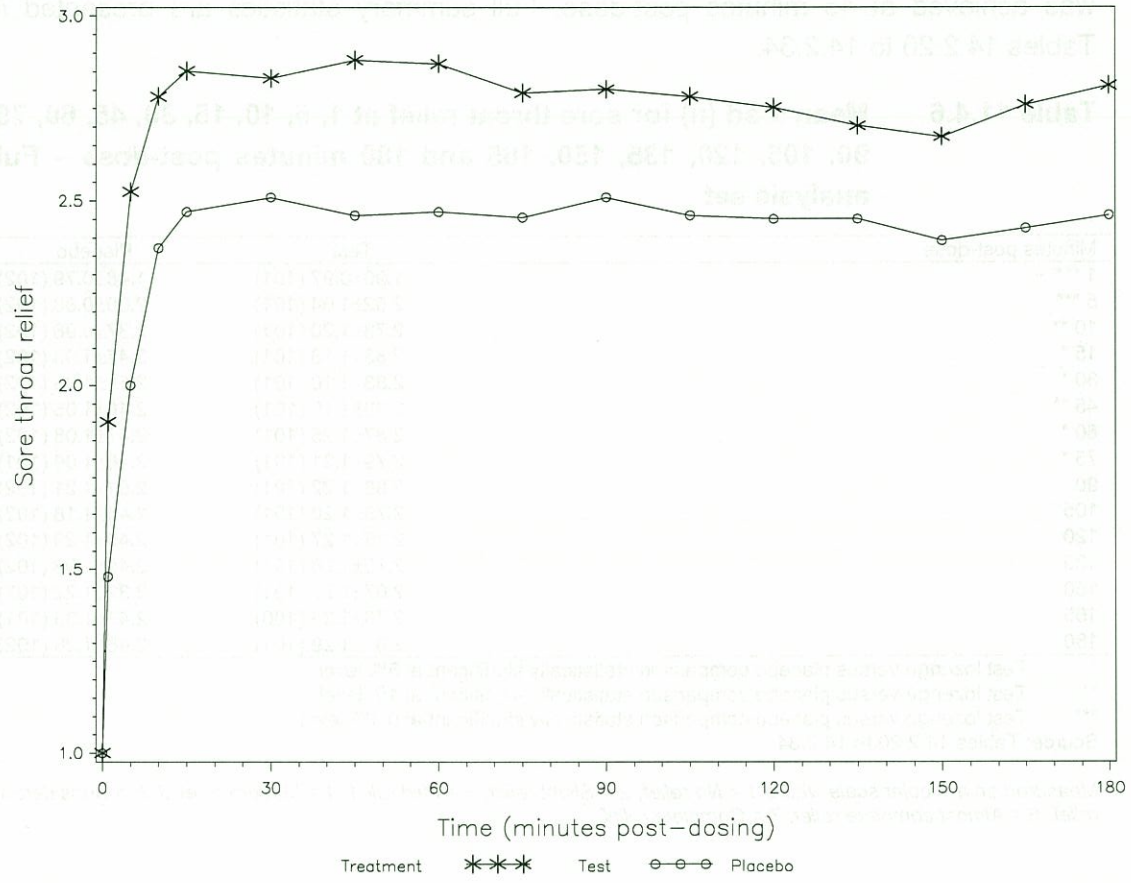
Table 11.4.6 Mean ± sd (n) for sore throat relief at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose – Full analysis set

Minutes post-dose	Test	Placebo
1 ***	1.90±0.97 (101)	1.48±0.79 (102)
5 ***	2.52±1.04 (101)	2.00±0.88 (102)
10 **	2.78±1.20 (101)	2.37±0.98 (102)
15 *	2.85±1.13 (101)	2.47±1.03 (102)
30 *	2.83±1.10 (101)	2.51±1.03 (102)
45 **	2.88±1.19 (101)	2.46±1.05 (102)
60 *	2.87±1.25 (101)	2.47±1.08 (102)
75 *	2.79±1.21 (101)	2.46±1.09 (101)
90	2.80±1.22 (101)	2.51±1.21 (102)
105	2.78±1.20 (101)	2.46±1.18 (102)
120	2.75±1.27 (101)	2.45±1.29 (102)
135	2.70±1.28 (101)	2.45±1.23 (102)
150	2.67±1.27 (101)	2.39±1.22 (102)
165	2.76±1.33 (100)	2.43±1.33 (101)
180	2.81±1.29 (101)	2.46±1.28 (102)

* Test lozenge versus placebo comparison statistically significant at 5% level
** Test lozenge versus placebo comparison statistically significant at 1% level
*** Test lozenge versus placebo comparison statistically significant at 0.1% level
Source: Tables 14.2.20 to 14.2.34

Measured on a 7-point scale where 1 = No relief, 2 = Slight relief, 3 = Mild relief, 4 = Moderate relief, 5 = Considerable relief, 6 = Almost complete relief, 7 = Complete relief

Figure 11.4.2 Mean sore throat relief from 1 to 180 minutes post first dose – Full analysis set



Measured on a 7-point scale where 1 = No relief, 2 = Slight relief, 3 = Mild relief, 4 = Moderate relief, 5 = Considerable relief, 6 = Almost complete relief, 7 = Complete relief

AUC from Baseline to 2 and 3 hours for Throat Dryness

Table 11.4.7 presents the AUC analyses from baseline to 2 and 3 hours post-dose for the change from baseline in throat dryness for the full analysis set. For the 2 hour analysis, LS means from the ANCOVA model were 1.87 (test lozenge) and 1.75 (placebo); the mean difference of 0.12 (95% CI -0.27, 0.50) was not statistically significantly (p=0.55); the term for baseline throat dryness was highly statistically significant (p<0.0001) whereas the term for baseline throat soreness was not statistically significant (p=0.21; Table 14.2.35). For the 3 hour analysis, the LS means were 1.74 (test lozenge) and 1.65 (placebo); the mean difference of 0.09 (95% CI -0.31, 0.48) was not statistically significantly (p=0.66); the term for baseline throat dryness was highly statistically significant (p<0.0001) whereas the term for baseline throat soreness was not statistically significant (p=0.23; Table 14.2.36).

Table 11.4.7 AUC from baseline to 2 and 3 hours post-dose for the change from baseline in throat dryness – Full analysis set

	Test lozenge		Placebo
AUC 0-2 hours			
N	101		102
Mean±sd	1.88±1.43		1.74±1.63
LS mean[a]	1.87		1.75
Difference between LS means[b]		0.12	
Se		0.19	
95% CI		-0.27, 0.50	
p-value for treatment[a]		0.55	
AUC 0-3 hours			
N	101		102
Mean±sd	1.75±1.42		1.64±1.68
LS mean[a]	1.74		1.65
Difference between LS means[b]		0.09	
Se		0.20	
95% CI		-0.31, 0.48	
p-value for treatment[a]		0.66	

a Estimated from ANCOVA model with factor for treatment and covariates for baseline throat soreness and baseline throat dryness

b Test lozenge minus placebo. A positive difference favours test lozenge.

Source: Tables 14.2.35 and 14.2.36

Measured on an 11-point scale 0 = Completely dry, 10 = Completely moist

Change from Baseline in Throat Dryness

Table 11.4.8 presents details of change in throat dryness at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose. Up to 135 minutes post-dose, mean changes from baseline were larger and therefore more favourable for the test lozenge, these differences were significant at the 5% level at 1 and 5 minutes post-dose. Figure 11.4.3 below presents the mean profile. Maximum mean improvements in throat dryness following administration of the test lozenge were achieved at 5 minutes post-dose. Full summary statistics are presented in Tables 14.2.37 to 14.2.51.

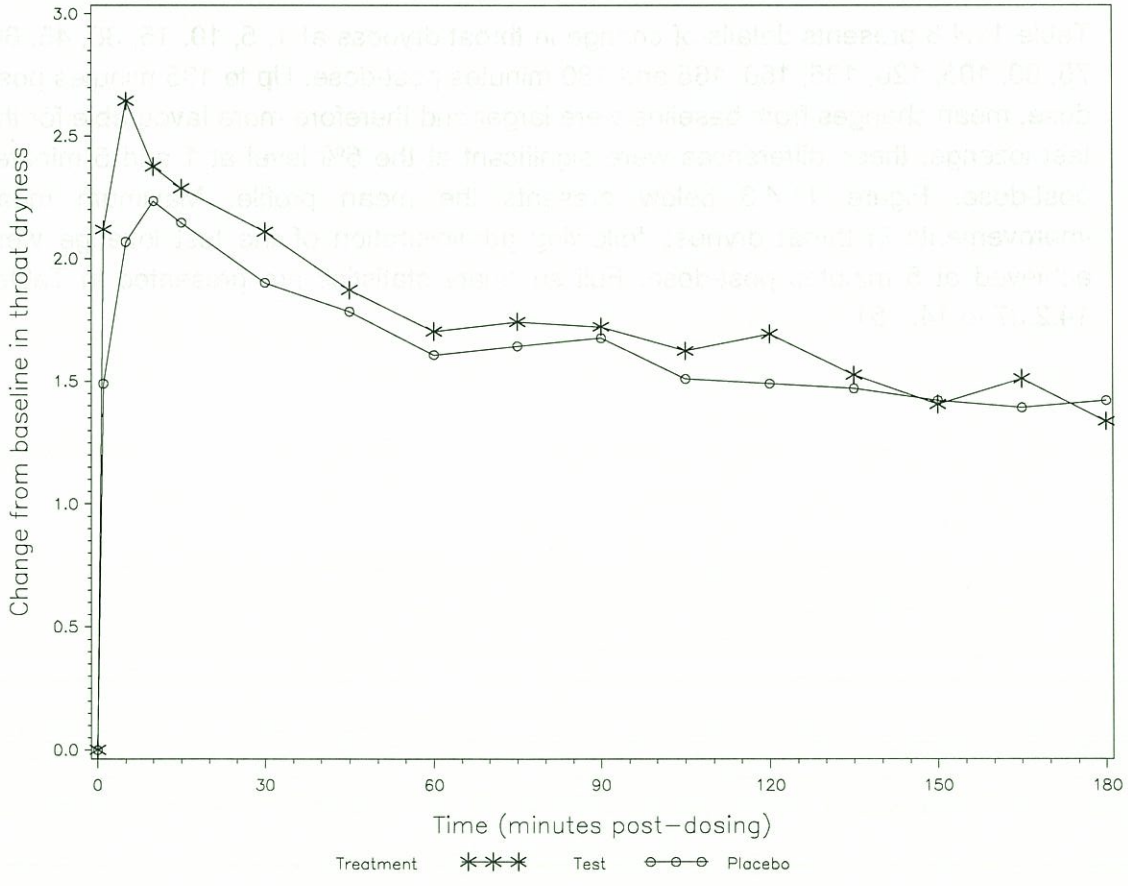
Table 11.4.8 Mean ± sd (n) for change from baseline in throat dryness at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose – Full analysis set

Minutes post-dose	Test	Placebo
Baseline	2.24±0.83 (101)	2.27±1.01 (102)
1 *	2.12±2.13 (101)	1.49±1.63 (102)
5 *	2.64±1.99 (101)	2.07±1.45 (102)
10	2.38±1.78 (101)	2.24±1.82 (102)
15	2.29±1.61 (101)	2.15±1.72 (102)
30	2.11±1.55 (101)	1.90±1.85 (102)
45	1.87±1.90 (101)	1.78±1.79 (102)
60	1.70±1.78 (101)	1.61±1.80 (102)
75	1.74±1.78 (101)	1.64±2.07 (101)
90	1.72±1.71 (101)	1.68±1.98 (102)
105	1.62±1.71 (101)	1.51±2.09 (102)
120	1.69±1.87 (101)	1.49±1.97 (102)
135	1.52±1.69 (101)	1.47±1.94 (102)
150	1.41±1.73 (101)	1.42±1.97 (102)
165	1.51±1.84 (100)	1.39±2.08 (102)
180	1.34±1.86 (101)	1.42±2.13 (102)

* Test lozenge versus placebo comparison statistically significant at 5% level
Source: Tables 14.2.37 to 14.2.51

Measured on an 11-point scale 0 = Completely dry, 10 = Completely moist

Figure 11.4.3 Mean change from baseline in throat dryness from 1 to 180 minutes post first dose – Full analysis set



Measured on an 11-point scale 0 = Completely dry, 10 = Completely moist

AUC from Baseline to 2 and 3 hours for Throat Irritation

Table 11.4.9 presents the AUC analyses from baseline to 2 and 3 hours post-dose for the change from baseline in throat irritation for the full analysis set. For the 2 hour analysis, LS means from the ANCOVA model were 1.55 (test lozenge) and 1.27 (placebo); the mean difference of 0.28 (95% CI -0.08, 0.65) was not statistically significantly (p=0.13); the term for baseline throat irritation was highly statistically significant (p<0.0001) whereas the term for baseline throat soreness was not statistically significant (p=0.33; Table 14.2.52). For the 3 hour analysis, the LS means were 1.48 (test lozenge) and 1.24 (placebo); the mean difference of 0.25 (95% CI -0.14, 0.63) was not statistically significantly (p=0.21); the term for baseline throat irritation was highly statistically significant (p<0.0001) whereas the term for baseline throat soreness was not statistically significant (p=0.28; Table 14.2.53).

Table 11.4.9 AUC from baseline to 2 and 3 hours post-dose for the change from baseline in throat irritation – Full analysis set

	Test lozenge		Placebo
AUC 0-2 hours			
N	101		102
Mean±sd	1.57±1.63		1.26±1.63
LS mean[a]	1.55		1.27
Difference between LS means[b]		0.28	
Se		0.18	
95% CI		-0.08, 0.65	
p-value for treatment[a]		0.13	
AUC 0-3 hours			
N	101		102
Mean±sd	1.49±1.69		1.23±1.70
LS mean[a]	1.48		1.24
Difference between LS means[b]		0.25	
Se		0.20	
95% CI		-0.14, 0.63	
p-value for treatment[a]		0.21	

a Estimated from ANCOVA model with factor for treatment and covariates for baseline throat soreness and baseline throat irritation

b Test lozenge minus placebo. A positive difference favours test lozenge.

Source: Tables 14.2.52 and 14.2.53

Measured on an 11-point scale 0 = Completely scratchy, tickly or itchy 10 = Not at all scratchy, tickly or itchy

Change from Baseline in Throat Irritation

Table 11.4.10 presents details of change in throat irritation at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose. For all these assessments, mean improvements from baseline were larger for the test lozenge as can be seen in Figure 11.4.4 below, with statistically significant differences at 1, 5 and 10 minutes post-dose. Maximum improvements following administration of the test lozenge were achieved at 10 minutes post-dose. Full summary statistics are presented in Tables 14.2.54 to 14.2.68.

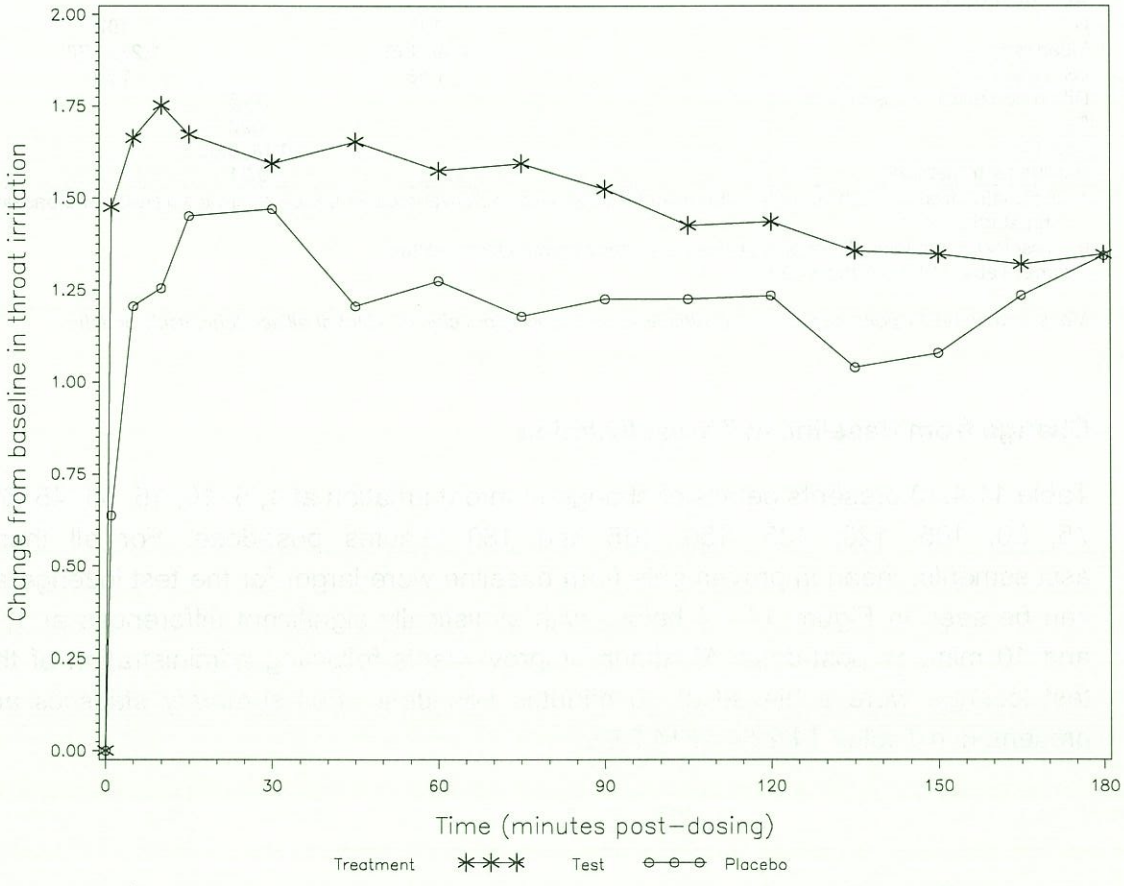
Table 11.4.10 Mean ± sd (n) for change from baseline in throat irritation at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose – Full analysis set

Minutes post-dose	Test	Placebo
Baseline	2.40±1.10 (101)	2.42±1.21 (102)
1 ***	1.48±1.95 (101)	0.64±1.18 (102)
5 *	1.66±2.02 (101)	1.21±1.37 (102)
10 *	1.75±1.80 (101)	1.25±1.53 (102)
15	1.67±1.81 (101)	1.45±1.76 (102)
30	1.59±1.67 (101)	1.47±1.82 (102)
45	1.65±2.01 (101)	1.21±1.86 (102)
60	1.57±2.08 (101)	1.27±1.80 (102)
75	1.59±1.86 (101)	1.18±1.83 (101)
90	1.52±1.91 (101)	1.23±1.96 (102)
105	1.43±1.92 (101)	1.23±1.97 (102)
120	1.44±2.02 (101)	1.24±1.91 (102)
135	1.36±2.09 (101)	1.04±1.91 (102)
150	1.35±2.07 (101)	1.08±2.10 (102)
165	1.32±2.09 (100)	1.24±2.23 (102)
180	1.35±2.14 (101)	1.34±2.23 (102)

* Test lozenge versus placebo comparison statistically significant at 5% level
*** Test lozenge versus placebo comparison statistically significant at 0.1% level
Source: Tables 14.2.54 to 14.2.68

Measured on an 11-point scale 0 = Completely scratchy, tickly or itchy 10 = Not at all scratchy, tickly or itchy

Figure 11.4.4 Mean change from baseline in throat irritation from 1 to 180 minutes post first dose – Full analysis set



Measured on an 11-point scale 0 = Completely scratchy, tickly or itchy, 10 = Not at all scratchy, tickly or itchy

Time to First Reporting of "Moderate Pain Relief"

Table 14.2.69 shows details of the analysis of time to first reporting of "moderate pain relief". In total, 50/101 (50%) reported moderate pain relief in the test lozenge group compared to 40/102 (39%) in the placebo group. With respect to the Cox regression analysis, the term for treatment was not statistically significant (p=0.08), whereas the term for baseline sore throat severity was statistically significant (p=0.047). The hazard ratio from the Cox model was 1.44 (95% CI 0.95, 2.19).

Overall Treatment Rating

Table 11.4.11 presents details of the overall treatment rating at 3 hours. The rating was graded on an 11-point scale where 0 = poor, 10 = excellent. The LS mean scores were 5.00 for the test lozenge and 4.21 for placebo, the mean difference of 0.79 (95% CI 0.01, 1.58) was statistically significant (p=0.049) in favour of the test lozenge. The covariate for baseline throat soreness severity was not statistically significant (p=0.73). More detailed information is shown in Table 14.2.70.

Table 11.4.11 Overall treatment rating at 3 hours – Full analysis set

	Test	Placebo
N	101	102
Mean±sd	5.00±2.79	4.21±2.90
LS mean[a]	5.00	4.21
Difference between LS means[b]	0.79	
Se	0.40	
95% CI	0.01, 1.58	
p-value for treatment[a]	0.049	

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b Test lozenge minus placebo. A positive difference favours test lozenge.
Source: Table 14.2.70

Measured on an 11-point scale where 0 = Poor, 10 = Excellent

Functional Impairment Scale

Table 11.4.12 presents the change from pre-dose to 3 hours post-dose in the functional impairment scale for each separate component and overall total score. Mean reductions for three of the four activities favoured the test lozenge, but none of the differences were statistically significant. In terms of the total score, LS mean reductions were -4.6 (test) and -3.7 (placebo), the mean difference of -0.9 (95% CI -2.6, 0.8) was not statistically significantly (p=0.27). Summary statistics are given in Table 14.2.71.

Table 11.4.12 Change from pre-dose to 3 hours post-dose for the functional impairment scale (each component and overall total score) – Full analysis set

	n	Mean±sd	LS mean[a]	Difference between LS means[b]	se	95% CI	p-value for treatment[a]
TALKING							
Test	101	-1.30±2.08	-1.27	-0.25	0.28	-0.81,-0.31	0.39
Placebo	102	-1.00±2.24	-1.03				
SWALLOWING							
Test	101	-1.14±2.22	-1.11	0.19	0.28	-0.35,0.73	0.49
Placebo	102	-1.26±1.99	-1.30				
CONCENTRATING							
Test	101	-1.33±1.87	-1.22	-0.34	0.26	-0.85,0.17	0.19
Placebo	102	-0.77±2.04	-0.88				
READING							
Test	101	-1.08±2.40	-0.95	-0.43	0.28	-0.98,0.12	0.12
Placebo	102	-0.39±2.34	-0.52				
TOTAL OF ALL FOUR RESPONSES							
Test	101	-4.8±6.9	-4.6	-0.9	0.9	-2.6,0.8	0.27
Placebo	102	-3.4±6.2	-3.7				

a Estimated from ANCOVA model with factors for treatment and covariates for baseline throat soreness and baseline score for the relevant variable
b Test lozenge minus placebo. A negative difference favours test lozenge.
Source: Table 14.2.71

Each activity measured on an 11-point scale where 0 = Would not interfere at all, 10 = Would completely interfere

Consumer Questionnaire

Table 14.2.72 presents a frequency distribution of type of sensation that the patient experienced 1 minute after dosing. Sixty (59%) patients reported a mouth-watering sensation following administration of the test lozenge compared to 28 (28%) patients after taking the placebo lozenge.

Table 11.4.13 below details the speed of onset of moistening/mouth water sensation. One patient in the test lozenge group failed to provide data. The speed of onset was highly statistically significant (p=0.0003) in favour of the test lozenge. A total of 51 (50%) patients in the test lozenge group had moistening/mouth watering sensation by 5 seconds post administration compared to 26 (26%) patients in the placebo group.

Table 11.4.13 Speed of onset of moistening/mouth-watering sensation – Full analysis set

	Test lozenge	Placebo
N	101	101
Instantly as soon as I started to suck	16 (15.8%)	13 (12.9%)
Started after 1 to 5 seconds	35 (34.7%)	13 (12.9%)
Started after 6 to 10 seconds	15 (14.9%)	16 (15.8%)
Started after 11 to 20 seconds	17 (16.8%)	24 (23.8%)
More than 20 seconds	17 (16.8%)	23 (22.8%)
No lubricating/mouth-watering sensation	1 (1.0%)	12 (11.9%)
Odds ratio[b]	2.53	
95% CI	1.53, 4.18	
p-value for treatment[a]	0.0003	

a Estimated from proportional odds model with factor for treatment and a covariate for baseline throat soreness
b A value > 1 indicates test lozenge had quicker time to onset of moistening/mouth-watering sensation.
Source: Table 14.2.73

Table 11.4.14 below details the degree of hydration of the throat at 1, 5, 20 and 60 minutes post-dose. At 1 and 5 minutes post-dose, statistically significant more hydration was achieved for patients within the test lozenge group. Further details are presented in Table 14.2.74.

Table 11.4.14 Mean ± sd (n) for degree of hydration of throat at 1, 5, 20 and 60 minutes – Full analysis set

Minutes post-dose	Test	Placebo
1 **	5.04±2.03 (101)	4.23±1.92 (101)
5 *	5.13±1.97 (101)	4.52±1.85 (102)
20	4.80±1.65 (101)	4.59±1.84 (102)
60	4.12±1.63 (101)	4.13±1.61 (102)

* Test versus placebo comparison statistically significant at 5% level
** Test versus placebo comparison statistically significant at 1% level
Source: Table 14.2.74

Measured on an 11-point scale where 0 = No hydration, 10 = Very hydrated

There was no statistically significant difference (p=0.84) between treatment groups in how deep down within the throat was hydration felt 5 minutes after dosing. Table 11.4.15 summarizing these data with further details given in Table 14.2.75.

Table 11.4.15 Consumer questionnaire: How deep down within the throat was hydration felt 5 minutes after dosing – Full analysis set

	Test		Placebo
N	101		102
Mean±sd	3.83±2.05		3.77±1.99
LS mean[a]	3.83		3.77
Difference between LS means[b]		0.06	
Se		0.28	
95% CI		-0.50, 0.62	
p-value for treatment[a]		0.84	

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b Test minus placebo. A positive difference favours test lozenge.
Source: Table 14.2.75

Measured on an 11-point scale where 0 = Not at all deep in the throat, 10 = Very deep in the throat

There was no statistically significant difference between the treatment groups in the degree of lubrication of throat at either 20 minutes (p=0.40) or 2 hours (p=0.96) post-dose. Table 11.4.16 summarizing these data with further details given in Table 14.2.76.

Table 11.4.16 Consumer questionnaire: Degree of lubrication of throat at 20 minutes and 2 hours post-dose – Full analysis set

	Test		Placebo
20 minutes			
N	101		102
Mean±sd	4.50±1.37		4.30±1.79
LS mean[a]	4.49		4.30
Difference between LS means[b]		0.19	
Se		0.22	
95% CI		-0.25, 0.63	
p-value for treatment[a]		0.40	
2 hours			
N	101		102
Mean±sd	3.91±1.80		3.92±1.90
LS mean[a]	3.91		3.92
Difference between LS means[b]		-0.01	
Se		0.26	
95% CI		-0.52, 0.50	
p-value for treatment[a]		0.96	

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b Test minus placebo. A positive difference favours test lozenge.
Source: Table 14.2.76

Measured on an 11-point scale where 0 = No lubrication, 10 = Very lubricated

There was no statistically significant difference between the treatment groups in the change from baseline in how bothering the throat discomfort was at 20 minutes (p=0.68), at 2 hours (p=0.73) and 3 hours (p=0.77) post-dose. Table 11.4.17 summarizes these data with further details given in Table 14.2.77.

Table 11.4.17 Consumer questionnaire: Change from baseline in how bothering the throat discomfort was at 20 minutes and 2 and 3 hours post-dose – Full analysis set

	Test		Placebo
20 minutes			
N	101		102
Mean±sd	-1.71±1.78		-1.43±1.95
LS mean[a]	-1.61		-1.53
Difference between LS means[b]		-0.08	
Se		0.21	
95% CI		-0.49, 0.32	
p-value for treatment[a]		0.68	
2 hours			
N	101		102
Mean±sd	-1.94±1.97		-1.69±2.02
LS mean[a]	-1.86		-1.77
Difference between LS means[b]		-0.08	
Se		0.24	
95% CI		-0.57, 0.40	
p-value for treatment[a]		0.73	
3 hours			
N	101		102
Mean±sd	-1.51±2.16		-1.43±2.10
LS mean[a]	-1.44		-1.51
Difference between LS means[b]		0.08	
Se		0.26	
95% CI		-0.44, 0.59	
p-value for treatment[a]		0.77	

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b Test lozenge minus placebo. A negative difference favours test lozenge.
Source: Table 14.2.77

Measured on an 11-point scale where 0 = Not bothering, 10 = Extremely bothering

There was a statistically significant difference (p=0.002) in favour of the test lozenge versus placebo with respect to the change from baseline in how much the patient felt like their best overall at 1 hour post-dose. LS mean improvements from baseline from the ANCOVA model were 0.96 (test) and 0.38 (placebo), with a mean difference of 0.59 (95% CI 0.22, 0.96). The term for baseline score was highly statistically significant in the ANCOVA model (p<0.0001), whereas the term for baseline throat soreness was not statistically significant (p=0.83). For the equivalent analysis at 3 hours, there was no statistically significant difference between the treatment groups (p=0.52). Table 11.4.18 below summarizes the data obtained for this variable; further detailed information is given in Table 14.2.78.

Table 11.4.18 Consumer questionnaire: Change from baseline in how much the patient felt like their best overall at 1 and 3 hours post-dose – Full analysis set

	Test		Placebo
1 hours			
N	101		102
Mean±sd	1.10±1.69		0.25±1.67
LS mean[a]	0.96		0.38
Difference between LS means[b]		0.59	
Se		0.19	
95% CI		0.22, 0.96	
p-value for treatment[a]		0.002	
3 hours			
N	101		102
Mean±sd	1.30±1.90		0.85±2.24
LS mean[a]	1.15		0.99
Difference between LS means[b]		0.16	
Se		0.25	
95% CI		-0.33, 0.65	
p-value for treatment[a]		0.52	

a Estimated from ANCOVA model with factor for treatment and covariates for baseline throat soreness and baseline value
b Test minus placebo. A positive difference favours test lozenge.
Source: Table 14.2.78

Measured on an 11-point scale where 0 = I feel at my very worst, 10 = I feel at my very best

There was no statistically significant difference between the treatment groups in the change from baseline in the degree of happiness in relation to their throat at 1 hour (p=0.54) and 3 hours (p=0.57) post-dose. Table 11.4.19 summarizing these data with further details given in Table 14.2.79.

Table 11.4.19 Consumer questionnaire: Change from baseline in degree of happiness in relation to their throat at 1 and 3 hours post-dose – Full analysis set

	Test		Placebo
1 hours			
N	101		102
Mean±sd	1.26±1.89		1.26±1.77
LS mean[a]	1.33		1.20
Difference between LS means[b]		0.13	
Se		0.21	
95% CI		-0.29, 0.55	
p-value for treatment[a]		0.54	
3 hours			
N	101		102
Mean±sd	1.50-±2.17		1.76±2.03
LS mean[a]	1.55		1.71
Difference between LS means[b]		-0.15	
Se		0.27	
95% CI		-0.68, 0.38	
p-value for treatment[a]		0.57	

a Estimated from ANCOVA model with factor for treatment and covariates for baseline throat soreness and baseline value
b Test minus placebo. A positive difference favours test lozenge.
Source: Table 14.2.79

Measured on an 11-point scale where 0 = Very unhappy with my throat, 10 = Very happy with my throat

A total of 50 (50%) patients in the test lozenge group considered they felt better than before they took the lozenge at 3 hours post-dose compared to 44 (43%) in the placebo group, this difference was not statistically significant (p=0.36; Table 11.4.20).

Table 11.4.20 Consumer questionnaire: Whether patient felt any better than before they took the lozenge at 3 hours post-dose – Full analysis set

	Test		Placebo
N	101		153
Number (%) reporting	50 (49.5%)		44 (43.1%)
Odds ratio[b]		1.29	
95% CI		0.74, 2.35	
p-value for treatment[a]		0.36	

a Estimated from logistic regression model with factor for treatment and a covariate for baseline throat soreness
b A value > 1 indicates test lozenge was favoured
Source: Table 14.2.80

A total of 38 (38%) patients in the test lozenge group considered they felt less distracted than before they took the lozenge at 3 hours post-dose compared to 29 (28%) in the placebo group, this difference was not statistically significant (p=0.18; Table 11.4.21).

Table 11.4.21 Consumer questionnaire: Whether patient felt less distracted than before they took the lozenge at 3 hours post-dose – Full analysis set

	Test		Placebo
N	101		102
Number (%) reporting	38 (37.6%)		29 (28.4%)
Odds ratio[b]		1.51	
95% CI		0.83, 2.74	
p-value for treatment[a]		0.18	

a Estimated from logistic regression model with factor for treatment and a covariate for baseline throat soreness
b A value > 1 indicates test lozenge was favoured.
Source: Table 14.2.81

A total of 37 (37%) patients in the test lozenge group considered they felt less frustrated than before they took the lozenge at 3 hours post-dose compared to 30 (29%) in the placebo group, this difference was not statistically significant (p=0.29; Table 11.4.22).

Table 11.4.22 Consumer questionnaire: Whether patient felt less frustrated than before they took the lozenge at 3 hours post-dose – Full analysis set

	Test		Placebo
N	101		102
Number (%) reporting	37 (36.6%)		30 (29.4%)
Odds ratio[b]		1.38	
95% CI		0.76, 2.50	
p-value for treatment[a]		0.29	

a Estimated from logistic regression model with factor for treatment and a covariate for baseline throat soreness
b A value > 1 indicates test lozenge was favoured.
Source: Table 14.2.82

A total of 45 (45%) patients in the test lozenge group considered they felt happier than before they took the lozenge at 3 hours post-dose compared to 39 (38%) in the placebo group, this difference was not statistically significant (p=0.37; Table 11.4.23).

Table 11.4.23 Consumer questionnaire: Whether patient felt happier than before they took the lozenge at 3 hours post-dose – Full analysis set

	Test		Placebo
N	101		102
Number (%) reporting	45 (44.6%)		39 (38.2%)
Odds ratio[b]		1.30	
95% CI		0.74, 2.28	
p-value for treatment[a]		0.37	

a Estimated from logistic regression model with factor for treatment and a covariate for baseline throat soreness
b A value > 1 indicates test lozenge was favoured.
Source: Table 14.2.83

Table 11.4.24 presents details of the patient rating of the lozenge as a treatment for dry/irritated sore throat at 3 hours. The rating was graded on an 11-point scale where 0 = poor, 10 = excellent. The LS mean scores were 5.03 for the test lozenge and 4.29 for placebo, the mean difference of 0.74 (95% CI -0.03, 1.51) was not statistically significant (p=0.06). The covariate for baseline throat soreness severity was not statistically significant (p=0.48). More detailed information is shown in Table 14.2.84.

Table 11.4.24 Patient rating of lozenge as a treatment for dry/irritated sore throat – Full analysis set

	Test		Placebo
N	101		102
Mean±sd	5.03±2.74		4.29±2.82
LS mean[a]	5.03		4.29
Difference between LS means[b]		0.74	
Se		0.39	
95% CI		-0.03, 1.51	
p-value for treatment[a]		0.06	

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b Test lozenge minus placebo. A positive difference favours test lozenge.
Source: Table 14.2.84

Measured on an 11-point scale where 0 = Poor, 10 = Excellent

Table 11.4.25 presents details of the patient assessment of the degree of coating of the lozenge at 3 hours. The rating was graded on an 11-point scale where 0 = no coating, 10 = throat completely coated. The LS mean scores were 4.75 for the test lozenge and 3.94 for placebo, the mean difference of 0.81 (95% CI 0.06, 1.56) was statistically significant (p=0.03). The covariate for baseline throat soreness severity was not statistically significant (p=0.87). More detailed information is shown in Table 14.2.85.

Table 11.4.25 Patient assessment of degree of coating of lozenge at 3 hours post-dose – Full analysis set

	Test		Placebo
N	101		102
Mean±sd	4.75±2.68		3.94±2.74
LS mean[a]	4.75		3.94
Difference between LS means[b]		0.81	
Se		0.38	
95% CI		0.06, 1.56	
p-value for treatment[a]		0.03	

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b Test lozenge minus placebo. A positive difference favours test lozenge.
Source: Table 14.2.85

Measured on an 11-point scale where 0 = No coating, 10 = Throat completely coated

Table 11.4.26 presents details of the patient assessment of the degree of watering/moistening of the lozenge at 3 hours. The rating was graded on an 11-point scale where 0 = not mouth watering/moistening at all, 10 = very mouth watering/moistening. The LS mean scores were 6.31 for the test lozenge and 4.94 for placebo, the mean difference of 1.37 (95% CI 0.65, 2.08) was highly statistically significant (p=0.0002). The covariate for baseline throat soreness severity was not statistically significant (p=0.61). More detailed information is shown in Table 14.2.86.

Table 11.4.26 Patient assessment of degree of watering/moistening of lozenge at 3 hours post-dose – Full analysis set

	Test		Placebo
N	101		102
Mean±sd	6.31±2.45		4.94±2.70
LS mean[a]	6.31		4.94
Difference between LS means[b]		1.37	
Se		0.36	
95% CI		0.65, 2.08	
p-value for treatment[a]		0.0002	

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b Test lozenge minus placebo. A positive difference favours test lozenge.
Source: Table 14.2.86

Measured on an 11-point scale where 0 = Not mouth watering/moistening at all, 10 = Very mouth watering/moistening

Table 11.4.27 presents details of the patient assessment of how deep down within the throat was relief felt 3 hours post-dose. The rating was graded on an 11-point scale where 0 = not at all deep in the throat, 10 = very deep in the throat. The LS mean scores were 4.22 for the test lozenge and 3.71 for placebo, the mean difference of 0.50 (95% CI -0.13, 1.14) was not statistically significant (p=0.12). The covariate for baseline throat soreness severity was not statistically significant (p=0.18). More detailed information is shown in Table 14.2.87.

Table 11.4.27 Consumer questionnaire: How deep down within the throat was relief felt 3 hours post-dose – Full analysis set

	Test		Placebo
N	101		102
Mean±sd	4.22±2.14		3.72±2.44
LS mean[a]	4.22		3.71
Difference between LS means[b]		0.50	
Se		0.32	
95% CI		-0.13, 1.14	
p-value for treatment[a]		0.12	

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b Test lozenge minus placebo. A positive difference favours test lozenge.
Source: Table 14.2.87

Measured on an 11-point scale where 0 = Not at all deep in the throat, 10 = Very deep in the throat

Table 11.4.28 presents details of the patient assessment of how deep down within the throat was moistening felt 3 hours post-dose. The rating was graded on an 11-point scale where 0 = not at all deep in the throat, 10 = very deep in the throat. The LS mean scores were 4.59 for the test lozenge and 3.75 for placebo, the mean difference of 0.84 (95% CI 0.20, 1.48) was statistically significant (p=0.011). The covariate for baseline throat soreness severity was not statistically significant (p=0.86). More detailed information is shown in Table 14.2.88.

Table 11.4.28 Consumer questionnaire: How deep down within the throat was moistening felt at 3 hours post-dose – Full analysis set

	Test		Placebo
N	101		102
Mean±sd	4.59±2.15		3.75±2.46
LS mean[a]	4.59		3.75
Difference between LS means[b]		0.84	
Se		0.33	
95% CI		0.20, 1.48	
p-value for treatment[a]		0.011	

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b Test lozenge minus placebo. A positive difference favours test lozenge.
Source: Table 14.2.88

Measured on an 11-point scale where 0 = Not at all deep in the throat, 10 = Very deep in the throat

Table 11.4.29 presents details of the patient assessment of how deep down within the throat was lubrication felt 3 hours post-dose. The rating was graded on an 11-point scale where 0 = not at all deep in the throat, 10 = very deep in the throat. The LS mean scores were 4.62 for the test lozenge and 3.73 for placebo, the mean difference of 0.90 (95% CI 0.24, 1.55) was statistically significant (p=0.007). The covariate for baseline throat soreness severity was not statistically significant (p=0.58). More detailed information is shown in Table 14.2.89.

Table 11.4.29 Consumer questionnaire: How deep down within the throat was lubrication felt at 3 hours post-dose – Full analysis set

	Test		Placebo
N	101		102
Mean±sd	4.62±2.19		3.73±2.53
LS mean[a]	4.62		3.73
Difference between LS means[b]		0.90	
Se		0.33	
95% CI		0.24, 1.55	
p-value for treatment[a]		0.007	

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b Test lozenge minus placebo. A positive difference favours test lozenge
Source: Table 14.2.89

Measured on an 11-point scale where 0 = Not at all deep in the throat, 10 = Very deep in the throat

Table 11.4.30 presents details of the patient assessment of whether their throat felt as normal at 3 hours post-dose. The rating was graded on an 11-point scale where 0 = feels much less moist than normal, 10 = feels at least as moist as normal. The LS mean scores were 4.27 for the test lozenge and 3.95 for placebo, the mean difference of 0.32 (95% CI -0.34, 0.97) was not statistically significant (p=0.34). The covariate for baseline throat soreness severity was not statistically significant (p=0.27). More detailed information is shown in Table 14.2.90.

Table 11.4.30 Consumer questionnaire: Whether throat felt as moist as normal at 3 hours post-dose – Full analysis set

	Test		Placebo
N	101		102
Mean±sd	4.27±2.39		3.95±2.32
LS mean[a]	4.27		3.95
Difference between LS means[b]		0.32	
Se		0.33	
95% CI		-0.34, 0.97	
p-value for treatment[a]		0.34	

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b Test lozenge minus placebo. A positive difference favours test lozenge
Source: Table 14.2.90

Measured on an 11-point scale where 0 = Feels much less moist than normal, 10 = Feels at least as moist as normal

11.4.2 Analytical Issues

Detailed documentation of statistical methods, as the final Statistical Analysis Plan, is presented in Appendix 16.1.9.

There was a slight evidence of non-normality for the analyses involving the primary endpoint, the AUC for the change from baseline in throat soreness at 2 hours and also for TOTPAR at 2 hours with the Shapiro-Wilk tests being statistically significant for both treatment groups. However on the inspection of the residual plots, there appeared to be no gross outliers. It was decided to appeal to the robustness of the F-test rather than perform additional non-parametric analyses.

There was also evidence of non-normality for some of the secondary endpoints, however given that the degree of non-normality was minor it was decided that the variables would be analysed as planned, rather than using the equivalent non-parametric methods.

11.4.2.1 Adjustments for Covariates

Pairwise treatment comparisons were made for each of the continuous efficacy variables using ANCOVA. All ANCOVA models included treatment group and a covariate for baseline throat soreness and the baseline score for the relevant variable of interest if appropriate.

For the time-to-event parameters, differences between the treatment groups were assessed using a Cox regression analysis with a factor for treatment and a covariate for baseline throat soreness.

11.4.2.2 Handling of Dropouts or Missing Data

All incomplete dates were entered on the database as they were recorded in the CRF. Thereafter, the incomplete dates were completed using pre-defined rules. If a day or month was recorded as unknown (UNK) or not applicable (NA), it was replaced by the first day of the month or January respectively, provided this did not contradict any other dates recorded. For missing adverse events and medications dates/times during the trial, the worst-case date was used (e.g. the end of the month for a stop date and 23:59 for the stop time, the randomisation date for start of AE).

For all non-AUC analyses, missing data were not replaced. The following data were not recorded (Table 11.4.31).

Table 11.4.31 Missing data

Patient number	Treatment	Assessments	Assessment time (min)
193	Test	Throat soreness, sore throat relief, throat dryness and throat irritation	165
008	Placebo	Throat soreness	5
103	Placebo	Sore throat relief	165
141	Placebo	Consumer questionnaire: Question 9 (describe the type of sensation you experienced) Question 10 (how quickly did you feel the moistening/mouth watering sensation) Question 11 (how hydrated does your throat feel)	1
150	Placebo	Throat soreness, sore throat relief, throat dryness and throat irritation	75
196	Placebo	Which phrase best describes your throat now when you swallow at screening?	Screening

Due to the very small number of missing data points, no additional sensitivity analyses were performed for the primary efficacy endpoint.

11.4.2.3 Interim Analyses and Data Monitoring

No interim analyses or data monitoring were planned or performed; therefore, this section is not applicable.

11.4.2.4 Multi-site Studies

As all patients were recruited through advertising and came to the central unit run by CPS research, the study was therefore considered as a single centre trial.

11.4.2.5 Multiple Comparison/Multiplicity

No attempt was made to adjust for the multiplicity for the secondary endpoints.

11.4.2.6 Use of an "Efficacy Subset" of Patients

The use of the per-protocol population (defined in Section 11.1) was restricted to the primary efficacy endpoint (the area under the change from baseline curve (AUC) in severity of throat soreness, from 0 to 2 hours) and the AUC from baseline to 2 hours in sore throat relief. Eight patients were excluded from the per-protocol set but the statistical conclusions drawn from this subset were qualitatively identical to the results obtained using the full analysis set.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

This study was not designed to test equivalence; therefore, this section is not applicable.

11.4.2.8 Examination of Subgroups

Analyses of the primary efficacy endpoint were performed by key baseline characteristics. For each subgroup, the main effect and treatment-by-subgroup interaction terms were added to the standard model used in the primary endpoint analysis. Key variables of interest were baseline throat soreness severity (≤median, >median; Table 14.2.91), baseline throat dryness (≤median, >median; Table 14.2.92), baseline throat irritation (≤median, >median; Table 14.2.93), cause of sore throat (URTI, environmental factors; Table 14.2.94), age at study entry (≤median, >median; Table 14.2.95), gender (Table 14.2.96) and total score from the TPA at baseline (≤median, >median; Table 14.2.97).

There was a statistically significant treatment group-by-baseline throat soreness score interaction (p=0.04). Patients with more severe throat soreness at baseline i.e. scores of 8 to 10 inclusive (n=75), LS means were -2.35 (test) compared to -1.92 (placebo). The opposite was true for patients with throat soreness scores of seven or less at baseline (n=128) where the LS means favoured placebo namely -0.88 (test) compared to -1.35 (placebo). Likewise, there was a statistically significant treatment group-by-baseline throat irritation score interaction (p=0.04). Patients with more severe throat irritation at baseline i.e. scores of 0 to 2 inclusive (n=109), LS means were -1.63 (test lozenge) compared to -1.31 (placebo). The opposite was true for patients with throat dryness scores of greater than 2 (n=94) where the LS means favoured placebo namely -1.32 (test lozenge) compared to -1.78 (placebo). The reasons for these qualitative interactions are not clear but it appears that patients with more severe symptoms at baseline seem to benefit more from the test lozenge in terms of improvement in throat soreness over the first 2 hours post-dose. The other five key baseline variables did not have statistically significant subgroup-by-treatment interactions.

11.4.3 Tabulation of Individual Response Data

In addition to tables giving group data for efficacy variables, relevant individual patient data, are presented in by-patient tabular listings in Appendix 16.2.6.

No individual response data are presented in the body of the report.

11.4.4 Drug Dose, Drug Concentration and Relationships to Response

This was not a dose response study and fixed doses of study medication were used, therefore this section is not applicable.

11.4.5 Drug-Drug and Drug-Disease Interactions

Drug/drug or drug/disease interactions were not examined in this study; therefore this section is not applicable.

11.4.6 By-Patient Displays

Group mean data represent the principal analysis in this study; therefore this section is not applicable.

11.4.7 Efficacy Conclusions

The specific efficacy variables selected to address the primary and secondary study objectives and the conclusions are presented in Table 11.4.32.

Table 11.4.32 Efficacy objectives, variables and conclusions

Objective / Variable	Conclusions
Primary objective	
To determine the analgesic properties of an experimental formulation of Strepsils lozenge in patients with a dry and irritated sore throat due to URTI or environmental factors	
Primary variable	
AUC for the change in baseline in severity of throat soreness, from 0 to 2 hours	There is no evidence that the test lozenge provides a greater reduction in the severity of throat soreness than a placebo lozenge over the first 2 hours after use.
Secondary variables	
AUC from baseline to 3 hours for the change in baseline in the severity of throat soreness	There is no evidence that the test lozenge provides a greater reduction in the severity of throat soreness than a placebo lozenge over the first 3 hours after use.
Change from baseline in severity of throat soreness (using the 11-point throat soreness scale) at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose	There is no evidence that the test lozenge provides a greater reduction in throat soreness than a placebo lozenge at any time point in the first 3 hours after use.
AUC from baseline to 2 hours post-dose for sore throat relief	The test lozenge provides greater sore throat relief than a placebo lozenge over the first 2 hours after use.
AUC from baseline to 3 hours post-dose for sore throat relief	The test lozenge provides greater sore throat relief than a placebo lozenge over the first 3 hours of use.
Sore throat relief at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose	The test lozenge provides effective pain relief greater than placebo from one to 75 minutes, with maximum relief with Strepsils Sugar free lozenges achieved at 45 minutes post-dose.
AUC from baseline to 2 hours for the change from baseline in throat dryness	There is no evidence that the test lozenge provides a greater throat moistening effect than a placebo lozenge in the first 2 hours after use.
AUC from baseline to 3 hours for the change from baseline in throat dryness	There is no evidence that the test lozenge provides a greater throat moistening effect than a placebo lozenge in the first 3 hours after use.
Change from baseline in throat dryness (using the 11 point throat dryness scale) at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose	The test lozenge is superior to placebo at reducing throat dryness at 1 and 5 minutes post-dose.
AUC from baseline to 2 hours for the change from baseline in throat irritation	There is no evidence that the test lozenge provides a greater improvement in throat irritation than a placebo lozenge in the first 2 hours after use.
AUC from baseline to 3 hours for the change from baseline in throat irritation	There is no evidence that the test lozenge provides a greater improvement in throat irritation than a placebo lozenge in the first 3 hours after use.
Change from baseline in throat irritation (using the 11 point throat irritation scale) at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes post-dose	The test lozenge is superior to placebo at improving throat irritation for the first 10 minutes post-dose (1, 5 and 10 minutes).
Onset of analgesia defined as time to first reporting 'moderate pain relief' (which is the midpoint on the 7 point sore throat relief scale)	There is some evidence (a non-significant trend) that the test lozenge provides a faster onset of analgesia than a placebo lozenge, as assessed by time to first reporting of moderate

Objective / Variable	Conclusions
	pain relief.
Overall treatment rating at 3 hours	The test lozenges are rated as a better overall treatment for sore throat than placebo lozenges at 3 hours.
Secondary objective	
To determine consumer acceptability of the product via responses to a consumer questionnaire	
Secondary variables	
Responses to the questions from the consumer questionnaire	
Please rate how your sore throat affects the daily activities: f talking, swallowing, concentrating and reading Each assessed on an 11-point categorical scale at 0 minutes (pre-dose) and 180 minutes	There is no evidence that the test lozenge provides a greater improvement from pre-dose in talking, swallowing, concentrating, reading or all combined than a placebo lozenge after 3 hours.
Please describe the type of sensation you experienced? Assessed by sensation response (mouth-watering, moisture, hydrating, lubricating, no) at 1 minute post-dose	Patients are more likely to experience a mouth-watering sensation within one minute of taking the test lozenge than with a placebo lozenge.
How quickly did you feel the moistening/mouth-watering sensation? Assessed by response (instantly, 1-5 s, 6-10 s, 11-20 s, >20 s or no sensation) at 1 minute post-dose	The test lozenges provide a faster onset of moistening /mouth-watering sensation than placebo lozenges.
How hydrated does your throat feel? Assessed on an 11-point categorical scale at 1, 5, 20, 60 minutes,	Taking the test lozenge provides a greater degree of throat hydration than a placebo lozenge at 1 and 5 minutes post-dose.
How deep down within the throat was the hydration felt? Assessed on an 11-point categorical scale at 5 minutes post-dose	There is no evidence that the test lozenge provides greater deep down hydration of the throat than placebo lozenges at 5 minutes post-dose.
How lubricated does your throat feel? Assessed on an 11-point categorical scale at 20, 120 minutes post-dose	There is no evidence that the test lozenge provides a greater degree of lubrication of the throat than a placebo lozenge at 20 minutes and 2 hours post-dose.
'How bothering do you find your throat discomfort' Assessed on an 11-point categorical scale at 0 minutes (pre-dose) and 20, 120 and 180 minutes post-dose	There is no evidence that throat discomfort bothers patients less at 20 minutes, 1 and 2 hours relative to baseline after taking the test lozenge rather than a placebo lozenge.
How much do you feel like your best overall? Assessed on an 11-point categorical scale at 0 minutes (pre-dose) and 60, and 180 minutes post-dose	Patients feel better overall after taking the test lozenge rather than a placebo lozenge at 1 hour post-dose, but not at 3 hours relative to baseline.
How happy are you, in relation to your throat? Assessed on an 11-point categorical scale at 0 minutes (pre-dose) and 60 and 180 minutes post-dose	There is no evidence that patients have a greater degree of happiness in relation to their throat after taking the test lozenge than those taking a placebo lozenge at 1 and 3 hours post-dose relative to baseline.
Do you feel any better than before you took the	A similar proportion of patients feel any better than before

Objective / Variable	Conclusions
lozenge? Assessed as yes/no at 180 minutes post-dose	taking the test or placebo lozenge at 3 hours post-dose.
Do you feel less distracted than before you took the lozenge? Assessed as yes/no at 180 minutes post-dose	A similar proportion of patients feel less distracted than before taking the test or placebo lozenge at 3 hours post-dose.
Do you feel less frustrated than before you took the lozenge? Assessed as yes/no at 180 minutes post-dose	A similar proportion of patients feel less frustrated than before taking the test or placebo lozenge at 3 hours post-dose.
Do you feel happier than before you took the lozenge? Assessed as yes/no at 180 minutes post-dose	A similar proportion of patients feel happier than before taking the test or placebo lozenge at 3 hours post-dose.
How would you rate this lozenge as a treatment for dry / irritated sore throat? Assessed on an 11-point categorical scale at 180 minutes post-dose	There is some evidence (a non-significant trend) that patients rate the test lozenge as a better treatment for dry/irritated sore throat than a placebo lozenge at 3 hours post-dose.
How much do you think the lozenge coated your throat? Assessed on an 11-point categorical scale at 180 minutes post-dose	The test lozenge is superior to a placebo lozenge in coating the throat at 3 hours post-dose.
How mouth watering/moistening is this lozenge? Assessed on an 11-point categorical scale at 180 minutes post-dose	The test lozenge has a superior mouth watering/moistening effect compared to a placebo lozenge at 3 hours post-dose.
How deep down within the throat was the relief felt? Assessed on an 11-point categorical scale at 180 minutes post-dose	There is no evidence that the test lozenge provides sore throat relief deeper down the throat than a placebo lozenge at 3 hours post-dose.
How deep down within the throat do you think this lozenge moisten the throat? Assessed on an 11-point categorical scale at 180 minutes post-dose	The test lozenge provides a moistening effect deeper down the throat than a placebo lozenge at 3 hours post-dose.
How deep down within the throat was the lubrication felt? Assessed on an 11-point categorical scale at 180 minutes post-dose	The test lozenge provides a lubricating effect deeper down the throat than a placebo lozenge at 3 hours post-dose.
Does your throat feel as moist as normal? Assessed on an 11-point categorical scale at 180 minutes post-dose	There is no evidence that the test lozenge is better than a placebo lozenge in making the throat feel as moist as normal at 3 hours post-dose.

12 SAFETY EVALUATION

All patients who received at least one dose of study medication are included in the safety analysis.

12.1 Extent of Exposure

This was a single dose study so all 203 randomised patients received one dose of study medication. A total of 101 patients received a single test lozenge and 102 patients received a placebo throat lozenge.

12.2 Adverse Events (AEs)

All treatment emergent adverse events for each patient are listed in Appendix 16.2, Listings 16.2.7.1 and 16.2.7.2, giving both preferred terms according to MedDRA (Version 13.1) and the original term used by the investigator. Events with start dates during follow-up (i.e. more than 24 hours after dosing) were not considered treatment emergent and are listed separately in Listings 16.2.7.3 and 16.2.7.4.

12.2.1 Brief Summary of Events

Eighteen (9%) patients reported a total of 22 treatment emergent adverse events. In the test lozenge group, 10 (10%) patients reported 11 events and in the placebo group, eight (8%) patients reported 11 events. All but one treatment emergent event was of mild severity and none were considered to be definitely, probably or possibly related to the study medication.

12.2.2 Display of Adverse Events

Table 14.3.3 presents a summary of treatment emergent adverse events by primary system organ class. The most common classes for events reported were nervous system disorders with 13 reports (seven in the test lozenge group and six in the placebo group) and respiratory, thoracic and mediastinal disorders with five reports (three in the test lozenge group and two in the placebo group).

Table 14.3.4 reports the number of patients reporting each preferred term. By far the most common treatment emergent adverse event reported was headache with 12 reports during the study; this involved six (6%) patients reporting seven headaches in the test lozenge group and five (5%) reporting five events in the placebo group.

Table 14.3.5 presents a summary of treatment emergent adverse events by primary system organ class, preferred term, severity and relationship to study medication. Within this tabulation, the severity of a recurrent AE for any patient was taken to be the most severe and the relationship to therapy as the most probable. All but one treatment emergent event was of mild severity; patient number 140 (test lozenge group) reported moderate oropharyngeal pain with no relationship to study medication.

More details about the severity and relationships of treatment emergent adverse events to study medication are given in Table 12.2.1 below.

Table 12.2.1 Severity and relationship of treatment emergent adverse events to therapy

	Test (n=101)		Placebo (n=102)	
	Number of patients reporting	Number of reports (% of total)	Number of patients reporting	Number of reports (% of total)
Total	10 (10%)	11	8 (8%)	11
Severity:				
Mild	9 (9%)	10 (91%)	8 (8%)	11 (100%)
Moderate	1 (1%)	1 (9%)	-	-
Severe	-	-	-	-
Relationship:				
Definite	-	-	-	-
Probable	-	-	-	-
Possible	-	-	-	-
Unlikely	5 (5%)	6 (55%)	2 (2%)	2 (18%)
None	5 (5%)	5 (45%)	7 (7%)	9 (82%)

Source: Appendix 16.2. Listings 16.2.7.1 and 16.2.7.2

Two events were reported during follow-up; these were not considered treatment emergent and are listed separately in Appendix 16.2, Listings 16.2.7.3 to 16.2.7.4.

12.2.3 Analysis of Adverse Events

There was no statistically significant difference between treatments in the proportion of patients reporting events (p=0.61).

12.3 Deaths, Other Serious Adverse Events (SAEs) and other Significant Adverse Events

There were no deaths, other serious or significant adverse events in this study.

12.4 Clinical Laboratory Evaluation

No clinical laboratory evaluations were performed in this study.

12.5 Vital Signs, Physical Findings and other Observations Related to Safety

Table 14.3.6 details concomitant medication commencing during the study, all these medications started after the 3-hour observation period immediately post-dose. Fifteen (15%) patients in the test lozenge group and six (6%) patients in the placebo reported starting at least one medication with 15 patients starting an analgesic (10 in the test lozenge group and five in the placebo group). Further details are given in Appendix 16.2, Listing 16.2.4.5.

There were no reported pregnancies. No other safety evaluations were performed in this study.

12.6 Safety Conclusions

The test lozenges are well tolerated and there are no apparent safety concerns regarding their use.

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

The primary aim of the study was to determine the analgesic properties of an experimental formulation of Strepsils lozenge in patients with a dry and irritated sore throat due to URTI or environmental factors. The test formulation contained a significantly higher proportion of tartaric acid than currently marketed formulations of Strepsils and was designed to produce mouth-watering effects.

A total of 203 patients were randomised to treatment (101 to test lozenge and 102 to placebo lozenge) and were analysed in a full analysis set. The variability observed for the primary efficacy endpoint in this study was 1.37 (root mean square error from the ANCOVA model of the full analysis set) which was lower than predicted and suggests that with 203 patients analysed, the study was more than adequately powered.

The study population consisted of 107 males and 96 females and had a mean age of 34 years. The majority of patients had a sore throat due to URTI (92%) and 8% had a sore throat due to environmental factors, as assessed by a study nurse. The treatment groups were generally well matched in the demographic and baseline sore throat characteristics apart from an imbalance in the proportion of patients describing their throats as swollen and inflamed. The patients were considered a representative sample of the general population of patients with a dry and irritated sore throat due to URTI or environmental factors. In this study, novel scales for throat dryness and throat irritation were used to obtain patients who had significant levels of throat irritation and dryness at study entry. Hence, the population differed from those used in previous studies with Strepsils lozenges. Treatment compliance was 100% as site staff monitored patients taking the study medication and hence is unlikely to influence the outcome of the study.

The primary analysis, comparing the AUC for the change from baseline in severity of throat soreness, from 0 to 2 hours did not find any statistically significant differences between the test lozenge and placebo. The analysis of the AUC in severity of throat soreness from 0 to 2 hours (using the 11-point Throat Soreness scale) gave LS mean reductions from baseline of -1.50 and -1.53 for the test and placebo lozenges respectively. The LS mean difference was 0.04 (95% CI -0.34 to 0.42) for the comparison of the test lozenge and the placebo lozenge. This treatment difference was considerably smaller than previously observed in comparisons between test lozenges and placebo. Similar results were obtained using a per-protocol population.

In addition, no significant differences were observed in the AUC for the change from baseline in severity of throat soreness, from 0 to 3 hours or from the changes in throat soreness from baseline at any time point.

However, the secondary analyses for sore throat relief indicated that the test lozenges provided superior pain relief compared with the placebo lozenges. Significant differences between treatment groups were observed for the AUC values for the change from baseline in sore throat relief (TOTPAR) to 2 hours (p=0.0102)

and 3 hours (p=0.02). Significantly greater pain relief was achieved in the test treatment group compared with placebo from 1 to 75 minutes post-dose (p<0.001 at 1 and 5 minutes, p<0.05 or p<0.01 for 10 to 75 minutes). Maximal improvements in sore throat relief were achieved with the test lozenge at 45 minutes post-dose. A single dose provided effective pain relief over the 3-hour period, although the treatment differences from 90 minutes onwards were not statistically significant.

The different findings arising from the analyses of the analgesic variables of throat soreness and sore throat relief were unexpected, and both the 7-point sore throat relief and 11-point throat soreness rating scales have been used previously to assess the analgesic properties of throat medications. A study has shown that patients with sore throats can independently assess PROs for pain on swallowing, swollen throat and difficulty swallowing[16], although a close correlation would have been expected between throat soreness and sore throat relief. Nevertheless the fact that patients were asked to assess "soreness" specifically on swallowing as opposed to pain relief which was elicited as a passive experience may explain this anomaly.

Analyses indicated that there was a significant interaction between the treatment group and baseline throat soreness with greater reductions with the test lozenge than the placebo lozenge in patients with more severe throat soreness at baseline. A similar interaction was evident with severity of throat irritation. These findings may indicate that patients with more severe symptoms at baseline could benefit more from treatment with the test lozenge. The analyses may also indicate that the additional inclusion criteria of dry and irritated throat may have changed the overall sensitivity of the population to treatment.

Patients entered the study with a known dry and irritated sore throat at baseline, as verified by their baseline scores on the 11-point rating scales for throat dryness and throat irritation. Although the scale for throat dryness had been used in previous in-house consumer studies, the scale for throat irritation was used for the first time in this study. Both scales were useful PRO measures for assessing throat dryness and throat irritation, although further work is need to validate the scales.

The test lozenges had both a rapid moistening and a calming effect on dry and irritated sore throats, as shown by the significantly greater moistening effect at 1 and 5 minutes post-dose and improvement in throat irritation at 1, 5 and 10 minutes post-dose compared with placebo. Maximal improvements in throat dryness and throat irritation are achieved with the test lozenge at 5 and 10 minutes post-dose, respectively.

These early moistening/lubricating sensations experienced by patients with a dry and irritated sore throat are supported by the responses to the consumer questionnaire. At 1 and 5 minutes post-dose, the test lozenges provided a significantly greater degree of throat hydration than placebo lozenges (p<0.01; p<0.05 respectively). The onset of a moistening/mouth watering sensation was also significantly faster with test lozenges compared with placebo (p=0.0003), with half of the patients taking test lozenges had experienced this sensation within 5 seconds compared to 26% taking placebo.

The moistening and lubricating effect of the test lozenges was also evident at later assessment times, long after the lozenge had dissolved in the mouth. At 3 hours post-dose, patients reported a significantly greater degree of mouth watering/moistening effect compared to placebo (p=0.0002). In addition to the moistening effect, the test lozenges provided a greater degree of coating of the throat than placebo lozenges at 3 hours post-dose (p=0.03). The moistening effect was felt deeper down the throat after taking the test lozenge than placebo lozenges at 3 hours post-dose (p=0.011), as was the lubricating effect (p=0.007). However, despite the superior deep down moistening and lubricating effect of the test lozenges at 3 hours post-dose, there was no significant difference between treatment groups in pain relief felt deeper down in the throat at this time. Furthermore, the pain relieving, moistening and lubricating actions of the test lozenges did not translate into improved functioning, with no significant differences between the treatment groups in the talking, swallowing, reading and concentrating variables on the functional impairment scale.

Patients did start to feel better after taking the test lozenges with the consumer questionnaire responses indicating that they began to feel more like their best overall at 1 hour post-dose (p=0.002), although there was no significant difference between the treatment groups at 3 hours post-dose.

The test lozenges were rated as a better treatment for sore throat than placebo lozenges at 3 hours post-dose. There was also a trend towards superiority in their rating of the test lozenge as a treatment of a dry/irritated sore throat (p=0.06).

There were no safety issues highlighted by this study with the test lozenges to indicate any change in the well-established safety profile of Strepsils. The test lozenges were tolerated as well as placebo lozenges with no significant differences between the treatment groups in the proportion of patients reporting an AE. All but one of the reported AEs was of mild intensity and no AEs were classified as severe. The most commonly reported treatment emergent AE in both treatment groups was headache and most AEs were related to the patient's URTI such as headache, cough, sinus congestion and runny nose. The potential risk to patients from taking the test lozenges is considered low.

Although the test lozenge showed some signs of benefit in a population with dry and irritated sore throat, the overall effect was marginal. It is possible that the enhanced mouth watering effects of an experimental formulation containing a high proportion of tartaric acid diminished the analgesic effects of AMC/DCBA locally in the throat.

13.2 Conclusion

The experimental formulation lozenge provides fast and effective pain relief for patients with a dry and irritated sore throat due to URTI or environmental factors. Following a single dose, pain relief is evident after 1 minute with peak analgesic effect occurring at 45 minutes and superior pain relief over 3 hours compared with placebo lozenges. The test lozenges also provide rapid improvements in throat dryness and throat irritation, with peak effects at 5 and 10 minutes after intake.

The lozenges are well accepted by consumers. They have moistening and lubricating effects, which are felt deep down in the throat and are rated as a better treatment for sore throat than placebo lozenges 3 hours after intake.

The test lozenges are well tolerated and there are no apparent safety concerns regarding their use.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

Table number	Table Title
14.1 Demographic Data	
14.1.1	Details of withdrawal – Safety set
14.1.2	Demographics – Full analysis set
14.1.3	Relevant previous medical history – Full analysis set
14.1.4	Relevant ongoing medical history – Full analysis set
14.1.5	Screening assessments – Full analysis set
14.1.6	Baseline efficacy assessments – Full analysis set
14.1.7	Concomitant medication ongoing at randomisation – Full analysis set
14.2 Efficacy Data	
14.2.1.1	Primary efficacy endpoint - AUC from baseline to two hours post dose for the change from baseline in throat soreness - Full analysis set
14.2.1.2	Primary efficacy endpoint - AUC from baseline to two hours post dose for the change from baseline in throat soreness – Per-protocol set
14.2.2	AUC from baseline to three hours post dose for the change from baseline in throat soreness - Full analysis set
14.2.3	Change from baseline in throat soreness at 1 minute post dose - Full analysis set
14.2.4	Change from baseline in throat soreness at 5 minutes post dose - Full analysis set
14.2.5	Change from baseline in throat soreness at 10 minutes post dose - Full analysis set
14.2.6	Change from baseline in throat soreness at 15 minutes post dose - Full analysis set
14.2.7	Change from baseline in throat soreness at 30 minutes post dose - Full analysis set
14.2.8	Change from baseline in throat soreness at 45 minutes post dose - Full analysis set
14.2.9	Change from baseline in throat soreness at 60 minutes post dose - Full analysis set
14.2.10	Change from baseline in throat soreness at 75 minutes post dose - Full analysis set
14.2.11	Change from baseline in throat soreness at 90 minutes post dose - Full analysis set
14.2.12	Change from baseline in throat soreness at 105 minutes post dose - Full analysis set

Table number	Table Title
14.2.13	Change from baseline in throat soreness at 120 minutes post dose - Full analysis set
14.2.14	Change from baseline in throat soreness at 135 minutes post dose - Full analysis set
14.2.15	Change from baseline in throat soreness at 150 minutes post dose - Full analysis set
14.2.16	Change from baseline in throat soreness at 165 minutes post dose - Full analysis set
14.2.17	Change from baseline in throat soreness at 180 minutes post dose - Full analysis set
14.2.18.1	AUC from baseline to two hours post dose for sore throat relief - Full analysis set
14.2.18.2	AUC from baseline to two hours post dose for sore throat relief - Per-protocol set
14.2.19	AUC from baseline to three hours post dose for sore throat relief - Full analysis set
14.2.20	Sore throat relief at 1 minute post dose - Full analysis set
14.2.21	Sore throat relief at 5 minutes post dose - Full analysis set
14.2.22	Sore throat relief at 10 minutes post dose - Full analysis set
14.2.23	Sore throat relief at 15 minutes post dose - Full analysis set
14.2.24	Sore throat relief at 30 minutes post dose - Full analysis set
14.2.25	Sore throat relief at 45 minutes post dose - Full analysis set
14.2.26	Sore throat relief at 60 minutes post dose - Full analysis set
14.2.27	Sore throat relief at 75 minutes post dose - Full analysis set
14.2.28	Sore throat relief at 90 minutes post dose - Full analysis set
14.2.29	Sore throat relief at 105 minutes post dose - Full analysis set
14.2.30	Sore throat relief at 120 minutes post dose - Full analysis set
14.2.31	Sore throat relief at 135 minutes post dose - Full analysis set
14.2.32	Sore throat relief at 150 minutes post dose - Full analysis set
14.2.33	Sore throat relief at 165 minutes post dose - Full analysis set
14.2.34	Sore throat relief at 180 minutes post dose - Full analysis set
14.2.35	AUC from baseline to two hours post dose for the change from baseline in throat dryness - Full analysis set
14.2.36	AUC from baseline to three hours post dose for the change from baseline in throat dryness - Full analysis set
14.2.37	Change from baseline in throat dryness at 1 minute post dose - Full analysis set

Table number	Table Title
14.2.38	Change from baseline in throat dryness at 5 minutes post dose - Full analysis set
14.2.39	Change from baseline in throat dryness at 10 minutes post dose - Full analysis set
14.2.40	Change from baseline in throat dryness at 15 minutes post dose - Full analysis set
14.2.41	Change from baseline in throat dryness at 30 minutes post dose - Full analysis set
14.2.42	Change from baseline in throat dryness at 45 minutes post dose - Full analysis set
14.2.43	Change from baseline in throat dryness at 60 minutes post dose - Full analysis set
14.2.44	Change from baseline in throat dryness at 75 minutes post dose - Full analysis set
14.2.45	Change from baseline in throat dryness at 90 minutes post dose - Full analysis set
14.2.46	Change from baseline in throat dryness at 105 minutes post dose - Full analysis set
14.2.47	Change from baseline in throat dryness at 120 minutes post dose - Full analysis set
14.2.48	Change from baseline in throat dryness at 135 minutes post dose - Full analysis set
14.2.49	Change from baseline in throat dryness at 150 minutes post dose - Full analysis set
14.2.50	Change from baseline in throat dryness at 165 minutes post dose - Full analysis set
14.2.51	Change from baseline in throat dryness at 180 minutes post dose - Full analysis set
14.2.52	AUC from baseline to two hours post dose for the change from baseline in throat irritation - Full analysis set
14.2.53	AUC from baseline to three hours post dose for the change from baseline in throat irritation - Full analysis set
14.2.54	Change from baseline in throat irritation at 1 minute post dose - Full analysis set
14.2.55	Change from baseline in throat irritation at 5 minutes post dose - Full analysis set
14.2.56	Change from baseline in throat irritation at 10 minutes post dose - Full analysis set
14.2.57	Change from baseline in throat irritation at 15 minutes post dose - Full analysis set

Table number	Table Title
14.2.58	Change from baseline in throat irritation at 30 minutes post dose - Full analysis set
14.2.59	Change from baseline in throat irritation at 45 minutes post dose - Full analysis set
14.2.60	Change from baseline in throat irritation at 60 minutes post dose - Full analysis set
14.2.61	Change from baseline in throat irritation at 75 minutes post dose - Full analysis set
14.2.62	Change from baseline in throat irritation at 90 minutes post dose - Full analysis set
14.2.63	Change from baseline in throat irritation at 105 minutes post dose - Full analysis set
14.2.64	Change from baseline in throat irritation at 120 minutes post dose - Full analysis set
14.2.65	Change from baseline in throat irritation at 135 minutes post dose - Full analysis set
14.2.66	Change from baseline in throat irritation at 150 minutes post dose - Full analysis set
14.2.67	Change from baseline in throat irritation at 165 minutes post dose - Full analysis set
14.2.68	Change from baseline in throat irritation at 180 minutes post dose - Full analysis set
14.2.69	Onset of analgesia - Time to first reporting of moderate pain relief - Full analysis set
14.2.70	Overall treatment rating at three hours post dose - Full analysis set
14.2.71	Consumer questionnaire: Change from baseline in the individual and total scores from Functional Impairment Scale at three hours post-dose - Full analysis set
14.2.72	Consumer questionnaire: Type of sensation the patient experienced one minute after dosing - Full analysis set
14.2.73	Consumer questionnaire: Speed of onset of moistening/mouth-watering sensation - Full analysis set
14.2.74	Consumer questionnaire: Degree of hydration of throat at 1, 5, 20 and 60 minutes after dosing - Full analysis set
14.2.75	Consumer questionnaire: How deep down within the throat was hydration felt five minutes after dosing - Full analysis set
14.2.76	Consumer questionnaire: Degree of lubrication of throat at 20 minutes and 2 hours post-dose - Full analysis set
14.2.77	Consumer questionnaire: Change from baseline in how bothering the throat discomfort was at 20 minutes and 2 and 3 hours post-dose - Full analysis set

Table number	Table Title
14.2.78	Consumer questionnaire: Change from baseline in how much the patient felt like their best overall at one and three hours post-dose - Full analysis set
14.2.79	Consumer questionnaire: Change from baseline in degree of happiness in relation to their throat at one and three hours post-dose - Full analysis set
14.2.80	Consumer questionnaire: Whether patient felt any better than before they took the lozenge at three hours post-dose - Full analysis set
14.2.81	Consumer questionnaire: Whether patient felt less distracted than before they took the lozenge at three hours post-dose - Full analysis set
14.2.82	Consumer questionnaire: Whether patient felt less frustrated than before they took the lozenge at three hours post-dose - Full analysis set
14.2.83	Consumer questionnaire: Whether patient felt happier than before they took the lozenge at three hours post-dose - Full analysis set
14.2.84	Consumer questionnaire: Patient rating of lozenge as a treatment for dry/irritated sore throat - Full analysis set
14.2.85	Consumer questionnaire: Patient assessment of degree of coating of lozenge at three hours post-dose - Full analysis set
14.2.86	Consumer questionnaire: Patient assessment of degree of watering/moistening of lozenge at three hours post-dose - Full analysis set
14.2.87	Consumer questionnaire: How deep down within the throat was relief felt three hours post-dose - Full analysis set
14.2.88	Consumer questionnaire: How deep down within the throat was moistening felt three hours post-dose - Full analysis set
14.2.89	Consumer questionnaire: How deep down within the throat was lubrication felt three hours post-dose - Full analysis set
14.2.90	Consumer questionnaire: Whether throat felt as moist as normal at three hours post-dose - Full analysis set
14.2.91	Primary efficacy endpoint – AUC from baseline to two hours post dose for the change from baseline in throat soreness by baseline throat soreness severity - Full analysis set
14.2.92	Primary efficacy endpoint – AUC from baseline to two hours post dose for the change from baseline in throat soreness by baseline throat dryness - Full analysis set
14.2.93	Primary efficacy endpoint – AUC from baseline to two hours post dose for the change from baseline in throat soreness by baseline throat irritation - Full analysis set
14.2.94	Primary efficacy endpoint – AUC from baseline to two hours post dose for the change from baseline in throat soreness by cause of sore throat - Full analysis set
14.2.95	Primary efficacy endpoint – AUC from baseline to two hours post dose for the change from baseline in throat soreness by age at study entry - Full analysis set
14.2.96	Primary efficacy endpoint – AUC from baseline to two hours post dose for the

Table number	Table Title
	change from baseline in throat soreness by gender - Full analysis set
14.2.97	Primary efficacy endpoint – AUC from baseline to two hours post dose for the change from baseline in throat soreness by total score from tonsillo-pharyngitis assessment at baseline - Full analysis set
14.3 Safety Data	
14.3.1	Extent of exposure to study medication - Safety set
14.3.2	Summary of treatment emergent adverse event reporting - Safety set
14.3.3	MedDRA Summary of treatment emergent adverse events by primary system organ class - Safety set
14.3.4	MedDRA Summary of treatment emergent adverse events by primary system organ class and preferred term - Safety set
14.3.5	MedDRA Summary of treatment emergent adverse events by primary system organ class, preferred term, severity and relationship to study medication - Safety set
14.3.6	Concomitant medication commencing during the study - Safety set

Figure number	Figure Title
14.2.1	Mean treatment profiles for change from baseline in throat soreness - Full analysis set
14.2.2	Mean treatment profiles for sore throat relief - Full analysis set
14.2.3	Mean treatment profiles for change from baseline in throat dryness - Full analysis set
14.2.4	Mean treatment profiles for change from baseline in throat irritation - Full analysis set

15 REFERENCE LIST

1) M88082 Clinical Study Report, The Boots Company PLC 1989. Berry P. Rapid relief of acute sore throat with Strepsils lozenges: a single blind, comparative study. Oxford JS ed. 2008. Berry P. Developments in acute sore throat relief – efficacy and sensorial benefits of medicated lozenges. London: Royal Society of Medicine Press Ltd; 2008: 4-12.

2) BH5013R Clinical Study Report, Boots Healthcare International 1996. Wade AG. A randomized double-blind, parallel group, placebo-controlled, multiple-dose study of the efficacy of Strepsil lozenges in the relief of acute sore throat. Oxford JS ed. 2008 Wade AG. Developments in acute sore throat relief – efficacy and sensorial benefits of medicated lozenges. London: Royal Society of Medicine Press Ltd; 2008: 22-32.

3) McNally D, Simpson M, Morris C, Shephard A, Goulder M. Rapid relief of acute sore throat with AMC/DCBA throat lozenges: randomized controlled trial. International Journal of Clinical Practice. 2010; 64(2):194-207.

4) TH0817 Clinical Study Report, Reckitt Benckiser, 2009. Wade AG, Morris C, Shephard A, Crawford GM, Goulder MA. A multicentre, randomised, double-blind, single-dose study assessing the efficacy of AMC/DCBA Warm lozenge or AMC/DCBA Cool lozenge in the relief of acute sore throat. BMC Fam Pract. 2011;12:6.

5) Gáspár L, Turi J, Tóth BZ, Suri C, Vágó P. [The use of benzyl-alcohol and Amyl-m-Cresol (Strepsils) in the oral cavity]. Fororvosi szemle 1998; 91(5):143-150.

6) Marazzi P. Strepsils anaesthetic lozenges versus control Strepsils lozenges in the relief of moderate to severe sore throat: A double blind crossover multiple dose randomized study. London: Royal Society of Medicine Press Ltd. 2008: 22-32

7) Burnett I, Schachtel B, Sanner K, Bey M, Grattan T, Littlejohn S. Onset of analgesia of paracetamol tablet containing sodium bicarbonate: a double-blind, placebo-controlled study in adult patients with acute sore throat. Clin Ther. 2006; 28(9):1273-1278

8) Watson N, Nimmo WS, Christian J, Charlesworth A, Speight J, Miller K. Relief of sore throat with the anti-inflammatory throat lozenge flurbiprofen 8.75mg: a randomised, double blind, placebo controlled study of efficacy and safety. Int J Clin Pract 2000; 54(8):490-496.

9) Benrimoj SI, Langford JH, Christian J, Charlesworth A, Steans A. Efficacy and Tolerability of the anti-inflammatory throat lozenge flurbiprofen 8.75mg in the treatment of sore throat. Clin Drug Invest 2001; 21(3):183-193.

10) Schachtel BP, Fillingim JM, Thoden WR, Lane AC, Baybutt RI. Sore throat pain in evaluation of mild analgesics. Clin Pharmacol Ther 1988; 44(6):704-711

11) Blagden M, Christian J, Miller K, Charlesworth A. Multidose flurbiprofen 8.75mg lozenges in the treatment of sore throat a randomised double blind, placebo-controlled study in UK General Practice Centres. Int J Clin Pract 2002; 56(2):95-100

12) Schachtel BP, Cleves GS, Konerman JP, Brown AT, Markham AO. A placebo controlled model to assay the onset of action of non prescription-strength analgesics drugs. Clin Pharmacol Ther 1994; 55(4):464-70

13) Schachtel BP, Fillingim JM, Beiter DJ, Lane AC, Schwartz LA. Subjective and Objectives Features of Sore Throat. Arch Inter Med 1984; 144(3):497-500

14) SAS Institute Inc. The SAS System, Version 9.2. Cary, NC, SAS Institute Inc. 2004.

15) McCullagh P. Regression models for ordinal data (with discussion). Journal of the Royal Statistical Society, Series B, 1980;42(2):109-142.

16) Schachtel BP, McCormick CG, Giefer EE. Patient-Reported Outcomes (PROs) in the Pharyngitis Pain Model. Poster presented at 13th World Congress on Pain of the International Association for the Study of Pain; August 29-September 2, 2010; Montréal, Canada.