Reckitt Benckiser

1 STUDY REPORT TITLE PAGE

EudraCT Number:	2008-00-5596-10
Study Number:	**TH0817**
Protocol Title:	A multi centre, randomised, double blind, placebo-controlled, parallel group, single dose study of the efficacy of two flavour variants of Strepsils throat lozenges in the relief of sore throat due to upper respiratory tract infection.
Study Phase:	III
Date First Subject Enrolled:	12th January 2009
Date Last Subject Completed:	20th February 2009
Report Date:	6th July 2009
Principal Investigator:	Dr Alan Wade
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:

C S Morris 7/7/09

Mr Christopher Morris BSc (Hons) — Date

Reckitt Benckiser Healthcare (UK)

Statistician:

Michael A Goulder 06-Jul-09

Mr Michael Goulder BSc (Hons) — Date

Worldwide Clinical Trials UK Ltd

R & D Manager: Strepsils

C Walker 08/07/09

Mrs Clare Walker BSc (Hons) — Date

Reckitt Benckiser Healthcare (UK)

Reviewed and Approved by:

R & D Manager Clinical (Healthcare)

06 July 09

Dr Sue Aspley BSc (Hons), PhD — Date

Reckitt Benckiser Healthcare (UK)

Global Medical Director:

6 July 2009

Dr P Berry MB, ChB, MPH — Date

Reckitt Benckiser Healthcare (UK)

Study Sponsor: Reckitt Benckiser Healthcare (UK), Dansom Lane, Hull, HU8 7DS, United Kingdom

2 SYNOPSIS

<table>
<tr><td>Name of Sponsor/ Company: Reckitt Benckiser Healthcare International Ltd</td><td>Individual Trial Table Referring to Part of the Dossier

Volume:

Page:</td><td>(For National Authority use only)</td></tr>
<tr><td>Name of Finished Product: Strepsils Cool and Strepsils Warm Throat lozenges</td><td></td><td></td></tr>
<tr><td>Name of Active Ingredient(s): 0.6mg 2,4-dichlorobenzylalcohol, 1.2 mg amylmetacresol,</td><td></td><td></td></tr>
<tr><td colspan="3">Title of Trial: A multi centre, randomised, double blind, placebo-controlled, parallel group, single dose study of the efficacy of two flavour variants of Strepsils throat lozenges in the relief of sore throat due to upper respiratory tract infection.</td></tr>
<tr><td colspan="3">Investigator: Dr Alan Wade</td></tr>
<tr><td colspan="3">Trial Centre: Community Pharmacology Services Ltd (CPS) recruited all patients by direct advertising or referrals from the following medical practices in the Glasgow area, Waverley GP Practice, Chapelhall GP practice and Rutherglen GP practice.</td></tr>
<tr><td colspan="3">Publication (reference): None</td></tr>
<tr><td colspan="2">Studied Period: 6 Weeks

Date first subject enrolled: 12th January 2009

Date last subject completed: 23rd February 2009</td><td>Phase of Development: III</td></tr>
<tr><td colspan="3">Objectives: The primary objective of this study was to determine the analgesic properties of two new Strepsils flavour variant throat lozenges (Strepsils Cool and Strepsils Warm) in patients with sore throat due to upper respiratory tract infection (URTI). The analgesic properties were assessed by comparing throat soreness and sore throat relief in patients treated with one of the two Strepsils flavour variant throat lozenges with patients treated with a placebo throat lozenge. In addition to the analgesic endpoints, functional measures of difficulty in swallowing and throat numbness were also assessed.

The secondary objective of this study was to determine consumer acceptability of the product via responses to a consumer questionnaire.</td></tr>
<tr><td colspan="3">Methodology: Patients with a sore throat due to URTI, either presented opportunistically following response to advertisements for patients in local media or were referred directly to CPS Research from a number of GP referral practices in the Glasgow area.

Patients were screened either at CPS Research or within the referral GP practice. Eligible patients (those who met the study inclusion criteria and not the exclusion criteria) were randomised to receive one of the three test products. Within 1 minute of the completion of baseline assessments of throat soreness (11 – point ordinal scale), difficulty in swallowing (100mm VAS) and a two-part consumer questionnaire, patients were blindfolded and dosed with the assigned trial medication according to their randomisation number (single active or placebo throat lozenge) by a staff member who was not part of the research team. At 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120 minutes post first dose, patients completed the throat soreness and difficulty in swallowing scales along with a 7–point categorical sore throat relief scale and a 5–point categorical throat numbness scale. Three questions on the consumer questionnaire concerning cooling sensation and relief were completed at 1 minute, two questions concerning the warming sensation were answered at 5 minutes, and other pain relief and sensation questions were completed at 20, 60 and 120 minutes post dose.

Following completion of the two-hour assessment, patients left CPS Research or the referral practice with a patient diary to record any concomitant medication or adverse events experienced up to 24 hours post the single dose of study medication. Between one and three days after completing the study, patients were followed up by a telephone call to capture any adverse events and concomitant medications recorded in the patient's diary. The patient diary was then transcribed into the CRF by the research team.</td></tr>
</table>

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

Number of Subjects: **Planned:** 225

Randomised: 225

Analysed: 225

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 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 the expanded Tonsillopharyngitis Assessment (TPA) scoring at least 3 points on the TPA and had to score at least 6 on the 11 point ordinal Throat Soreness Scale at baseline, to be dosed.

Exclusion criteria excluded patients with conditions that could interfere with the assessment of sore throat analgesic activity and patients with any contraindications to any of the study medication.

Test Products: Strepsils Cool Throat lozenges and Strepsils Warm Throat lozenges containing 1.2 mg, 2, 4 – dichlororbenzyl alcohol and 0.6 mg amylmetacresol. Batch Nos. 8M024 and 8M025 respectively.

Each patient was blindfolded and provided with one throat lozenge by a staff member who was not part of the research team, within either CPS Research or the referral GP practice, with instructions to suck it slowly, moving the throat lozenge around the mouth until dissolved and not to chew or crunch the throat lozenge.

Assessment Period: 2 Hours

Reference Therapy: Shape matched non-medicated sugar-based throat lozenge. Batch No. 0172727

Criteria for Evaluation:

Efficacy: Efficacy was assessed by subjective rating scales. The primary efficacy variable was the area under the curve (AUC) for the change from baseline in throat soreness (using the 11 point Throat Soreness Scale) for the Strepsils Cool throat lozenge group and the Strepsils Warm throat lozenge group versus the placebo throat lozenge group for the first two hours post dose.

There were a number of secondary endpoints including the change from baseline in severity of throat soreness, difficulty swallowing and sore throat relief. Onset of analgesia defined as time to first reporting moderate pain relief, overall treatment rating and throat numbness were also included as secondary efficacy measures.

Safety: Safety and tolerability were assessed in terms of the overall proportion of patients with adverse events (AEs) and serious adverse events (SAEs).

Statistical Methods: All statistical tests were performed using a two-tailed 5% overall significance level, unless stated otherwise. The null hypothesis at all times was that the test and reference treatments were equivalent. All comparisons between the treatments were reported with 95% confidence intervals for the difference. For each statistical test, an observed significance level was quoted.

Normality assumptions were assessed by examination of the residual plots and by the Shapiro-

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Wilk test of normality. Depending on the degree of departure from these assumptions, an alternate nonparametric approach could have been used instead.

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.

The primary efficacy variable and key secondary efficacy variables were analysed using analysis of covariance (ANCOVA) with baseline throat soreness severity as a covariate and a factor for treatment group. Confidence intervals for treatment group differences were estimated using the mean square error from the ANCOVA. Differences between treatment groups in the proportion of patients reporting treatment emergent adverse events were compared using the chi-square test.

Concomitant medications ongoing at randomisation were coded using the ATC level 2 categories from the WHO dictionary Enhanced March 2007 Version. All adverse events were listed and tabulated by treatment, severity, relationship to therapy and primary system organ class according to Version 12.0 of MedDRA.

SUMMARY & CONCLUSIONS

EFFICACY RESULTS: In general the treatment groups were well balanced for the demographic variables. Overall, patient ages ranged from 16 to 71 years with a mean age of 31.7 years. The majority of patients, 218 (97%) were Caucasian and there were more females than males. The superiority of Strepsils Cool and Warm throat lozenges over the placebo throat lozenge was clearly apparent with highly statistically significant differences for all the analgesic variables related to sore throat relief, throat soreness, throat numbness and difficulty in swallowing. The results were robust with identical conclusions drawn from the equivalent per-protocol analyses where performed. Results for the primary efficacy variable are summarised in Table 1.

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TABLE 1 **AUC from baseline to two hours post dose for the change from baseline in throat soreness**

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

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo
FULL ANALYSIS SET			
N	77	74	74
Mean±sd	-1.83±1.50	-2.07±1.47	-1.00±1.61
LS mean[a]	-1.78	-2.06	-0.98
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	-0.80	-1.27,-0.33	0.001 **
Strepsils Cool throat lozenge vs Placebo	-1.08	-1.56,-0.60	<0.0001 ***
PER-PROTOCOL SET			
N	75	64	64
Mean±sd	-1.87±1.50	-2.16±1.50	-1.25±1.39
LS mean[a]	-1.83	-2.09	-1.11
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	-0.72	-1.21,-0.23	0.004 **
Strepsils Cool throat lozenge vs Placebo	-0.98	-1.48,-0.47	0.0002 ***

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A negative difference favours the first treatment against second treatment
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level

Key secondary efficacy variable data are summarised in Tables 2-5.

TABLE 2 **Mean ± sd for change from baseline in throat soreness at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post dose – Full analysis set**

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

Minutes post-dose	Strepsils Warm throat lozenge (n)	Strepsils Cool throat lozenge (n)	Placebo (n)	Strepsils Warm versus Placebo	Strepsils Cool versus Placebo
0	6.91±1.02 (77)	6.81±1.24 (74)	6.81±1.57 (74)		
1	-0.40±0.94 (77)	-0.84±1.44 (74)	-0.23±1.32 (74)	ns	**
5	-1.32±1.47 (77)	-1.77±1.49 (74)	-0.77±1.66 (74)	*	***
10	-1.75±1.60 (77)	-2.34±1.66 (74)	-0.97±1.50 (74)	**	***
15	-1.97±1.68 (77)	-2.54±1.70 (74)	-1.11±1.69 (74)	**	***
30	-2.16±1.84 (77)	-2.09±1.46 (74)	-1.05±1.72 (74)	***	***
45	-2.00±1.79 (77)	-2.12±1.67 (73)	-1.04±1.82 (74)	**	***
60	-1.88±1.77 (77)	-2.19±1.94 (74)	-1.05±1.86 (74)	**	***
75	-1.77±1.64 (77)	-2.14±1.88 (74)	-1.07±1.83 (74)	*	***
90	-1.81±1.81 (77)	-1.95±1.87 (74)	-1.01±1.82 (74)	**	**
105	-1.78±1.85 (77)	-1.95±1.99 (74)	-0.96±1.88 (74)	**	**
120	-1.74±1.89 (77)	-1.97±1.91 (73)	-0.95±1.86 (74)	*	***

ns Comparison not statistically significant
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level

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TABLE 3 **Mean ± sd (n) for sore throat relief at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post first dose – Full analysis set**

Measured on a 7-point scale where 0 = No relief, 1 = Slight relief, 2 = Mild relief, 3 = Moderate relief, 4 = Considerable relief, 5 = Almost complete relief, 6 = Complete relief

Minutes post-dose	Strepsils Warm throat lozenge (n)	Strepsils Cool throat lozenge (n)	Placebo (n)	Strepsils Warm throat lozenge versus Placebo	Strepsils Cool throat lozenge versus Placebo
1	0.86±1.05 (77)	1.41±1.22 (74)	0.53±0.95 (74)	ns	***
5	1.49±1.17 (77)	2.15±1.34 (74)	0.93±1.00 (74)	**	***
10	1.88±1.32 (77)	2.55±1.25 (74)	1.11±1.04 (74)	***	***
15	2.00±1.32 (77)	2.70±1.31 (74)	1.19±1.18 (74)	***	***
30	1.90±1.35 (77)	2.30±1.35 (74)	1.05±1.23 (74)	***	***
45	1.88±1.37 (77)	2.18±1.45 (73)	0.95±1.10 (74)	***	***
60	1.70±1.38 (77)	2.07±1.60 (74)	0.93±1.20 (74)	***	***
75	1.57±1.39 (77)	1.99±1.59 (74)	0.89±1.15 (74)	**	***
90	1.56±1.43 (77)	1.80±1.62 (74)	0.89±1.22 (74)	**	***
105	1.60±1.56 (77)	1.72±1.68 (74)	0.84±1.21 (74)	**	***
120	1.66±1.57 (77)	1.79±1.69 (73)	0.92±1.24 (74)	**	***

ns Comparison not statistically significant
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level

TABLE 4 **Mean ± sd (n) for change from baseline in difficulty in swallowing at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post dose – Full analysis set**

Difficulty in swallowing measured on 100mm VAS where 0mm = Not difficult, 100mm = Very difficult

Minutes post-dose	Strepsils Warm throat lozenge (n)	Strepsils Cool throat lozenge (n)	Placebo (n)	Strepsils Warm throat lozenge versus Placebo	Strepsils Cool throat lozenge versus Placebo
0	62.4±14.0 (77)	62.2±15.4 (74)	63.1±15.5 (74)		
1	-0.8±7.1 (77)	-6.6±13.0 (74)	-0.5±7.1 (74)	ns	***
5	-9.2±10.8 (77)	-15.9±14.2 (74)	-4.6±10.7 (74)	*	***
10	-12.1±16.1 (77)	-21.0±16.0 (74)	-6.6±13.0 (74)	*	***
15	-14.8±17.2 (77)	-22.7±16.2 (74)	-7.6±14.6 (74)	**	***
30	-15.5±17.8 (77)	-19.3±16.9 (74)	-7.2±14.8 (74)	**	***
45	-15.4±17.8 (77)	-20.4±17.1 (73)	-8.1±15.2 (74)	**	***
60	-14.3±16.5 (77)	-20.6±18.6 (74)	-8.3±15.6 (74)	*	***
75	-12.8±15.8 (77)	-19.7±19.2 (74)	-9.1±15.3 (74)	ns	***
90	-13.5±16.4 (77)	-18.4±18.5 (74)	-8.4±14.9 (73)	*	***
105	-12.9±17.0 (77)	-18.2±19.7 (74)	-8.0±16.0 (73)	ns	***
120	-11.8±18.7 (77)	-17.4±19.2 (73)	-7.9±15.5 (73)	ns	**

ns Comparison not statistically significant
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level

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Table 5 Summary of Additional Key Secondary Efficacy Variables – Full Analysis Set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo
AUC from baseline to two hours post-dose for sore throat relief *Measured on a 7-point scale where 0 = No relief, 1 = Slight relief, 2 = Mild relief, 3 = Moderate relief, 4 = Considerable relief, 5 = Almost complete relief, 6 = Complete relief*			
N	77	74	74
Mean±sd	1.70±1.19	2.06±1.30	0.94±1.04
LS mean[a]	1.74	2.10	0.98
Parameter estimates	LS mean[b]	95% CI	P
Strepsils Warm throat lozenge vs Placebo	0.76	0.38,1.14	0.0001 ***
Strepsils Cool throat lozenge vs Placebo	1.12	0.73,1.50	<0.0001 ***
AUC from baseline to two hours post first dose for the change from baseline in difficulty in swallowing *Difficulty in swallowing measured on 100mm VAS where 0mm = Not difficult, 100mm = Very difficult*			
N	77	74	74
Mean±sd	-13.4±14.4	-19.2±14.6	-7.7±13.2
LS mean[c]	-13.5	-19.3	-7.5
Parameter estimates	LS mean[d]	95% CI	P
Strepsils Warm throat lozenge vs Placebo	-5.9	-10.4,-1.5	0.009 ***
Strepsils Cool throat lozenge vs Placebo	-11.7	-16.2,-7.2	<0.0001 ***
Consumer questionnaire : how would you rate this throat lozenge as a treatment for sore throat *Measured on 11 point scale where 0 = poor, 10 = excellent*			
N	77	74	74
Mean±sd	4.84±2.83	5.27±2.66	2.30±2.71
LS mean[a]	4.71	5.15	2.14
Parameter estimates	LS mean[b]	95% CI	P
Strepsils Warm throat lozenge vs Placebo	2.57	1.68,3.45	<0.0001 ***
Strepsils Cool throat lozenge vs Placebo	3.00	2.11,3.90	<0.0001 ***

a	Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b	A positive difference favours the first treatment against second treatment
c	Estimated from ANCOVA model with factors for treatment and centre and covariates for baseline throat soreness and baseline score for difficulty in swallowing
d	A negative difference favours the first treatment against second treatment

*** Comparison statistically significant at 0.1% level

Pain relief was evident by 1 minute for the Strepsils Cool throat lozenge and by 5 minutes for the Strepsils Warm throat lozenge and lasted for at least 2 hours with both Strepsils throat lozenges. Throat soreness, pain relief, difficulty in swallowing all implied that peak effect was achieved at 15 minutes for the Strepsils Cool throat lozenge. For the Strepsils Warm throat lozenge peak pain relief effect was seen at 15 minutes while peak throat soreness and difficulty swallowing effects were achieved at 30 minutes. The duration of effect for all efficacy parameters for both throat lozenges was 2 hours with the exception of difficulty swallowing for the Strepsils Warm throat lozenge.

Throat numbness was evident by 1 minute for both Strepsils throat lozenges with peak effect

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throat lozenge. The throat numbness lasted 2 hours for the Strepsils Cool throat lozenge and 45 minutes for the Strepsils Warm throat lozenge.

The pain relief element of the consumer questionnaire completed after the first dose supported the findings of the subjective rating scales. At one minute post dose subjects treated with the Strepsils Cool throat lozenge / Strepsils Warm throat lozenge perceived greater cooling relief / warming relief (as appropriate) compared to the placebo throat lozenge group. These differences were statistically significant for both Strepsils throat lozenges ($p<0.0001$ in each case). At one minute post dose the incidence of soreness, burning and soothing relief in the Strepsils Cool throat lozenge group was statistically significantly greater than that with the placebo throat lozenge group and the incidence of general pain relief in both active treatment groups at 2 hours was statistically significantly higher than that for placebo throat lozenge group.

For the functional element of the consumer questionnaire statistically significant differences in favour of both Strepsils throat lozenges compared with the placebo throat lozenge were obtained for the area most impaired at baseline; swallowing ($p=0.018$ Strepsils Warm throat lozenge and $p=0.011$ Strepsils Cool throat lozenge) Furthermore patients began to feel more like their best at 2 hours for both Strepsils throat lozenges

SAFETY RESULTS:

There were no safety issues within this study. There were no statistically significant differences between the treatment groups in relation to the proportion of patients reporting adverse events. A total of 23 reports from 18 patients were recorded. There were no serious adverse events (SAEs). The majority of adverse events were mild with no treatment emergent events classified as severe. Most adverse events were events related to the patient's URTI such as headache, cough and nasal congestion.

All of the 23 reports were classified as not or unlikely to be related to the Strepsils throat lozenges.

CONCLUSION:

Strepsils Cool and Warm throat lozenges provide fast, safe and effective relief for sore throats due to URTIs. Following a single dose, relief is evident from 1 minute post dose and lasts for at least 2 hours with maximal effects from 15 minutes post dose. Patients can feel relief as soon as they swallow and feel better at 2 hours.

Date of the report: 26th May 2009

3 TABLE OF CONTENTS

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

3.2 List of Appendices

16.2.3 Patients Excluded from the Efficacy Analysis

16.2.4 Demographic data

16.2.5 Compliance and/or drug concentration data

16.2.6 Individual efficacy response data

16.2.7 Adverse event listings (each patient)

16.2.8 Listing of individual laboratory measurements by patient. No laboratory measurements were performed in the study, so this appendix is not present.

16.2.9 Other data listings. None

16.3 CASE REPORT FORMS

16.3.1 No subjects died, experienced adverse events or withdrew because of adverse events, so no CRFs are appended

16.4 INDIVIDUAL SUBJECT DATA LISTINGS

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Abbreviation in Full
ABPI	Association of the British Pharmaceutical Industry
AIDS	Acquired Immune Deficiency Syndrome
AMC	Amylmetacresol BP
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
ATC	Anatomic Therapeutic Class
AUC	Area under the curve
BNF	British National Formulary
AE	Adverse event
AR	Adverse reaction
CFR	Code of Federal Regulations
CPM	Clinical Project Manager
CPS	Community Pharmacology Services
CRF	Case report form
CRO	Contract research organisation
CTA	Clinical Trial Application
CV	Curriculum vitae
DCBA	2,4-Dichlorobenzyl alcohol
EC	Ethics Committee
eCRF	Electronic case report form
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IMSU	Investigational Material Supplies Unit
IND	Investigational New Drug
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Authorities.

NCR	No carbon required
ITT	Intent-to-treat
NHS	National Health Service
NSAID	Non steroidal anti-inflammatory drug
OTC	Over the Counter
PK	Pharmacokinetic
QA	Quality assurance
QC	Quality control
RB	Reckitt Benckiser
R & D	Research and Development
SAE	Serious adverse event
SDV	Source data verification
SMO	Site management organisation
SOP	Standard operating procedure
TPA	Tonsillopharyngitis Assessment
UK	United Kingdom (of Great Britain and Northern Ireland)
URTI	Upper Respiratory Tract Infection
US	United States (of America)
VAS	Visual Analogue Scale
WHO	World Health Organisation
WCT	Worldwide Clinical Trials

5 ETHICS

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

The name and full address and approval letter of the IEC consulted is provided in Appendix 16.1.3. The study documentation was initially reviewed on 4th November 2008 when the ethics committee requested changes to the participant information Sheet. The final protocol together with the amended participant information sheet and original consent document were reviewed and approved by Fife, Forth Valley & Tayside Research Ethics Service on 15th December 2008.

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 Subject Information and Consent

Copies of the representative participant information sheet dated 20th November 2008 and a blank consent form version 2 dated 20th November 2008 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 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. The study was managed by personnel from the Global Clinical Affairs department at Reckitt Benckiser Healthcare International (RBHI) Data management and the statistical analyses were performed by Worldwide Clinical Trials.

Strepsils Cool throat lozenges, Strepsils Warm throat lozenges and placebo throat lozenges were manufactured by RBHI (Reckitt Benckiser Healthcare International Ltd) (Nottingham, UK). The study drug supplies were packed and shipped to CPS Research in Glasgow by the Investigational Medicinal Supplies Unit (IMSU), RBHI. Project management and report writing were performed in house by RBHI. RBHI was also responsible for the expedited reporting of any serious adverse events (SAEs) occurring during the study, to the relevant Regulatory Authorities.

7 INTRODUCTION

This study was conducted to provide additional efficacy support for the Strepsils throat lozenges brand and support the launch of both Strepsils Cool throat lozenges and Strepsils Warm throat lozenges globally.

Strepsils Cool throat lozenges and Strepsils Warm throat lozenges contain the active antimicrobial ingredients amylmetacresol BP (0.6 mg) and 2,4-dichlorobenzyl alcohol (1.2 mg) (AMC/DCBA). The throat lozenges are indicated for the symptomatic relief of mouth and throat infections and are from the leading sore throat relief brand in many markets around the world. Previous studies support the efficacy of AMC/DCBA and Strepsils throat lozenges[1,2,3,4,5] .

This study examined the effect of Strepsils Cool and Warm throat lozenges versus a non-medicated sugar-based placebo throat lozenge in patients with sore throat over a period of two hours. Efficacy was assessed by analgesic rating scales and additional data regarding consumer acceptability of the product was obtained via a consumer questionnaire.

The study was a follow-up to two previous studies in sore throat BH5013[2] and TH0705[3] with Strepsils Original throat lozenges. The previous study TH0705 demonstrated a statistically significant difference in favour of Strepsils Original throat lozenges compared with placebo (non-medicated sugar based throat lozenge) on the primary efficacy end point of reduction in throat soreness at 2 hours. Therefore, RBHI wished to conduct a study of similar design. The methodology utilised was based on that used in TH0705, but using a single dose design in the current study.

8 STUDY OBJECTIVES

The primary objective of this study was to determine the analgesic properties of two new Strepsils flavour variant throat lozenges (Strepsils Cool throat lozenges and Strepsils Warm throat lozenges) in patients with sore throat due to upper respiratory tract infection (URTI). The analgesic properties were assessed by comparing throat soreness and sore throat relief in patients treated with one of two Strepsils throat lozenges with patients treated with a placebo throat lozenge. In addition to the analgesic endpoints, functional measures of difficulty in swallowing and throat numbness were also assessed.

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

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan – Description

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

This was a multi-centre (multi referral practices), randomised, double-blind, parallel-group, placebo-controlled, single-dose study of the efficacy of Strepsils Cool throat lozenges and Strepsils Warm throat lozenges in the relief of sore throat due URTI.

Patients were those with a sore throat due to URTI. Patients with a sore throat due to URTI, either presented opportunistically following response to advertisements for patients in local media or were referred directly to CPS Research from a number of GP referral practices in the Glasgow area.

Patients were screened at CPS Research premises or at the referral GP practices of Rutherglen, Waverley and Chapelhall. Eligible patients (those that met the study inclusion and not the exclusion criteria) were randomised to receive one of the three test products. Following the baseline assessments, patients were dosed with the assigned trial medication according to their randomisation number (an active or placebo throat lozenge) and completed the two-hour assessment period under supervision in a designated area within the investigative site or referral practice No food, drink, additional medication/throat lozenges or smoking was permitted during the 2-hour assessment period.

Following completion of the two-hour assessment, patients left CPS Research or the referral practice with a patient diary to record any concomitant medication or adverse events experienced up to 24 hours post the single dose of study medication. Between one and three days after completing the study, patients were followed up by a telephone call to capture any adverse events and concomitant medications recorded in the diary. The patient diary was then transcribed into the CRF by the research team.

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

Two hundred and twenty five patients (75 per group) were required to complete the first two-hour assessment period to provide data for the primary endpoint (the change from baseline in severity of throat soreness at two hours post dose).

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

The methodology used in this study is accepted and validated analgesic methodology based on the Sore Throat Pain Model described in the literature by Schachtel [6,7,8]. The methodology has been previously used in studies BH5013 and TH0705 with Strepsils Original throat lozenges and in sore throat studies investigating the analgesic properties of a sore throat lozenge containing the non-steroidal anti inflammatory drug flurbiprofen[9, 10, 11].

In order to discriminate between active 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 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.

As with the previous Strepsils Original throat lozenges studies BH5013 and TH0705, a non-medicated sugar-based placebo throat lozenge was used as a control. A throat lozenge format has a number of key advantages for sore throat and in itself contributes to relief of sore throat by having a soothing, demulcent effect – the action of sucking a throat lozenge helps to increase saliva production[12, 13] and the mucosa remains lubricated[14]. In order to control for the contribution of the throat lozenge formulation to the efficacy of the active throat lozenges a non-medicated sugar based throat lozenge was used. This placebo control was the same size and shape as the Strepsils Cool throat lozenges and Strepsils Warm throat lozenges and provided the appropriate control.

9.3 Selection of Study Population

Patients were those with a sore throat due to URTI who attended a GP referral practice or attended CPS Research directly after responding to media advertising. For patients that rang CPS Research in response to advertising, some initial screening took place over the telephone according to a pre-determined script.

9.3.1 Inclusion Criteria

i) Age: ≥16 to ≤75.
i) Both male and female patients were included.
ii) Primary diagnosis: Patients with sore throat of onset within the past 4 days (i.e. ≤ 4 days) due to URTI.
iii) 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 was when you swallow. Ratings on this 0-10 ordinal scale were marked with 0= Not score(besides ‘0’ rating) and 10=Very Sore (beside ’10).
iv) Objective findings that confirm the presence of tonsillopharyngitis (≥ 3 points on the expanded 21-point Tonsillopharyngitis Assessment).
v) Patients who gave written informed consent.

9.3.2 Exclusion Criteria

i) Any previous history of allergy or known intolerance to the study drug or the following formulation constituents, AMC, DCBA, anise oil, peppermint oil, natural menthol, menthol synthetic, xylitol, mint, eucalyptus oil, liquid sucrose, liquid glucose, tartaric acid gran 571 GDE, ponceau 4R, edicol E124, carmoisine edicol E122, sugar, cream, anthocyanin, ginger, wasabi, blackcurrant and plum
ii) Those whose sore throat had been present for more than 4 days.
iii) Those who had evidence of mouth breathing.
iv) Those who had evidence of severe coughing.
v) Those who had any disease that could compromise breathing e.g. bronchopneumonia.
vi) 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.
vii) Those who had used any sore throat medication containing a local anaesthetic within the past 4 hours.
viii) Those who had used any analgesic, antipyretic or cold medication (e.g. decongestant, antihistamine, antitussive or throat lozenge) within the previous 8 hours.
ix) Those who have used a longer acting or slow release analgesic during the previous 24 hours e.g. Piroxicam and Naproxen.
x) Those taking antibiotics during the previous 14 days
xi) Those with any painful condition that may have distracted attention from sore throat pain e.g. mouth ulcers etc.
xii) Those with a history of severe renal impairment.
xiii) Those with a history of severe hepatic impairment
xiv) Those with a history of alcohol abuse or who stated that they regularly consume alcohol in excess of the recommended amounts (excessive alcohol >21 units per week for females and >28 units per week for males.).
xv) Those unable to refrain from smoking during their stay in the investigative site.
xvi) 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 should also include abstinence, barrier contraception and partner vasectomy. A women of child bearing potential was defined as any female who is less than 2 years post-menopausal or has not undergone an hysterectomy or surgical sterilisation, e.g. bilateral tubal ligation, bilateral ovariectomy (oophorectomy).
xvii) Those previously randomised into the study.
xviii) Those who have 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.

xix) 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 Subjects 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 may have caused severe or permanent harm (significant clinical deterioration is an AE)
- Violation of the study protocol
- In the Investigators judgement , it was in the patients best interest
- Patient declined further study participation

The primary reason for withdrawal was documented as one of the following: AE, lack of efficacy, lost to follow-up, protocol violation, withdrawal of consent, death or other. 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 were to be recorded.
- The clinical assessments detailed in section 11.2.3.1 (follow up visit) and any others that were deemed appropriate for the clinical care of the patient.
- Patient diary reviewed.

9.4 Treatments

9.4.1 Treatments Administered

The following medications were administered:

i. Strepsils Cool Throat lozenges, containing 1.2 mg DCBA and 0.6 mg AMC
ii. Strepsils Warm Throat lozenges, containing 1.2 mg DCBA and 0.6 mg AMC
iii. Non-medicated sugar-based placebo throat lozenges

Each patient was provided with the throat lozenge in the investigational site with instructions to suck it slowly, moving the throat lozenge around the mouth, until it had dissolved. Patients were instructed not to chew or crunch the throat lozenges.

9.4.2 Identity of Investigational Product(s)

The identity of the medications supplied in the study were:

i. Strepsils Cool Throat lozenges, containing 1.2 mg DCBA and 0.6 mg AMC; Batch No. 8M024
ii. Strepsils Warm Throat lozenges, containing 1.2 mg DCBA and 0.6 mg AMC; Batch No. 8M025
iii. Non-medicated sugar-based placebo throat lozenges; Batch No. 0172727

Strepsils Cool throat lozenges and Strepsils Warm throat lozenges and the non-medicated sugar-based placebo throat lozenges were manufactured and primary packed to Good Manufacturing Practice standards by RBHI, Nottingham NG90 2DB.

All drug supplies were secondary packed and labelled to GMP standards by the Investigational Material Supplies Unit (IMSU), Reckitt Benckiser Healthcare UK Ltd, Dansom Lane, Hull HU8 7DS, UK.

9.4.3 Method of Assigning Subjects to Treatment Groups

The randomisation code is presented in Appendix 16.1.7. Randomisation was generated for 300 patients in blocks of 6.

Drug supplies were packed and labelled by the IMSU, according to a computer produced randomisation schedule generated by the RBHI statistician not involved with the statistical analysis of the study and checked by a RBHI co-worker.

At screening patients were allocated a unique patient (screening) number. At randomisation, study patients were then allocated a randomisation number in numerical sequence. Issue of the study drug in this sequence ensured randomisation. A listing linking patient number to randomisation number is provided in Appendix 16.1.7.

9.4.4 Selection of Doses in the Study

The dose selected in this study represent the normal non-prescription unit doses for Strepsils Throat lozenges.

9.4.5 Selection of Timing of Dose for Each Subject

This was a single dose study.

9.4.6 Blinding

RBHI IMSU held the master code for the randomisation schedule and supplied CPS Research with the randomisation code for each of their patients as code break envelopes.

The code was only to be broken for an individual patient in an emergency such as a SAE that required knowledge of which study treatment group the patients had been randomised to in order to ascertain which study drug was taken and provide appropriate treatment. If the code for a patient was broken, the Investigator had to withdraw the patient from the study, document the details of the event in the patient's CRF and promptly inform the RBHI Clinical Project Manager. In the event the randomisation code was not broken for any patients during the study.

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.

The code for the analysis was broken on 24 April 2009, only after all data queries had been answered and the database had been locked.

A third party blinding method was employed. Each patient was blindfolded and was provided with a single throat lozenge in the clinic by an independent member of the investigational staff who was not involved in the study assessments. The patient was given the instruction to suck it slowly, moving the throat lozenge around the mouth, until it dissolves in the mouth, and not to chew or crunch the throat lozenge. The independent member of the investigational site staff watched the patients put the throat lozenge in their mouths. Once the throat lozenge has been put in the mouth the blindfold was removed.

9.4.7 Prior and Concomitant Therapy

Concomitant therapies were 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 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 recorded on this form.

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

The use of the following treatments was not permitted during the study and the following washout periods were observed prior to study entry:

- sore throat medication containing a local anaesthetic in the 4 hours before enrolment into the study (i.e. before first dose);
- any analgesic, antipyretic or 'cold' medication (e.g. decongestant, antihistamine, antitussive, or throat lozenge) in the 8 hours before enrolment into the study (i.e. before first dose);
- longer acting or slow release analgesic e.g. piroxicam, in the 24 hours before enrolment into the study (i.e. before first dose);
- medicated confectionary, throat pastille, spray or any products with demulcent properties such as boiled sweets, in the 2 hours before enrolment into the study (i.e. before first dose);
- antibiotics in the 14 days before enrolment into the study (i.e. before first dose);

9.4.8 Treatment Compliance

Compliance with the throat lozenge administration was monitored by site staff. The independent staff member watched the patients put the throat lozenge in their mouths and compliance was checked by conducting a mouth inspection after the throat lozenge was swallowed.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flowchart

An overview of the study procedures is presented in Table 9.5.1.

Table 9.5.1 Flowchart of Study Procedures

Study Period	Screening	Treatment Period		Telephone Follow-up
	Pre-dose	Time (mins) after 1st dose (Day 1)		(1-3 days Post dose)
Study Day	N/A	0	1,5,10,15,30,45,60, 75,90,105,120	
Informed Consent	X			
Demographics	X			
Washout (if required)	X			
Medical History	X			
Concomitant Medication	X			X (up to 24 hours post dose)
Females: Pregnancy, fertility, contraceptive precaution questions	X			X*
Tonsillopharyngitis Score	X			
Eligibility	X			
Randomisation		X		
Time of First Dose		X		
Adverse Events		X (pre dose)	X (120 mins)	X (up to 24 hours post dose)
Give out diary cards. Instruct patient on how to complete.		X		
Telephone call to patient for review of Adverse Event and Concomitant Medication Diary				X
Throat Soreness	X	X	X	
Difficulty in Swallowing		X	X	
Numbness rating			X	
Sore Throat Relief			X	
Treatment Rating			X (120 mins)	
Consumer Questionnaire.		X	X (1, 5,20,60,120 mins)	

All assessments were conducted by the Investigator or a delegated individual qualified by education and experience to perform the delegated task(s).

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

Medical History & Current Medical Status: A medical history was taken at screening and the patient's current medical status was confirmed.

Concomitant Medication (and history at pre-study): At the screening visit, current medication use and therapy history in the previous 14 days was recorded. At study treatment visits, any unscheduled visits and at the post-study visit, patients were asked about any concomitant medication used since the previous visit and details were recorded.

Questions for Female Patients Only: At the screening visit female patients were asked if they might be pregnant, if they were lactating or seeking pregnancy, or if they were taking adequate contraceptive precautions, were at least 2 years post-menopausal, or had been sterilised or had a hysterectomy.

Tonsillopharyngitis Assessment (TPA): At screening oral temperature, size of tonsils, oropharyngeal colour, number of oropharyngeal enanthems, and size, number and tenderness of the anterior cervical lymph nodes were scored 0 – 3 according to the expanded TPA as detailed in Appendix 1 of the protocol.

Throat soreness: At screening, 1 minute pre first dose (time 0),1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120 minutes post first dose the patient completed the throat soreness scale. 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 0 = 'not sore' and 10 = 'very sore'.

Difficulty in Swallowing: 1 minute pre first dose (time 0),1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120 minutes post first dose, the patient completed the difficulty in swallowing scale. Patients were asked to 'swallow and place a line through the scale'. This was a horizontal 100 mm visual analogue scale with endpoints of 'not difficult' on the left hand side and 'very difficult' on the right hand side.

Throat Numbness using a 5 point categorical Scale: 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120 minutes post first dose, the patient was asked by the study nurse to 'circle the phrase which best describes the numbness of your throat now' on a 5-point categorical scale (none, mild, moderate, considerable complete).

Sore Throat Relief: 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120 minutes post first dose, the patient completed sore throat relief scale. Patients were instructed to 'tick the phrase that best describes the relief of your sore throat now'. Scores were collected on a 7–point category scale ('no relief', 'slight relief', 'mild relief', 'moderate relief', 'considerable relief', 'almost complete relief', 'complete relief').

Consumer Questionnaire: The consumer questionnaire was in two different parts. 1 minute pre first dose (time 0) patients completed the 'Functional Impairment Scale' and were asked if they were suffering from a burning sore throat. At 1,5,20,60 minutes post first dose patients completed Questions 5-18 of the second part of the questionnaire regarding pain relief and 120 minutes post first dose patients completed the remaining questions for the second part of the questionnaire (Q19-Q34). As part of the 120 minutes post-dose consumer questions patients were asked 'How would you rate this throat lozenge as a treatment for sore throat?' The patient selected a number from 0 (indicating 'poor') to 10 (indicating 'excellent') on an 11-point ordinal scale.

Patients remained quiet and isolated from any other patient subjects, in a designated area within the investigative site, during dosing and throughout the 2-hour in-clinic evaluation, under constant supervision by clinic staff. This was to avoid any discussion between patients and help prevent patients from knowing that they had to attain a sore throat rating of at least 6 in order to proceed in the study and also to prevent discussion regarding their allocated medication.

To minimise variability in the application of the analgesic rating scales and consumer questionnaire, the study nurse or Investigator at each site instructed the patients on how to complete the self-assessment forms and the consumer questionnaire according to a script. Each patient was asked to swallow and complete his/her four rating scales at each time point within 90 seconds. To ensure accurate completion of the assessments, each patient was supervised by the study nurse or investigator during the 2-hour evaluation. The study nurse ensured that the time schedule for assessments was adhered to throughout the in-clinic assessment period and prompted patients at each of the assessment time points. Apart from the patient's baseline score, the patients were unable to see their previous post-baseline scores.

Adverse Events: All AEs reported spontaneously by the patient or in response to questioning or observation by the Investigator and/or the supervising study nurse were recorded in the patient's case report form. The Investigator or a designated deputy asked the patient: "Are you experiencing any symptoms or complaints?" after randomisation, and "Have you had any symptoms or complaints since you were last asked?" pre-first dose, 2 hours post first dose and at the follow-up visit.

All AEs were followed up wherever possible to resolution or until the Investigator believed there would be no further change, whichever was the earlier.

Each AE was recorded according to the criteria given in Table 9.5.2. "Relationship to study medication" was determined by the Investigator or by a medically qualified Co investigator.

The rating systems used to determine the severity and relationship to study medication are given in Table 9.5.2.

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

Variable	Category	Definition
Severity		Severity was determined by the Investigator. For symptomatic AEs the following definitions were applied but medical experience and judgement was also used in the assessment of 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 experience 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 scales, a 100 mm VAS scale and categorical scales. Throat soreness, pain relief, throat numbness and difficulty in swallowing over the 2-hour period were analysed by way of area under the curve (AUC) rather than the sum of the pain intensity or pain relief scores (SPID or TOTPAR) in accordance with published literature that suggests this as a more

appropriate way of handling serial measurement data[14, 15]. The AUC analyses were based on actual rather than scheduled timings and allowed for the uneven time interval between assessments. The AUC data provides numerical data more related to the original rating scales and is still highly correlated with SPID and TOTPAR scores. Safety was assessed by standard AE reporting methodologies.

9.5.3 Primary Efficacy Variable(s)

The primary efficacy endpoint for this study is the area under the change from baseline curve (AUC) in severity of throat soreness, from 0 to 2 hours.

The secondary efficacy endpoints were:

- 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 and 120 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).
- Total sum of pain relief ratings: defined as the AUC from baseline to 2 hours post first dosing for sore throat relief.
- Sore throat relief at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post-dose.
- AUC from baseline to 2 hours for the change from baseline in difficulty swallowing.
- Change from baseline in difficulty in swallowing at 1,5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post-dose
- AUC for throat numbness measurements from 1 to 120 minutes
- Throat numbness at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post-dose.
- Overall treatment rating at 2 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

All data were entered onto the Worldwide Clinical Trials (WCT) NODES computer database by a member of the Data Management Section and then verified by repeat data entry by a further Section member. SAS Version 9.1[20] edit checks were used for consistency checks.

Before database lock, a database audit was performed which had three components.

Audit component 1: Consistency checking and query generation

Twelve cases randomly were selected to undergo full consistency checking where an error would be failure to issue a query when current procedure called for a data enquiry to be raised, or another failure to appropriately respond to a consistency check. A total of three queries were missed on two of the 12 subjects.

Audit component 2: Transcription and annotation procedures

The twelve subjects selected for component 1 were also selected for full audit where errors could be either transcription or other failures with respect to standard procedures for annotating working copies etc. The total error rate for component 2 was 0.097%. The error rate for 'significant data errors' (any error in a data field which had the potential to affect the statistical analysis or any summary table) was 0.02%. The acceptance level for the significant data error rate in the interim audit was the default error rate of 0.1%.

Audit component 3: Critical data fields

The critical fields were checked for 100% of cases. Any errors found were corrected. The fields were determined by the Study Statistician and Clinical Project Leader and were:

- Randomisation number
- Date and time of taking throat lozenge
- Times of assessments for all observations recorded from pre-dose to 120 minutes post-dose (inclusive)
- All throat soreness and pain relief data recorded from pre-dose to 120 minutes post-dose
- All Adverse Event data

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

The following aspects of this study were subject to a GCP compliance audit, conducted by appropriately trained and experienced personnel at WCT:

- Study database
- Statistical analyses
- Clinical Study Report

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 WCT on behalf of RBHI. A copy of the final statistical analysis plan is presented in 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 area under curve 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 were divided by the total time the scale was assessed for reporting purposes.

As only a small number of patients were recruited in the Waverley and Chapelhall referral centres, these two centres were combined as one referral centre within the formal statistical analysis.

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

All calculations and figures were produced using SAS Version 9.1[20] or S-PLUS 6.2[21].

For continuous variables, the mean, median, standard deviation, standard error of the mean, minimum, maximum and lower and upper 95% confidence limits for the mean for the population and for the individual treatment groups were computed.

Categorical data were presented in contingency tables with cell frequencies and percentages for the patient population and for the individual treatment groups.

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.

Concomitant medications ongoing at randomisation were coded using the ATC level 2 categories from the WHO dictionary Enhanced 3.9 Version.

9.7.1 Statistical and Analytical Plans

9.7.1.1 Efficacy

The full analysis set and per-protocol (PP) populations were used in the analysis of efficacy, as described in Section 11.1.

Primary Endpoint

The primary efficacy endpoint was assessed by analysis of covariance (ANCOVA) with baseline throat soreness severity as a covariate and factors for treatment group and centre. Treatment group differences were estimated using the mean square error from the ANCOVA and using Fisher's protected LSD method i.e. if the overall treatment effect in the ANCOVA model was significant at the 5% level, the comparisons of the Strepsils Warm throat lozenge and Strepsils Cool throat lozenge groups versus the placebo throat lozenge group were performed without any requirement to adjust the significance level for the pairwise comparisons.

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:

- 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 and 120 minutes post-dose.

- AUC from baseline to two hours post-dose for sore throat relief.

- Sore throat relief at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post-dose.
- AUC for throat numbness measurements from 1 to 120 minutes.
- Throat numbness at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post-dose.

The AUC for change from baseline in difficulty in swallowing and the change from baseline in difficulty swallowing at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post-dose were analysed by ANCOVA with factors for treatment group and centre and covariates for the baseline value for difficulty in swallowing 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 factors for treatment group and centre 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 two hours post-dose in the functional impairment scale (each component and overall total score) was analysed by ANCOVA with factors for treatment group and centre 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 factors for treatment group and centre and a covariate for baseline throat soreness severity. Questions on non-numeric ordinal scales were analysed using a proportional odds model[3] using PROC LOGISTIC in SAS with factors for treatment group and centre 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 two questions asked at one and two hours post-dose, viz: “How much do you feel like your best overall?” and “How happy are you, in relation to your throat?”, these were analysed by ANCOVA with factors for treatment group and centre 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 not formally analysed.

Mean profiles from baseline to two hours were presented by treatment group for change from baseline in throat soreness, sore throat relief, and change from baseline in difficulty in swallowing and throat numbness.

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 centre, baseline throat soreness severity, age at study entry, gender, total score from tonsillo-pharyngitis assessment at baseline and baseline VAS for difficulty in swallowing. 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.

For those subjects suffering from a burning sore throat at the pre-dose assessment, logistic regression models with factors for treatment group and centre and a covariate for baseline throat soreness severity were fitted for whether (yes/no) the throat lozenge providing cooling relief at the first moment of swallowing and at two hours post-dose.

9.7.1.2 Safety

All treatment emergent adverse events were listed and tabulated by treatment, severity, relationship to therapy and primary system organ class according to MedDRA Version 12. In counting the number of events reported, a continuous event, i.e. an event reported more than once and which did not cease, was 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.

Pairwise differences between treatment groups in the proportion of patients reporting treatment emergent adverse events were compared via chi-square tests.

Concomitant medications commencing during the study were coded using the ATC level 2 categories from the WHO dictionary.

9.7.2 Determination of Sample Size

In a previous study conducted with Strepsils Original Throat lozenges[2] at the same research centre, 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 to 2 hours between Strepsils Original throat lozenge and placebo throat lozenge for patients with a TPA ≥3 was 0.76 with a standard deviation of 1.09. Assuming that the variability for the same variable for the two Strepsils throat lozenges was of a similar magnitude as for Strepsils Original in the previous study, 75 patients per group would be sufficient to provide 90% power to detect a difference of 0.58 in the mean AUC

(75% of the effect seen in the previous study) between either of the two test products and placebo using a 2 tailed two sample t-test at the 5% significance level.

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

None.

10 STUDY SUBJECTS

10.1 Disposition of Subjects

A total of 225 subjects were randomised into the study (77 subjects received the Strepsils Warm throat lozenge, 74 subjects received the Strepsils Cool throat lozenge and 74 subjects received a placebo throat lozenge) between 12th January 2009 and 20th February 2009. All subjects completed the study.

The study utilised three referral centres where patients were directed to CPS Research for their study assessments. If it was more convenient for the patient to be seen at the referral centre then the study assessments were performed there instead of at CPS Research. The referral centres used were Rutherglen, Waverley and Chapelhall GP practices.

The largest centre was CPS who randomised 166 subjects. Rutherglen GP practice randomised 49 subjects. Waverley and Chapelhall GP practices randomised seven and three subjects respectively. In accordance with the statistical analysis plan these latter two centres were pooled for formal statistical analysis.

10.2 Protocol Deviations

A listing of individual patients who deviated from the protocol is presented in Appendix 16.2.2 and summarised in Table 10.2.1.

A total of 19 subjects had a baseline throat soreness score of less than six, 10 in the placebo throat lozenge group, eight in the Strepsils Cool throat lozenge group and one subject in the Strepsils Warm throat lozenge group, and were thus ineligible for the study. Two subjects in the Strepsils Cool throat lozenge group had missing assessments, one at 45 minutes post-dose and one at 120 minutes post-dose. One subject in the Strepsils Warm throat lozenge group had their 10-minute follow-up assessment, two minutes late and therefore outside the admissible window for that particular follow-up assessment. These 22 subjects were excluded from the per-protocol dataset.

There were no treatment administration errors and no subjects were taking inadmissible concomitant medication.

Table 10.2.1 Protocol Deviations – Full Analysis Set

Pt number	Treatment group	Throat soreness <6 at baseline	Inadmissible timing of assessments	Missing assessments
001	Placebo throat lozenge	Yes		
003	Placebo throat lozenge	Yes		
027	Strepsils Cool throat lozenge			Yes
048	Placebo throat lozenge	Yes		
049	Strepsils Cool throat lozenge	Yes		
063	Strepsils Cool throat lozenge	Yes		
072	Strepsils Warm throat lozenge		Yes	
078	Strepsils Warm throat lozenge	Yes		
089	Strepsils Cool throat lozenge			Yes
122	Placebo throat lozenge	Yes		
124	Strepsils Cool throat lozenge	Yes		
128	Placebo throat lozenge	Yes		
135	Strepsils Cool throat lozenge	Yes		
136	Placebo throat lozenge	Yes		
142	Placebo throat lozenge	Yes		
143	Strepsils Cool throat lozenge	Yes		
144	Placebo throat lozenge	Yes		
149	Strepsils Cool throat lozenge	Yes		
163	Strepsils Cool throat lozenge	Yes		
206	Placebo throat lozenge	Yes		
213	Placebo throat lozenge	Yes		
215	Strepsils Cool throat lozenge	Yes		
Source: Appendix 16.2, Listings 16.2.2.1				

11 EFFICACY EVALUATION

11.1 Data Sets Analysed

Three analysis sets were used in the analysis. These populations were defined as follows:

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

The analysis of efficacy data used two datasets.

Firstly the **full analysis set.** This analysis set consisted of all subjects who were randomised to the study and took the study medication. Any patients with treatment administration errors were to be analysed according to the treatment to which they were randomised. This was the primary efficacy analysis population. For this study the full analysis and safety sets were identical and consisted of all 225 subjects randomised into the study.

Secondly the **per-protocol set.** This analysis set 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 timing of the follow-up assessments within the first 2 hours post-dosing.
    - 1, 5, 10 and 15 minute assessment not performed within +/- 1 minutes of the scheduled times.
    - 30, 45, 60, 75, 90, 105 and 120 minute assessments not performed within +/- 5 minutes of the scheduled times.

Twenty two subjects (2 in the Strepsils Warm throat lozenge group, 10 in the Strepsils Cool throat lozenge group and 10 in the placebo throat lozenge group) were excluded from the per-protocol analysis set, which therefore consisted of 203 subjects.

The only variables which were assessed using the per-protocol analysis set were the primary efficacy endpoint (the area under the change from baseline curve (AUC) in

severity of throat soreness, from baseline to 2 hours) and the total sum of pain relief ratings.

11.2 Demographic and Other Baseline Characteristics

A summary of subject demographics is presented in Tables 14.1.2 to 14.1.7. 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.

Overall, the age ranged from 16 to 71 years, with a mean age of 31.7 years and 133 (59%) subjects were female. The majority of subjects, namely 218 (97%) were Caucasian. A total of 184 (82%) subjects drank alcohol, 82 (36%) were current smokers and 44 (20%) were former smokers. The duration of the sore throat on study entry ranged from zero to four days with a mean of 2.2 days. The maximum duration recorded for URTI was 51 days with a mean duration of 3.0 days. Mean duration of URTI was somewhat imbalanced between the three treatment groups, namely 3.6 days for the placebo throat lozenge group, 3.0 days for the Strepsils Warm throat lozenge group and 2.4 days for the Strepsils Cool throat lozenge group.

Table 14.1.2 presents full summary statistics of demographic variables.

Table 11.2.1 Demographics – Full Analysis Set

Variable	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge	Overall
Number of subjects	77	74	74	225
Age (yr) (Mean ± sd)	30.3±12.2	32.4±14.7	32.6±13.2	31.7±13.3
Gender (% male)	41.6%	39.2%	41.9%	40.9%
Race (% Caucasian)	97.4%	97.3%	95.9%	96.9%
Alcohol drinker (%)	83.1%	86.5%	75.7%	81.8%
Current smoker (%)	36.4%	37.8%	35.1%	36.4%
Former smoker (%)	26.0%	17.6%	14.9%	19.6%
Duration of sore throat (days) (Mean ± sd)	2.3±0.8	2.2±0.7	2.0±0.9	2.2±0.8
Duration of URTI (days) (Mean ± sd)	3.0±2.7	2.4±1.0	3.6±7.1	3.0±4.4

Source: Table 14.1.6

A total of 54 (24%) subjects reported a previous medical condition (Table 14.1.3) and 103 (46%) subjects reported an ongoing medical condition of which 32 (14%) subjects had allergies/drug sensitivity and 27 (12%) had conditions of the musculoskeletal system (Table 14.1.4).

The mean total score from the tonsillo-pharyngitis assessment at screening was 5.7 with a range of 3 to 14. The mean throat soreness score at screening (measured on an 11-point scale where 0 = not sore and 10 = very sore) was 6.84 (range 6 to 10) (Table 14.1.5).

Table 14.1.6 presents a summary of the efficacy variables recorded immediately before dosing. These are further summarised in Table 11.2.2 below. With respect to the functional impairment scale, of the four activities referenced, swallowing (mean score 6.59) and talking (mean score 4.74) were most critically affected by the sore throat. The mean pre-dose throat soreness score was 6.84 (range 2 to 10) and the mean pre-dose VAS for difficulty in swallowing was 62.6 mm (range 16, 98 mm). A total of 118 (52%) subjects were suffering from a burning throat, ranging from 59% in the Strepsils Cool throat lozenge group to 48% in the Strepsils Warm throat lozenge group.

Table 11.2.2 Mean ± sd for pre-dose efficacy variables – Full analysis set

Variable	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge	Overall
Number of subjects	77	74	74	225
Functional Impairment Scale (How sore throat affected)				
Each activity measured on a 11-point scale where 0 = Would not interfere at all				
Talking	4.74±2.05	4.54±2.58	4.93±2.48	4.74±2.37
Swallowing	6.65±1.36	6.51±1.47	6.61±1.69	6.59±1.51
Concentrating	2.61±2.59	3.16±2.78	2.93±2.66	2.90±2.67
Reading	1.79±2.36	2.05±2.73	2.04±2.52	1.96±2.53
Total score (0 to 40)	15.8±6.3	16.3±7.8	16.5±7.0	16.2±7.0
Assessment of throat soreness on a 11-point scale (0 = Not Sore and 10 = Very Sore)	6.91±1.02	6.81±1.24	6.81±1.57	6.84±1.28
VAS of difficulty swallowing (0mm = Not difficult, 100mm = Very difficult)	62.4±14.0	62.2±15.4	63.1±15.5	62.6±14.9
Suffering from a burning throat	48.1%	59.5%	50.0%	52.4%
How much do you feel like your best overall on a 11-point scale (0 = I feel at my very worst and 10 = I feel at my very best)	4.74±1.63	4.64±1.96	4.85±1.96	4.74±1.85
How happy are you, in relation to your throat (0 = Very unhappy with my throat, 100mm = Very happy with my throat)	3.13±1.67	2.93±1.76	2.92±1.81	3.00±1.74

Source: Table 14.1.6

Details of concomitant medication ongoing at time of randomisation are presented in Table 14.1.7; 86 (38%) subjects reported the use of at least one concomitant medication. In terms of WHO ATC level 2 categories, the most commonly reported categories were sex hormones and modulators of the genital system with 48 (21%)

subjects reporting and drugs for obstructive airways disease with 13 (6%) subjects reporting.

11.3 Measurements of Treatment Compliance

All subjects took their study medication dose in their respective clinic under the supervision of clinic staff who were able to ensure compliance.

11.4 Efficacy Results

11.4.1 Analysis of Efficacy

11.4.1.1 Primary Endpoint

The primary endpoint was the area under the change from baseline curve (AUC) in severity of throat soreness, from baseline to 2 hours. All subjects provided data for this measure. In the ANCOVA model for the full analysis set (n=225), the terms for treatment and baseline throat soreness were both highly statistically significant ($p<0.0001$) whereas the term for centre was not significant ($p=0.84$). The LS means reductions were -1.78 (Strepsils Warm throat lozenge), -2.06 (Strepsils Cool throat lozenge) and -0.98 (placebo throat lozenge). The pairwise differences between each of the actives and placebo were both statistically significant ($p<0.0001$ for Strepsils Cool throat lozenge and $p=0.001$ for Strepsils Warm throat lozenge. (Table 14.2.1.1).

Twenty-two (10%) subjects were excluded from the equivalent per-protocol analysis. However, the statistical conclusions based on this reduced data set were qualitatively identical to those obtained with the full analysis set as described above. The LS means reductions were -1.83 (Strepsils Warm throat lozenge), -2.09 (Strepsils Cool throat lozenge) and -1.11 (placebo throat lozenge). (Table 14.2.1.2).

Table 11.4.1 below summarises these results.

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

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
FULL ANALYSIS SET			
N	77	74	74
Mean±sd	-1.83±1.50	-2.07±1.47	-1.00±1.61
LS mean[a]	-1.78	-2.06	-0.98
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	-0.80	-1.27,-0.33	0.001 **
Strepsils Cool throat lozenge vs Placebo	-1.08	-1.56,-0.60	<0.0001 ***
PER-PROTOCOL SET			
N	75	64	64
Mean±sd	-1.87±1.50	-2.16±1.50	-1.25±1.39
LS mean[a]	-1.83	-2.09	-1.11
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	-0.72	-1.21,-0.23	0.004 **
Strepsils Cool throat lozenge vs Placebo	-0.98	-1.48,-0.47	0.0002 ***

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A negative difference favours the first treatment against second treatment
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.1.1 and 14.2.1.2
Throat soreness measured on a 11-point scale where 0 = Not sore, 10 = Very sore

11.4.1.2 Secondary Endpoints

The change from baseline in throat soreness at each follow-up assessment is summarised in Table 11.4.2 below and presented in more detail in Tables 14.2.2 to 14.2.12. The comparisons between the Strepsils Cool throat lozenge and placebo throat lozenge were statistically significant at each time point and the Strepsils Warm throat lozenge versus placebo comparison was statistically significant at all time points except at one minute post-dose. The Strepsils Cool throat lozenge and Strepsils Warm throat lozenge produced a 29% and 25% mean percentage change from baseline respectively in severity of throat soreness at two hours post-dose compared to 10% for the placebo lozenge (Table 14.2.12).

Table 11.4.2 Mean (SD) for Change from Baseline in Throat Soreness at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes Post Dose – Full Analysis Set

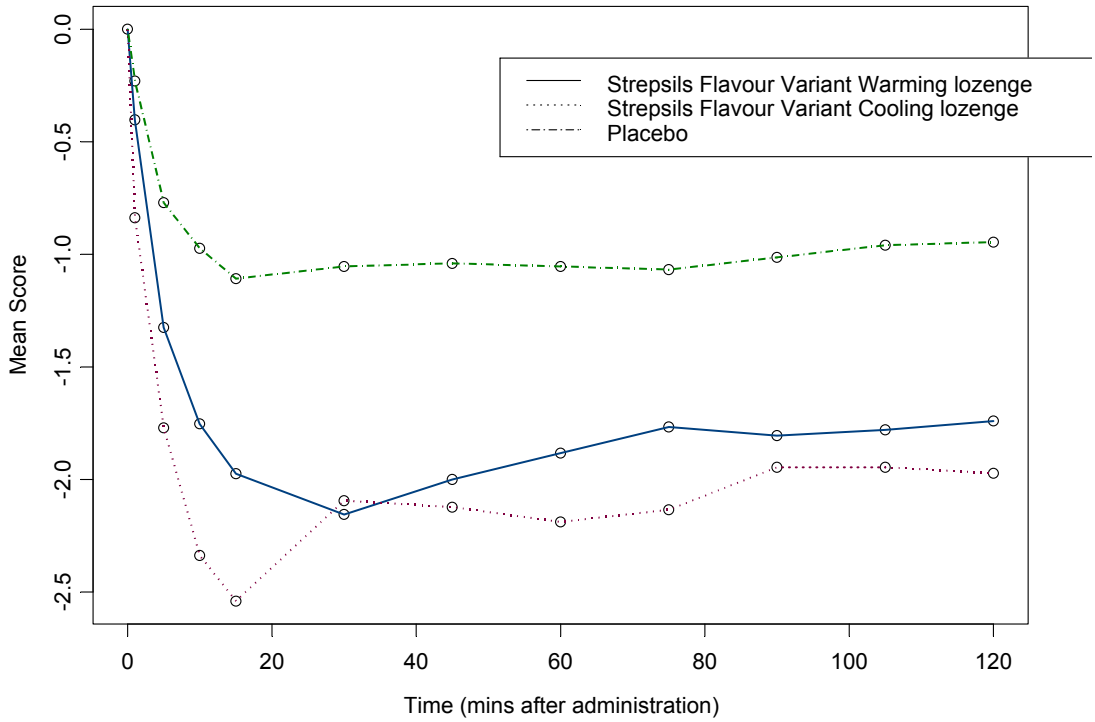
Minutes post-dose	Strepsils Warm throat lozenge (n)	Strepsils Cool throat lozenge (n)	Placebo throat lozenge (n)	Strepsils Warm throat lozenge versus Placebo	Strepsils Cool throat lozenge versus Placebo
0	6.91±1.02 (77)	6.81±1.24 (74)	6.81±1.57 (74)		
1	-0.40±0.94 (77)	-0.84±1.44 (74)	-0.23±1.32 (74)	ns	**
5	-1.32±1.47 (77)	-1.77±1.49 (74)	-0.77±1.66 (74)	*	***
10	-1.75±1.60 (77)	-2.34±1.66 (74)	-0.97±1.50 (74)	**	***
15	-1.97±1.68 (77)	-2.54±1.70 (74)	-1.11±1.69 (74)	**	***
30	-2.16±1.84 (77)	-2.09±1.46 (74)	-1.05±1.72 (74)	***	***
45	-2.00±1.79 (77)	-2.12±1.67 (73)	-1.04±1.82 (74)	**	***
60	-1.88±1.77 (77)	-2.19±1.94 (74)	-1.05±1.86 (74)	**	***
75	-1.77±1.64 (77)	-2.14±1.88 (74)	-1.07±1.83 (74)	*	***
90	-1.81±1.81 (77)	-1.95±1.87 (74)	-1.01±1.82 (74)	**	**
105	-1.78±1.85 (77)	-1.95±1.99 (74)	-0.96±1.88 (74)	**	**
120	-1.74±1.89 (77)	-1.97±1.91 (73)	-0.95±1.86 (74)	*	***

ns Comparison not statistically significant
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.2 to 14.2.12

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

The maximum reductions in throat soreness were recorded at 15 minutes post-dose for the Strepsils Cool throat lozenge and placebo throat lozenge groups, whereas the largest mean reduction for Strepsils Warm throat lozenge was at 30 minutes post-dose. This difference in the change from baseline profiles is clearly seen in Figure 11.4.1 below.

Figure 11.4.1 Mean change from baseline in throat soreness from 1 to 120 minutes post first dose – Full Analysis Set



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

The results of the analyses related to the AUC from baseline to two hours post-dose for sore throat relief are given in Table 11.4.3 below. In the ANCOVA model for the full analysis set (n=225) the term for treatment was highly statistically significant (p<0.0001) whereas the terms for centre (p=0.91) and baseline throat soreness (p=0.45) were not statistically significant. The LS means were 1.74 (Strepsils Warm throat lozenge), 2.10 (Strepsils Cool throat lozenge) and 0.98 (placebo throat lozenge). The pairwise differences between each of the actives and placebo were both statistically significant (p<0.0001 for the Strepsils Cool throat lozenge and p=0.0001 for the Strepsils Warm throat lozenge). (Table 14.2.13.1).

Twenty-two (10%) subjects were excluded from the equivalent per-protocol analysis. However, the statistical conclusions based on this reduced data set were qualitatively identical to those obtained with the full analysis set as described above. The LS means reductions were 1.73 (Strepsils Warm throat lozenge), 2.06 (Strepsils Cool throat lozenge) and 0.98 (placebo throat lozenge). (Table 14.2.13.2)

Table 11.4.3 AUC from Baseline to Two Hours Post First Dose for Sore Throat Relief

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
FULL ANALYSIS SET			
N	77	74	74
Mean±sd	1.70±1.19	2.06±1.30	0.94±1.04
LS mean[a]	1.74	2.10	0.98
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	0.76	0.38,1.14	0.0001 ***
Strepsils Cool throat lozenge vs Placebo	1.12	0.73,1.50	<0.0001 ***
PER-PROTOCOL SET			
N	75	64	64
Mean±sd	1.72±1.19	2.05±1.29	0.96±1.05
LS mean[a]	1.73	2.06	0.98
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	0.75	0.35,1.16	0.0003 ***
Strepsils Cool throat lozenge vs Placebo	1.08	0.67,1.50	<0.0001 ***

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness

b A positive difference favours the first treatment against second treatment

*** Comparison statistically significant at 0.1% level

Source: Tables 14.2.13.1 and 14.2.13.2

Measured on a 7-point scale where 0 = No relief, 1 = Slight relief, 2 = Mild relief, 3 = Moderate relief, 4 = Considerable relief, 5 = Almost complete relief, 6 = Complete relief

The sore throat relief scores at each follow-up assessment are summarised in Table 11.4.4 below and presented in more detail in Tables 14.2.14 and 14.2.24. The comparisons between the Strepsils Cool throat lozenge and placebo throat lozenge were statistically significant at each time point and the Strepsils Warm throat lozenge

versus placebo comparison was statistically significant at all time points except at one minute post-dose.

Table 11.4.4 Mean ± sd (n) for sore throat relief at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post-dose – Full analysis set

Minutes post-dose	Strepsils Warm throat lozenge (n)	Strepsils Cool throat lozenge (n)	Placebo throat lozenge (n)	Strepsils Warm throat lozenge versus Placebo	Strepsils Cool throat lozenge versus Placebo
1	0.86±1.05 (77)	1.41±1.22 (74)	0.53±0.95 (74)	ns	***
5	1.49±1.17 (77)	2.15±1.34 (74)	0.93±1.00 (74)	**	***
10	1.88±1.32 (77)	2.55±1.25 (74)	1.11±1.04 (74)	***	***
15	2.00±1.32 (77)	2.70±1.31 (74)	1.19±1.18 (74)	***	***
30	1.90±1.35 (77)	2.30±1.35 (74)	1.05±1.23 (74)	***	***
45	1.88±1.37 (77)	2.18±1.45 (73)	0.95±1.10 (74)	***	***
60	1.70±1.38 (77)	2.07±1.60 (74)	0.93±1.20 (74)	***	***
75	1.57±1.39 (77)	1.99±1.59 (74)	0.89±1.15 (74)	**	***
90	1.56±1.43 (77)	1.80±1.62 (74)	0.89±1.22 (74)	**	***
105	1.60±1.56 (77)	1.72±1.68 (74)	0.84±1.21 (74)	**	***
120	1.66±1.57 (77)	1.79±1.69 (73)	0.92±1.24 (74)	**	***

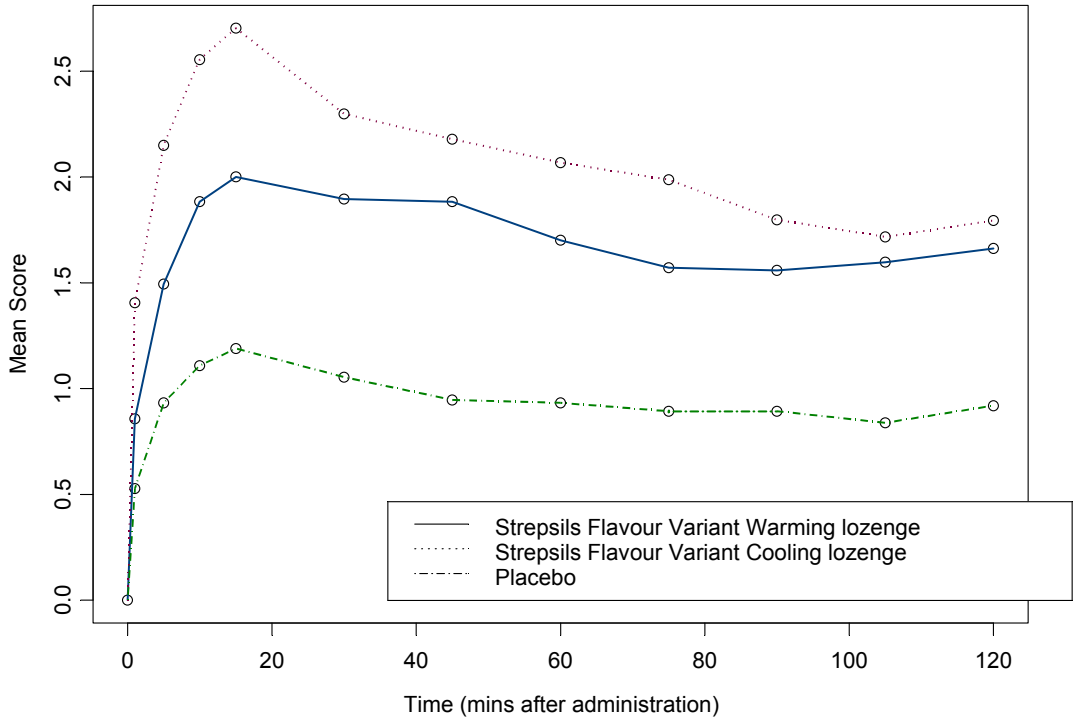
ns Comparison not statistically significant
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level

Source: Tables 14.2.14 to 14.2.24

Measured on a 7-point scale where 0 = No relief, 1 = Slight relief, 2 = Mild relief, 3 = Moderate relief, 4 = Considerable relief, 5 = Almost complete relief, 6 = Complete relief

Maximum mean pain relief was reported at 15 minutes post-dose for all three treatments, see Figure 11.4.2 below.

Figure 11.4.2 Mean sore throat relief from 1-120 minutes post-dose – Full analysis set



Measured on a 7-point scale where 0 = No relief, 1 = Slight relief, 2 = Mild relief, 3 = Moderate relief, 4 = Considerable relief, 5 = Almost complete relief, 6 = Complete relief

Details of the analysis of the AUC from baseline to two hours post-dose for the change from baseline in difficulty in swallowing (100 mm VAS scale where 0mm = Not difficult, 100mm = Very difficult) are presented in Table 11.4.5 below. In the ANCOVA model for the full analysis set (n=225) the terms for treatment (p<0.0001) and baseline score for difficulty in swallowing (p=0.003) were statistically significant whereas the terms for centre (p=0.97) and baseline throat soreness (p=0.51) were not statistically significant. The LS mean reductions were -13.5 mm (Strepsils Warm throat lozenge), -19.3 mm (Strepsils Cool throat lozenge) and -7.5 mm (placebo throat lozenge). The pairwise differences between each of the actives and placebo were both statistically significant (p<0.0001 for Strepsils Cool throat lozenge and p=0.009 for Strepsils Warm throat lozenge). (Table 14.2.25).

Table 11.4.5 AUC from baseline to two hours post-dose for the change from baseline in difficulty swallowing – Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	74	74
Mean±sd	-13.4±14.4	-19.2±14.6	-7.7±13.2
LS mean[a]	-13.5	-19.3	-7.5
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	-5.9	-10.4,-1.5	0.009 ***
Strepsils Cool throat lozenge vs Placebo	-11.7	-16.2,-7.2	<0.0001 ***

a Estimated from ANCOVA model with factors for treatment and centre and covariates for baseline throat soreness and baseline score for difficulty in swallowing

b A negative difference favours the first treatment against second treatment

*** Comparison statistically significant at 0.1% level

Source: Tables 14.2.25

Difficulty in swallowing measured on 100mm VAS where 0mm = Not difficult, 100mm = Very difficult

The change from baseline in difficulty in swallowing at each follow-up assessment is summarised in Table 11.4.6 below and presented in more detail in Tables 14.2.26 to 14.2.36. The comparisons between the Strepsils Cool throat lozenge and placebo throat lozenge were statistically significant at each time point and the Strepsils Warm throat lozenge versus placebo throat lozenge comparison was statistically significant from five to 60 minutes post-dose inclusive and at 90 minutes post-dose.

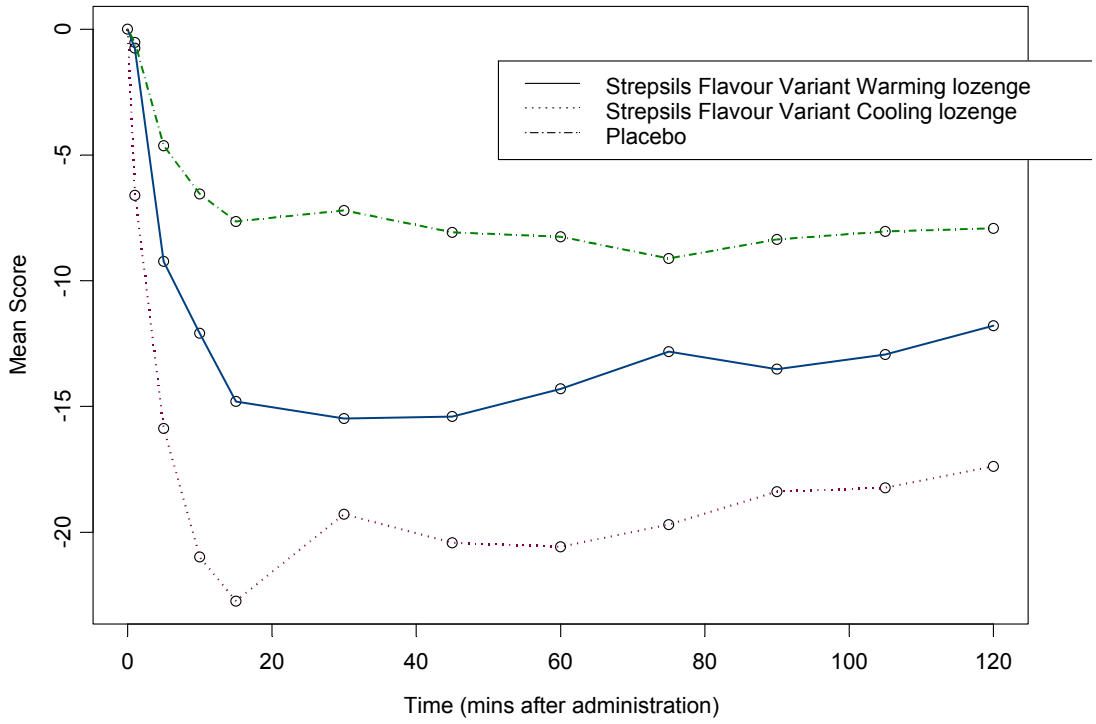
Table 11.4.6 Mean (SD) for Change from Baseline in Difficulty in Swallowing at 1,5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post dose – Full Analysis Set

Minutes post-dose	Strepsils Warm throat lozenge (n)	Strepsils Cool throat lozenge (n)	Placebo throat lozenge (n)	Strepsils Warm throat lozenge versus Placebo	Strepsils Cool throat lozenge versus Placebo
0	62.4±14.0 (77)	62.2±15.4 (74)	63.1±15.5 (74)		
1	-0.8±7.1 (77)	-6.6±13.0 (74)	-0.5±7.1 (74)	ns	***
5	-9.2±10.8 (77)	-15.9±14.2 (74)	-4.6±10.7 (74)	*	***
10	-12.1±16.1 (77)	-21.0±16.0 (74)	-6.6±13.0 (74)	*	***
15	-14.8±17.2 (77)	-22.7±16.2 (74)	-7.6±14.6 (74)	**	***
30	-15.5±17.8 (77)	-19.3±16.9 (74)	-7.2±14.8 (74)	**	***
45	-15.4±17.8 (77)	-20.4±17.1 (73)	-8.1±15.2 (74)	**	***
60	-14.3±16.5 (77)	-20.6±18.6 (74)	-8.3±15.6 (74)	*	***
75	-12.8±15.8 (77)	-19.7±19.2 (74)	-9.1±15.3 (74)	ns	***
90	-13.5±16.4 (77)	-18.4±18.5 (74)	-8.4±14.9 (73)	*	***
105	-12.9±17.0 (77)	-18.2±19.7 (74)	-8.0±16.0 (73)	ns	***
120	-11.8±18.7 (77)	-17.4±19.2 (73)	-7.9±15.5 (73)	ns	**

ns Comparison not statistically significant
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.26 to 14.2.36
Difficulty in swallowing measured on 100mm VAS where 0mm = Not difficult, 100mm = Very difficult

Maximum mean reductions in difficulty in swallowing pain relief were reported at 15 minutes post-dose for the Strepsils Cool throat lozenge, 30 minutes post-dose for the Strepsils Warm throat lozenge and 75 minutes post-dose for the placebo throat lozenge group, see Figure 11.4.3 below.

Figure 11.4.3 Mean change from baseline in difficulty swallowing from 1-120 minutes post dose– Full analysis set



Difficulty in swallowing measured on 100mm VAS where 0mm = Not difficult, 100mm = Very difficult

Details of the analysis of the AUC from one minute to two hours post dose for throat numbness are presented in Table 11.4.7 below. In the ANCOVA model for the full analysis set (n=225) the term for treatment was highly statistically significant (p<0.0001) whereas the terms for centre (p=0.72) and baseline throat soreness (p=0.89) were not statistically significant. The LS mean scores for throat numbness were 1.80 (Strepsils Warm throat lozenge), 2.12 (Strepsils Cool throat lozenge) and 1.48 (placebo throat lozenge). The pairwise differences between each of the actives and placebo were both statistically significant (p<0.0001 for Strepsils Cool throat lozenge and p=0.017 for Strepsils Warm throat lozenge). (Table 14.2.37).

Table 11.4.7 AUC for throat numbness measurements from 1 to 120 minutes post dose – Full Analysis Set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	74	74
Mean±sd	1.86±0.83	2.18±0.86	1.54±0.72
LS mean[a]	1.80	2.12	1.48
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	0.32	0.06,0.58	0.017 *
Strepsils Cool throat lozenge vs Placebo	0.64	0.38,0.90	<0.0001 ***

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
* Comparison statistically significant at 5% level
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.37
Throat numbness measured on a 5-point scale where 1 = None, 2 = Mild, 3 = Moderate, 4 = Considerable, 5 = Complete

Throat numbness at each follow-up assessment is summarised in Table 11.4.8 below and presented in more detail in Tables 14.2.38 to 14.2.48. The comparisons between the Strepsils Cool throat lozenge and placebo throat lozenge were statistically significant at each time point and the Strepsils Warm throat lozenge versus placebo throat lozenge comparison was statistically significant from one to 45 minutes post-dose inclusive.

Table 11.4.8 Mean ± sd (n) for throat numbness at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post dose – Full analysis set

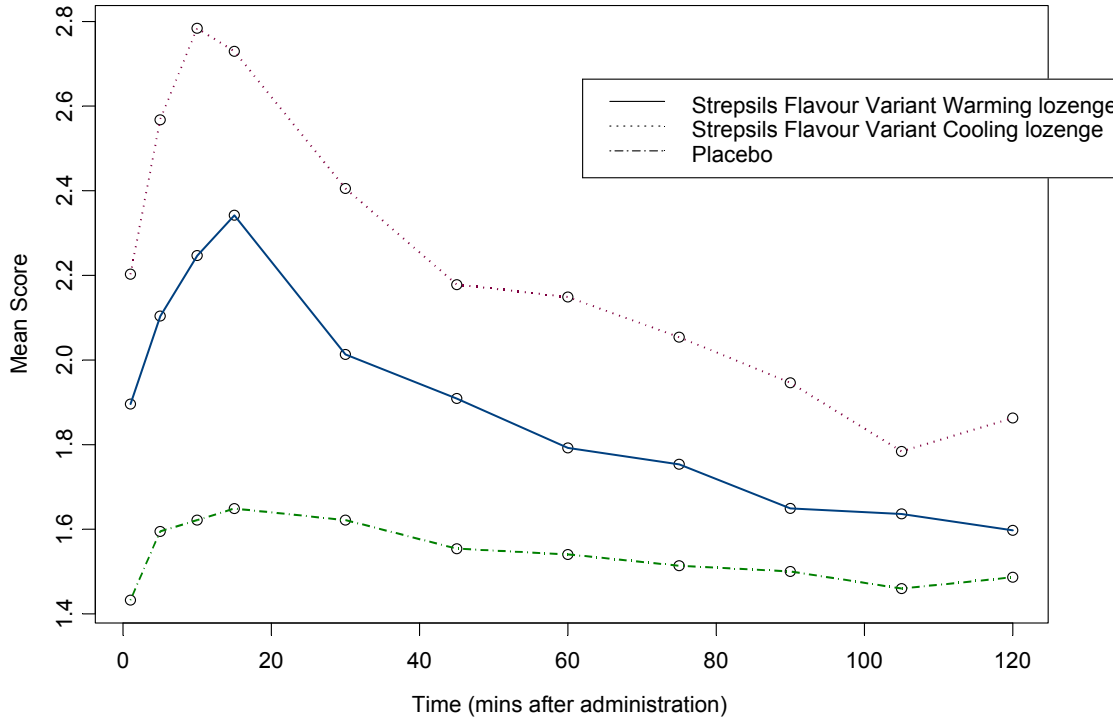
Minutes post-dose	Strepsils Warm throat lozenge (n)	Strepsils Cool throat lozenge (n)	Placebo throat lozenge (n)	Strepsils Warm throat lozenge versus Placebo	Strepsils Cool throat lozenge versus Placebo
1	1.90±0.84 (77)	2.20±0.86 (74)	1.43±0.76 (74)	***	***
5	2.10±0.95 (77)	2.57±0.86 (74)	1.59±0.72 (74)	***	***
10	2.25±0.96 (77)	2.78±0.98 (74)	1.62±0.72 (74)	***	***
15	2.34±1.01 (76)	2.73±0.96 (74)	1.65±0.78 (74)	***	***
30	2.01±0.97 (77)	2.41±0.96 (74)	1.62±0.84 (74)	*	***
45	1.91±0.98 (77)	2.18±0.99 (73)	1.55±0.81 (74)	*	***
60	1.79±0.94 (77)	2.15±1.06 (74)	1.54±0.81 (74)	ns	***
75	1.75±0.95 (77)	2.05±1.10 (74)	1.51±0.80 (74)	ns	***
90	1.65±0.90 (77)	1.95±1.11 (74)	1.50±0.80 (74)	ns	**
105	1.64±0.96 (77)	1.78±1.04 (74)	1.46±0.81 (74)	ns	*
120	1.60±0.99 (77)	1.86±1.12 (73)	1.49±0.86 (74)	ns	*

ns Comparison not statistically significant
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.38 to 14.2.48

Throat numbness measured on a 5-point scale where 1 = None, 2 = Mild, 3 = Moderate, 4 = Considerable, 5 = Complete

Maximum mean throat numbness was obtained at 15 minutes post-dose for the Strepsils Warm throat lozenge and placebo throat lozenge and 10 minutes post-dose for the Strepsils Cool throat lozenge, see Figure 11.4.4 below.

Figure 11.4.4 Mean throat numbness from 1 to 120 minutes post-dose – Full analysis set



Throat numbness measured on a 5-point scale where 1 = None, 2 = Mild, 3 = Moderate, 4 = Considerable, 5 = Complete

Table 14.2.49 summarises the results of the analysis relating to the time taken for subjects to be report moderate pain relief. In total, 51/74 (69%) in the Strepsils Cool throat lozenge group reported moderate pain relief within the 2 hour assessment period, 38/77 (49%) reported moderate pain relief in the Strepsils Warm throat lozenge group and 25/74 (34%) in the placebo throat lozenge group. The comparisons between the Strepsils Cool throat lozenge group and the placebo throat lozenge group in time to reporting moderate relief was statistically significant ($p<0.0001$), whereas the comparison between the Strepsils Warm throat lozenge and placebo throat lozenge groups did not achieve statistical significance ($p=0.054$).

Table 11.4.9 presents details of the changes from pre-dose to two hours post-dose in the functional impairment scale. Both Strepsils throat lozenges gave statistically significant improvements in swallowing compared to the placebo throat lozenge (p=0.011 for the Strepsils Cool throat lozenge and p=0.018 for the Strepsils Warm throat lozenge). For talking and the overall score the Strepsils Warm throat lozenge achieved statistically significant reductions versus the placebo throat lozenge (p=0.003 for talking and p=0.03 for the overall score), none of the other pairwise comparisons were statistically significant. There were no statistically significant differences between treatment groups for concentrating and reading (Table 14.2.50).

Table 11.4.9 Change from pre-dose to two hours post-dose in the functional impairment scale (each component and overall total score) – Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
TALKING			
N	77	73	74
Mean±sd	-1.09±2.10	-0.56±2.06	-0.20±2.04
LS mean[a]	-1.49	-0.99	-0.53
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	-0.96	-1.59,-0.33	0.003 **
Strepsils Cool throat lozenge vs Placebo	-0.46	-1.10,0.18	0.15
SWALLOWING			
N	77	73	74
Mean±sd	-1.35±1.89	-1.36±2.07	-0.65±1.86
LS mean[a]	-1.51	-1.57	-0.80
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	-0.71	-1.30,-0.13	0.018 *
Strepsils Cool throat lozenge vs Placebo	-0.77	-1.36,-0.17	0.011 *
CONCENTRATING			
N	77	73	74
Mean±sd	-0.57±1.82	-0.70±1.83	-0.43±1.28
LS mean[a]	-0.86	-0.82	-0.63
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	-0.23	-0.71,0.25	0.34
Strepsils Cool throat lozenge vs Placebo	-0.19	-0.68,0.29	0.44
READING			
N	77	73	74
Mean±sd	-0.21±1.84	-0.41±1.57	-0.22±1.00
LS mean[a]	-0.41	-0.54	-0.36
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	-0.05	-0.49,0.39	0.82
Strepsils Cool throat lozenge vs Placebo	-0.18	-0.63,0.27	0.43
TOTAL OF ALL FOUR RESPONSES			
N	77	73	74
Mean±sd	-3.2±6.1	-3.0±5.5	-1.5±4.3
LS mean[a]	-4.1	-3.8	-2.3

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	-1.9	-3.6,-0.2	0.03 *
Strepsils Cool throat lozenge vs Placebo	-1.5	-3.2,0.1	0.07

a Estimated from ANCOVA model with factors for treatment and centre and covariates for baseline throat soreness and baseline score for the relevant variable
b A negative difference favours the first treatment against second treatment
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level

Source: Table 14.2.50

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

At both one and two hours post-dose, subjects who received the Strepsils Cool throat lozenge reported statistically significantly greater improvements from baseline than placebo throat lozenge treated subjects in their assessment of "how much do you feel like your best overall" (p=0.003 and p=0.0002 respectively). In addition at two hours post-dose, subjects who received the Strepsils Warm throat lozenge had statistically significantly greater improvements from baseline compared to the placebo throat lozenge (p=0.046). Table 11.4.10 summarises these data; further details are given in Tables 14.2.51 and 14.2.52.

Table 11.4.10 Consumer questionnaire: Change from pre-dose in the 11 point scale for how much do you feel like your best overall - Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
	ONE HOUR		
N	77	74	73
Baseline (mean±sd)	4.74±1.63	4.64±1.96	4.84±1.97
One hour (mean±sd)	4.99±1.56	5.27±1.85	4.66±1.81
Change from baseline (mean±sd)	0.25±1.50	0.64±1.71	-0.18±1.84
LS mean[a]	0.20	0.54	-0.18
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	0.39	-0.08,0.85	0.10
Strepsils Cool throat lozenge vs Placebo	0.72	0.25,1.19	0.003 **
	TWO HOURS		
N	77	73	74
Baseline (mean±sd)	4.74±1.63	4.62±1.97	4.85±1.96
Two hours (mean±sd)	5.27±2.02	5.78±2.02	4.72±2.04
Change from baseline (mean±sd)	0.53±2.06	1.16±2.08	-0.14±2.21
LS mean[a]	0.82	1.36	0.21
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	0.61	0.01,1.20	0.046 *
Strepsils Cool throat lozenge vs Placebo	1.15	0.55,1.76	0.0002 ***

a Estimated from ANCOVA model with factors for treatment and centre and covariates for baseline throat soreness and baseline score for the relevant variable
b A positive difference favours the first treatment against second treatment
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.51 and 14.2.52
Measured on a 11-point scale where 0 = I feel at my very worst, 10 = I feel at my very best

At both one and two hours post-dose, subjects who received one of the Strepsils throat lozenges reported statistically significantly greater improvement from baseline than placebo throat lozenge treated subjects in their assessment of "how happy are you, in relation to your throat" (p<0.046 in all cases). Table 11.4.11 summarises these data; further details are given in Tables 14.2.53 and 14.2.54.

Table 11.4.11 Consumer questionnaire: Change from pre-dose in the 11 point scale for how happy are you, in relation to your throat - Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
	ONE HOUR		
N	77	74	73
Baseline (mean±sd)	3.13±1.67	2.93±1.76	2.96±1.79
One hour (mean±sd)	4.23±1.82	4.49±2.16	3.59±1.73
Change from baseline (mean±sd)	1.10±2.12	1.55±1.90	0.63±1.93
LS mean[a]	0.97	1.32	0.39
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	0.58	0.01,1.14	0.046 *
Strepsils Cool throat lozenge vs Placebo	0.93	0.36,1.50	0.002 **
	TWO HOURS		
N	77	74	74
Baseline (mean±sd)	3.13±1.67	2.93±1.76	2.92±1.81
Two hours (mean±sd)	4.66±2.11	4.80±2.14	3.64±2.06
Change from baseline (mean±sd)	1.53±2.39	1.86±2.25	0.72±2.38
LS mean[a]	1.52	1.74	0.54
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	0.98	0.33,1.63	0.003 **
Strepsils Cool throat lozenge vs Placebo	1.20	0.54,1.85	0.0004 ***

a Estimated from ANCOVA model with factors for treatment and centre and covariates for baseline throat soreness and baseline score for the relevant variable
b A positive difference favours the first treatment against second treatment
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.53 and 14.2.54
Measured on a 11-point scale where 0 = Very unhappy with my throat, 10 = Very happy with my throat

Both Strepsils throat lozenges were judged to be statistically significantly faster than the placebo throat lozenge with respect to the assessment “how quickly did you feel the cooling sensation” at one minute post-dose (p=0.011 for the Strepsils Warm throat lozenge and p<0.0001 for the Strepsils Cool throat lozenge) . The number of subjects who reported a cooling sensation either “Instantly as soon as I started to suck” or “Started after 1 to 5 seconds” was 45 (61%) for the Strepsils Cool throat lozenge, 11 (14%) for the Strepsils Warm throat lozenge and four (5%) for placebo. Table 11.4.12 summarises these data.

Table 11.4.12 At one minute post-dose, how quickly did you feel the cooling sensation - Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	74	73
Instantly as soon as I started to suck	1 (1.3%)	16 (21.6%)	2 (2.7%)
Started after 1 to 5 seconds	10 (13.0%)	29 (39.2%)	2 (2.7%)
Started after 6 to 10 seconds	9 (11.7%)	13 (17.6%)	6 (8.2%)
Started after 11 to 20 seconds	9 (11.7%)	1 (1.4%)	7 (9.6%)
Started after more than 20 seconds	7 (9.1%)	2 (2.7%)	2 (2.7%)
No cooling sensation	41 (53.2%)	13 (17.6%)	54 (74.0%)
Parameter estimates	Odds ratio[b]	95% CI	p
Strepsils Warm throat lozenge vs. Placebo	2.41	1.22,4.75	0.011 *
Strepsils Cool throat lozenge vs. Placebo	20.10	9.69,41.69	<0.0001 ***

a Estimated from proportional odds model with factors for treatment and centre and a covariate for baseline throat soreness
b A value > 1 indicates the first treatment has quicker time to feel the cooling sensation
* Comparison statistically significant at 5% level
*** Comparison statistically significant at 0.1% level
Source: Table 14.2.55

Table 11.4.13 presents a summary of how deep down within the throat the cooling was felt at one-minute post-dose, measured on an 11-point scale. Cooling was reported statistically significantly deeper within the throat ($p<0.0001$) for subjects who received the Strepsils Cool throat lozenge compared to the placebo throat lozenge. The comparison between Strepsils Warm throat lozenge and placebo failed to achieve statistical significance ($p=0.11$). Further details are presented in Table 14.2.56.

Table 11.4.13 Consumer questionnaire: At one minute post-dose, how deep down within the throat was the cooling felt - Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	73	73
Mean±sd	1.81±2.47	4.71±2.67	1.16±2.20
LS mean[a]	1.47	4.40	0.82
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	0.65	-0.14,1.44	0.11
Strepsils Cool throat lozenge –vs Placebo	3.58	2.77,4.38	<0.0001 ***

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
*** Comparison statistically significant at 0.1% level
Source: Table 14.2.56
Measured on a 11-point scale where 0 = No cooling, 10 = Very deep in the throat

Table 11.4.14 summarises assessments of whether the throat lozenge provided warming relief at the first moment of swallowing and two hours post-dose. At both time points statistically significantly more warming relief (p<0.0001) was reported by subjects who received the Strepsils Warm throat lozenge compared to the placebo throat lozenge. The comparison between the Strepsils Cool throat lozenge and the placebo throat lozenge was not significant at either assessment. Further details are given in Table 14.2.57.

Table 11.4.14 Did the throat lozenge provide warming relief at the first moment you swallowed it and at two hours post-dose - Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
AT THE FIRST MOMENT OF SWALLOWING			
N	77	74	73
Number (%) reporting	36 (46.8%)	12 (16.2%)	10 (13.7%)
Parameter estimates	Odds ratio[b]	95% CI	p
Strepsils Warm throat lozenge vs. Placebo	5.62	2.50,12.62	<0.0001 ***
Strepsils Cool throat lozenge vs. Placebo	1.22	0.49,3.04	0.67
TWO HOURS POST-DOSE			
N	77	74	74
Number (%) reporting	66 (85.7%)	24 (32.4%)	22 (29.7%)
Parameter estimates	Odds ratio[b]	95% CI	p
Strepsils Warm throat lozenge vs. Placebo	15.70	6.83,36.07	<0.0001 ***
Strepsils Cool throat lozenge vs. Placebo	1.19	0.59,2.42	0.63

a Estimated from a logistic regression model with factors for treatment and centre and a covariate for baseline throat soreness
b A value > 1 indicates the first treatment is favoured over the second treatment
*** Comparison statistically significant at 0.1% level
Source: Table 14.2.57

Table 11.4.15 summarises assessments of whether the throat lozenge provided cooling relief at the first moment of swallowing and two hours post-dose. At both time points statistically significantly more cooling relief (p<0.0001) was reported by subjects who received the Strepsils Cool throat lozenge compared to the placebo throat lozenge. The comparison between the Strepsils Warm throat lozenge and the placebo throat lozenge was not significant at either assessment. Further details are given in Table 14.2.58.

Table 11.4.15 Did the throat lozenge provide cooling relief at the first moment you swallowed it and at two hours post-dose - Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
AT THE FIRST MOMENT OF SWALLOWING			
N	77	74	73
Number (%) reporting	6 (7.8%)	46 (62.2%)	7 (9.6%)
Parameter estimates	Odds ratio[b]	95% CI	p
Strepsils Warm throat lozenge vs. Placebo	0.81	0.26,2.54	0.72
Strepsils Cool throat lozenge vs. Placebo	15.78	6.32,39.42	<0.0001 ***
TWO HOURS POST-DOSE			
N	77	74	74
Number (%) reporting	5 (6.5%)	51 (68.9%)	6 (8.1%)
Parameter estimates	Odds ratio[b]	95% CI	p
Strepsils Warm throat lozenge vs. Placebo	0.78	0.23,2.69	0.70
Strepsils Cool throat lozenge vs. Placebo	25.13	9.52,66.36	<0.0001 ***

[a] Estimated from a logistic regression model with factors for treatment and centre and a covariate for baseline throat soreness

[b] A value > 1 indicates the first treatment is favoured over the second treatment

*** Comparison statistically significant at 0.1% level

Source: Table 14.2.58

Table 11.4.16 summarises the number of subjects reporting each of several types of relief provided by the throat lozenge at the first moment of swallowing. The Strepsils Cool throat lozenge provided statistically significantly more soreness relief, relief from burning and soothing relief than the placebo throat lozenge. The number of subjects reporting no relief was 39 (53%) for the placebo throat lozenge, 18 (23%) for the Strepsils Warm throat lozenge and six (8%) for Strepsils Cool throat lozenge; the pairwise treatment comparisons between each of the Strepsils throat lozenges and the placebo throat lozenge were both statistically significant (p<0.001). Further details are given in Tables 14.2.59 to 14.2.66.

Table 11.4.16 Number (%) of subjects reporting each type of relief the throat lozenge provided at the first moment of swallowing – Full analysis set

Type	Strepsils Warm throat lozenge (n)	Strepsils Cool throat lozenge (n)	Placebo throat lozenge (n)	Strepsils Warm throat lozenge versus Placebo	Strepsils Cool throat lozenge versus Placebo
N	77	74	73		
Comforting	9 (11.7%)	11 (14.9%)	10 (13.7%)	ns	ns
Pain	6 (7.8%)	7 (9.5%)	1 (1.4%)	ns	ns
Soreness	4 (5.2%)	18 (24.3%)	3 (4.1%)	ns	**
Relief from burning	5 (6.5%)	16 (21.6%)	4 (5.5%)	ns	**
Soothing	13 (16.9%)	23 (31.1%)	9 (12.3%)	ns	**
Coating	12 (15.6%)	6 (8.1%)	13 (17.8%)	ns	ns
Relief from swelling	4 (5.2%)	-	1 (1.4%)	ns	ns
No relief	18 (23.4%)	6 (8.1%)	39 (53.4%)	***	***

ns Comparison not statistically significant
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.59 to 14.2.66

Table 11.4.17 summarises the number of subjects reporting each of several types of relief provided by the throat lozenge at two hours post-dose. The Strepsils Cool throat lozenge provided statistically significantly more pain relief, soreness relief, relief from burning and soothing relief than the placebo throat lozenge. The Strepsils Warm throat lozenge provided statistically significantly more pain relief and soreness relief than the placebo throat lozenge. The number of subjects reporting no relief in each treatment group was 27 (36%) for the placebo throat lozenge, six (8%) for the Strepsils Warm throat lozenge and two (3%) for Strepsils Cool throat lozenge; the pair wise treatment comparisons between each of the Strepsils throat lozenges and the placebo throat lozenge were both statistically significant ($p<0.001$). Further details are given in Tables 14.2.59 to 14.2.66.

Table 11.4.17 Number (%) subjects reporting each type of relief the throat lozenge provided at two hours post-dose – Full analysis set

Type	Strepsils Warm throat lozenge (n)	Strepsils Cool throat lozenge (n)	Placebo throat lozenge (n)	Strepsils Warm throat lozenge versus Placebo	Strepsils Cool throat lozenge versus Placebo
N	77	74	74		
Comforting	18 (23.4%)	19 (25.7%)	17 (23.0%)	ns	ns
Pain	18 (23.4%)	17 (23.0%)	4 (5.4%)	**	**
Soreness	19 (24.7%)	30 (40.5%)	8 (10.8%)	*	***
Relief from burning	7 (9.1%)	13 (17.6%)	5 (6.8%)	ns	*
Soothing	18 (23.4%)	32 (43.2%)	18 (24.3%)	ns	*
Coating	13 (16.9%)	10 (13.5%)	14 (18.9%)	ns	ns
Relief from swelling	6 (7.8%)	2 (2.7%)	1 (1.4%)	ns	ns
No relief	6 (7.8%)	2 (2.7%)	27 (36.5%)	***	***

ns Comparison not statistically significant
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.59 to 14.2.66

Table 11.4.18 gives details of the type of warming sensation experienced at five minutes post-dose. The number of subjects reporting no warming sensation was 35 (47%) for the placebo throat lozenge, 29 (39%) for the Strepsils Cool throat lozenge and five (6%) for the Strepsils Warm throat lozenge.

Table 11.4.18 Consumer questionnaire: At five minutes post-dose, describe the type of warming sensation experienced - Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	74	74
A warming sensation like one gets from a hot drink	11 (14.3%)	3 (4.1%)	3 (4.1%)
Comforting warming sensation	23 (29.9%)	16 (21.6%)	19 (25.7%)
Deeply warming sensation	21 (27.3%)	12 (16.2%)	0 (0.0%)
Gentle warming sensation	26 (33.8%)	19 (25.7%)	25 (33.8%)
No warming sensation	5 (6.5%)	29 (39.2%)	35 (47.3%)

Source: Table 14.2.67

Table 11.4.19 presents a summary of how deep down within the throat the warming was felt at five minutes post-dose measured on an 11-point scale. Warming was reported statistically significantly deeper within the throat ($p<0.0001$) for subjects who received the Strepsils Warm throat lozenge compared to the placebo throat lozenge. The comparison between the Strepsils Cool throat lozenge and the placebo throat lozenge was also statistically significant in favour of the Strepsils throat lozenge ($p=0.004$). Further details are presented in Table 14.2.68.

Table 11.4.19 Consumer questionnaire: At five minutes post-dose, how deep down within the throat was the warming felt – Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	74	74
Mean±sd	4.21±2.21	3.11±2.95	1.96±2.22
LS mean[a]	3.90	2.81	1.63
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	2.27	1.47,3.07	<0.0001 ***
Strepsils Cool throat lozenge vs Placebo	1.18	0.38,1.99	0.004 **

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level

Source: Tables 14.2.68

Measured on a 11-point scale where 0 = No warming, 10 = Very deep in the throat

Table 11.4.20 gives details of the where the subject felt the cooling sensation working at 20 minutes post-dose. The number of subjects reporting no cooling was 53 (72%) for the placebo throat lozenge, 49 (64%) for the Strepsils Warm throat lozenge and nine (12%) for the Strepsils Cool throat lozenge. Further details are presented in Table 14.2.70.

Table 11.4.20 Consumer questionnaire: At 20 minutes post-dose, where did you feel the cooling sensation working - Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	74	74
No cooling	49 (63.6%)	9 (12.2%)	53 (71.6%)
Back of the mouth	11 (14.3%)	24 (32.4%)	6 (8.1%)
Back of the throat	15 (19.5%)	38 (51.4%)	12 (16.2%)
Chest	2 (2.6%)	5 (6.8%)	0 (0.0%)
Deep in throat	5 (6.5%)	12 (16.2%)	4 (5.4%)
Nose	2 (2.6%)	7 (9.5%)	1 (1.4%)
Tongue	16 (20.8%)	45 (60.8%)	8 (10.8%)
Tonsils	9 (11.7%)	16 (21.6%)	6 (8.1%)
Whole of the mouth	5 (6.5%)	27 (36.5%)	2 (2.7%)
Whole of throat	4 (5.2%)	7 (9.5%)	1 (1.4%)

Source: Table 14.2.69

Table 11.4.21 presents a summary of the subjects rating of the intensity of the cooling sensation at 20 minutes post-dose measured on an 11-point scale. The intensity of cooling reported was statistically significantly higher ($p<0.0001$) for subjects who received the Strepsils Cool throat lozenge compared to the placebo throat lozenge. The comparison between the Strepsils Warm throat lozenge and the placebo throat lozenge was not significant ($p=0.24$). Further details are presented in Table 14.2.71.

Table 11.4.21 Consumer questionnaire: At 20 minutes post-dose, describe the intensity of the cooling sensation – Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	74	74
Mean±sd	1.83±2.61	5.70±2.90	1.32±2.26
LS mean[a]	1.62	5.50	1.12
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	0.50	-0.34,1.34	0.24
Strepsils Cool throat lozenge vs Placebo	4.38	3.53,5.23	<0.0001 ***

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.71

Measured on a 11-point scale where 0 = No cooling, 10 = Very-intense cooling

Table 11.4.22 gives details of the where the subject felt the warming sensation working at 20 minutes post-dose. The number of subjects reporting no warming was 38 (51%) for the placebo throat lozenge, 30 (41%) for the Strepsils Cool throat lozenge and two (3%) for the Strepsils Warm throat lozenge. Further details are presented in Table 14.2.73.

Table 11.4.22 Consumer questionnaire: At 20 minutes post-dose, where did you feel the warming sensation working - Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	74	74
No warming	2 (2.6%)	30 (40.5%)	38 (51.4%)
Back of the mouth	30 (39.0%)	13 (17.6%)	11 (14.9%)
Back of the throat	41 (53.2%)	19 (25.7%)	17 (23.0%)
Chest	1 (1.3%)	3 (4.1%)	1 (1.4%)
Deep in throat	20 (26.0%)	10 (13.5%)	6 (8.1%)
Nose	1 (1.3%)	3 (4.1%)	0 (0.0%)
Tongue	47 (61.0%)	15 (20.3%)	13 (17.6%)
Tonsils	14 (18.2%)	4 (5.4%)	4 (5.4%)
Whole of the mouth	18 (23.4%)	14 (18.9%)	5 (6.8%)
Whole of throat	5 (6.5%)	6 (8.1%)	3 (4.1%)

Source: Table 14.2.72

Table 11.4.23 presents a summary of the subjects rating of the intensity of the warming sensation at 20 minutes post-dose measured on an 11-point scale. The intensity of warming was statistically significantly higher (p<0.0001) for subjects who received the Strepsils Warm throat lozenge compared to the placebo throat lozenge. The comparison between the Strepsils Cool throat lozenge and the placebo throat lozenge was also statistically significant in favour of the Strepsils throat lozenge (p=0.0008). Further details are presented in Table 14.2.74.

Table 11.4.23 Consumer questionnaire: At 20 minutes post-dose, describe the intensity of the warming sensation – Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	76	74	74
Mean±sd	5.75±2.04	3.16±3.17	1.76±2.12
LS mean[a]	5.67	3.07	1.68
Parameter estimates	LS mean[b]	95% CI	P
Strepsils Warm throat lozenge vs Placebo	3.99	3.18,4.80	<0.0001 ***
Strepsils Cool throat lozenge vs Placebo	1.40	0.58,2.21	0.0008 ***

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.74

Measured on a 11-point scale where 0 = No warming, 10 = Very-intense warming

Both Strepsils throat lozenges were judged statistically significantly faster than the placebo throat lozenge (p<0.02) at 20 minutes post-dose with respect to the assessment "how quickly did you feel the warming sensation". The number of subjects who reported a warming sensation either "Instantly as soon as I started to suck" or "Started within 5 seconds" was 32 (42%) for the Strepsils Warm throat lozenge, 18 (24%) for the Strepsils Cool throat lozenge and three (4%) for the placebo throat lozenge. Table 11.4.24 summarises these data.

Table 11.4.24 Consumer questionnaire: At 20 minutes post-dose, how quickly did you feel the warming sensation - Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	74	74
Instantly, soon as I started to suck	8 (10.4%)	7 (9.5%)	1 (1.4%)
Started within 5 seconds	24 (31.2%)	11 (14.9%)	2 (2.7%)
Started within 30 seconds	16 (20.8%)	9 (12.2%)	9 (12.2%)
Started within 1 minute	14 (18.2%)	3 (4.1%)	7 (9.5%)
Started within 5 minutes	9 (11.7%)	8 (10.8%)	14 (18.9%)
Started within 10 minutes	3 (3.9%)	4 (5.4%)	4 (5.4%)
Started within 20 minutes	1 (1.3%)	2 (2.7%)	0 (0.0%)
Did not feel any warming sensation	2 (2.6%)	30 (40.5%)	37 (50.0%)
Parameter estimates	Odds ratio[b]	95% CI	p
Strepsils Warm throat lozenge vs. Placebo	8.80	4.70,16.49	<0.0001 ***
Strepsils Cool throat lozenge vs. Placebo	2.07	1.14,3.74	0.02 *

a Estimated from proportional odds model with factors for treatment and centre and a covariate for baseline throat soreness
b A value > 1 indicates the first treatment has quicker time to feel the warming sensation
* Comparison statistically significant at 5% level
*** Comparison statistically significant at 0.1% level
Source: Table 14.2.75

Statistically significantly more subjects considered themselves to be better at two hours post-dose than before treatment after receiving one of the Strepsils throat lozenges compared to those receiving the placebo throat lozenge (p<0.0001 in both cases). The number of subjects who reported feeling better was 42 (58%) for the Strepsils Cooling throat lozenge, 40 (52%) for the Strepsils Warm throat lozenge and 14 (19%) for the placebo throat lozenge. Table 11.4.25 summarises these data.

Table 11.4.25 At two hours post-dose, do you feel any better than before you took the throat lozenge - Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	73	73
Number (%) reporting	40 (51.9%)	42 (57.5%)	14 (19.2%)
Parameter estimates	Odds ratio[b]	95% CI	p
Strepsils Warm throat lozenge vs. Placebo	4.58	2.20,9.57	<0.0001 ***
Strepsils Cool throat lozenge vs. Placebo	5.72	2.71,12.08	<0.0001 ***

a Estimated from a logistic regression model with factors for treatment and centre and a covariate for baseline throat soreness

b A value > 1 indicates the first treatment is favoured over the second treatment

*** Comparison statistically significant at 0.1% level

Source: Table 14.2.76

Statistically significantly more subjects considered themselves to be less distracted at two hours post-dose than before treatment after receiving one of the Strepsils throat lozenges compared to those receiving the placebo throat lozenge (p<0.02 in both cases). The number of subjects who reported feeling less distracted was 21 (29%) for the Strepsils Cool throat lozenge, 21 (27%) for the Strepsils Warm throat lozenge and eight (11%) for the placebo throat lozenge. Table 11.4.26 summarises these data.

Table 11.4.26 At two hours post-dose, do you feel less distracted than before you took the throat lozenge - Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	73	74
Number (%) reporting	21 (27.3%)	21 (28.8%)	8 (10.8%)
Parameter estimates	Odds ratio[b]	95% CI	p
Strepsils Warm throat lozenge vs. Placebo	3.10	1.27,7.54	0.013 *
Strepsils Cool throat lozenge vs. Placebo	3.33	1.36,8.13	0.008 **

a Estimated from a logistic regression model with factors for treatment and centre and a covariate for baseline throat soreness
b A value > 1 indicates the first treatment is favoured over the second treatment
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
Source: Table 14.2.77

Statistically significantly more subjects considered themselves to be less frustrated at two hours post-dose than before treatment after receiving one of the Strepsils throat lozenges compared to those receiving the placebo throat lozenge ($p \leq 0.02$ in both cases). The number of subjects who reported feeling less frustrated was 26 (36%) for the Strepsils Cool throat lozenge, 23 (30%) for the Strepsils Warm throat lozenge and 10 (14%) for the placebo throat lozenge. Table 11.4.27 summarises these data.

Table 11.4.27 At two hours post-dose, do you feel less frustrated than before you took the throat lozenge - Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	73	74
Number (%) reporting	23 (29.9%)	26 (35.6%)	10 (13.5%)
Parameter estimates	Odds ratio[b]	95% CI	p
Strepsils Warm throat lozenge vs. Placebo	2.72	1.19,6.22	0.02 *
Strepsils Cool throat lozenge vs. Placebo	3.60	1.58,8.21	0.002 **

a Estimated from a logistic regression model with factors for treatment and centre and a covariate for baseline throat soreness
b A value > 1 indicates the first treatment is favoured over the second treatment
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
Source: Table 14.2.78

Statistically significantly more subjects considered themselves to be happier at two hours post-dose than before treatment after receiving one of the Strepsils throat lozenges compared to those receiving the placebo throat lozenge ($p<0.005$ in both

cases). The number of subjects who reported feeling happier was 39 (53%) for Strepsils Cool throat lozenge, 34 (45%) for the Strepsils Warm throat lozenge and 17 (23%) for the placebo throat lozenge. Table 11.4.28 summarises these data.

Table 11.4.28 At two hours post-dose, do you feel happier than before you took the throat lozenge - Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	75	73	74
Number (%) reporting	34 (45.3%)	39 (53.4%)	17 (23.0%)
Parameter estimates	Odds ratio[b]	95% CI	p
Strepsils Warm throat lozenge vs. Placebo	2.78	1.37,5.65	0.005 **
Strepsils Cool throat lozenge vs. Placebo	3.85	1.89,7.85	0.0002 ***

a Estimated from a logistic regression model with factors for treatment and centre and a covariate for baseline throat soreness
b A value > 1 indicates the first treatment is favoured over the second treatment
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level
Source: Table 14.2.79

Both Strepsils throat lozenges gave statistically significantly higher scores than the placebo throat lozenge ($p<0.0001$ in both cases) with respect to the question asked at two hours concerning "how you would rate this lozenge as a treatment for sore throat" recorded on an 11-point scale where 0 = Poor and 10 = Excellent. The LS mean scores estimated from the ANCOVA model were 4.71, 5.15 and 2.14 for the Strepsils Warm throat lozenge, Strepsils Cool throat lozenge and the placebo throat lozenge respectively. Table 11.4.29 summarises these data and more detailed information is presented in Table 14.2.80.

Table 11.4.29 Consumer questionnaire: At two hours post-dose, how you would rate this throat lozenge as a treatment for sore throat – Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	74	74
Mean±sd	4.84±2.83	5.27±2.66	2.30±2.71
LS mean[a]	4.71	5.15	2.14
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	2.57	1.68,3.45	<0.0001 ***
Strepsils Cool throat lozenge vs Placebo	3.00	2.11,3.90	<0.0001 ***

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.80

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

Both Strepsils throat lozenges gave statistically significantly higher scores than the placebo throat lozenge (p≤0.0005 in both cases) with respect to the question asked at two hours concerning "how much do you think the lozenge coated your throat" recorded on an 11-point scale where 0 = No coating and 10 = Throat completely coated. The LS mean scores estimated from the ANCOVA model were 3.74, 4.14 and 2.31 for the Strepsils Warm throat lozenge, Strepsils Cool throat lozenge and the placebo throat lozenge respectively. Table 11.4.30 summarises these data and more detailed information is presented in Table 14.2.81.

Table 11.4.30 Consumer questionnaire: At two hours post-dose, how much do you think the throat lozenge coated your throat – Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	74	74
Mean±sd	3.94±2.52	4.32±2.49	2.51±2.41
LS mean[a]	3.74	4.14	2.31
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	1.43	0.63,2.23	0.0005 ***
Strepsils Cool throat lozenge vs Placebo	1.83	1.02,2.63	<0.0001 ***

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.81
Measured on a 11-point scale where 0 = No coating, 10 = Throat completely coated

Both Strepsils throat lozenges gave statistically significantly higher scores than the placebo throat lozenge (p<0.0001 in both cases) with respect to the question asked at two hours concerning "how much do you think the lozenge soothed your throat" recorded on an 11-point scale where 0 = No soothing and 10 = Very soothing. The LS mean scores estimated from the ANCOVA model were 4.14, 5.18 and 2.28 for the Strepsils Warm throat lozenge, Strepsils Cool throat lozenge and the placebo throat lozenge respectively. Table 11.4.31 summarises these data and more detailed information is presented in Table 14.2.82.

Table 11.4.31 Consumer questionnaire: At two hours post-dose, how much do you think the throat lozenge soothed your throat – Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	74	74
Mean±sd	4.35±2.82	5.36±2.50	2.50±2.46
LS mean[a]	4.14	5.18	2.28
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	1.87	1.03,2.70	<0.0001 ***
Strepsils Cool throat lozenge vs Placebo	2.91	2.06,3.75	<0.0001 ***

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.82
Measured on a 11-point scale where 0 = No soothing, 10 = Very soothing

Both Strepsils throat lozenges gave statistically significantly higher scores than the placebo throat lozenge (p≤0.01 in both cases) with respect to the question asked at two hours concerning "how moisturising/lubricating is this lozenge" recorded on an 11-point scale where 0 = Not moisturising/lubricating at all and 10 = Very moisturising/lubricating. The LS mean scores estimated from the ANCOVA model were 3.49, 4.04 and 2.47 for the Strepsils Warm throat lozenge, Strepsils Cool throat lozenge and the placebo throat lozenge respectively. Table 11.4.32 summarises these data and more detailed information is presented in Table 14.2.83.

Table 11.4.32 Consumer questionnaire: At two hours post-dose, how moisturising/lubricating is this throat lozenge – Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	73	74
Mean±sd	4.00±2.33	4.52±2.48	2.99±2.44
LS mean[a]	3.49	4.04	2.47
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	1.02	0.25,1.79	0.01 **
Strepsils Cool throat lozenge vs Placebo	1.57	0.79,2.36	0.0001 ***

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.83
Measured on a 11-point scale where 0 = Not moisturising/lubricating at all, 10 = Very moisturising/lubricating

Both Strepsils throat lozenges gave statistically significantly higher scores than the placebo throat lozenge (p≤0.0002 in both cases) with respect to the question asked at two hours concerning "how comforting did you find this lozenge" recorded on an 11-point scale where 0 = Not comforting and 10 = Very comforting. The LS mean scores estimated from the ANCOVA model were 4.18, 4.98 and 2.59 for the Strepsils Warm throat lozenge, Strepsils Cool throat lozenge and placebo throat lozenge respectively. Table 11.4.33 summarises these data and more detailed information is presented in Table 14.2.84.

Table 11.4.33 Consumer questionnaire: At two hours post-dose, how comforting did you find this throat lozenge – Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	73	74
Mean±sd	4.64±2.72	5.40±2.56	3.05±2.56
LS mean[a]	4.18	4.98	2.59
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	1.59	0.75,2.43	0.0002 ***
Strepsils Cool throat lozenge vs Placebo	2.39	1.54,3.24	<0.0001 ***

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness

b A positive difference favours the first treatment against second treatment

*** Comparison statistically significant at 0.1% level

Source: Tables 14.2.84

Measured on a 11-point scale where 0 = Not comforting, 10 = Very comforting

Both Strepsils throat lozenges gave statistically significantly higher scores than the placebo throat lozenge (p<0.0001 in both cases) with respect to the question asked at two hours concerning "how deep down within the throat was the relief felt" recorded on an 11-point scale where 0 = Not at all deep in the throat and 10 = Very deep in the throat. The LS mean scores estimated from the ANCOVA model were 3.62, 4.57 and 1.87 for the Strepsils Warm throat lozenge, Strepsils Cool throat lozenge and placebo throat lozenge respectively. Table 11.4.34 summarises these data and more detailed information is presented in Table 14.2.85.

Table 11.4.34 Consumer questionnaire: At two hours post-dose, how deep down within the throat was the relief felt – Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	73	74
Mean±sd	3.99±2.71	4.90±2.51	2.24±2.46
LS mean[a]	3.62	4.57	1.87
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	1.75	0.93,2.58	<0.0001 ***
Strepsils Cool throat lozenge vs Placebo	2.70	1.86,3.54	<0.0001 ***

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.85

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

Both Strepsils throat lozenges gave statistically significantly higher scores than the placebo throat lozenge ($p<0.0001$ in both cases) with respect to the question asked at two hours concerning "how deep down within the throat do you think this lozenge coats the throat" recorded on an 11-point scale where 0 = Not at all deep in the throat and 10 = Very deep in the throat. The LS mean scores estimated from the ANCOVA model were 3.31, 3.57 and 1.71 for the Strepsils Warm throat lozenge, Strepsils Cool throat lozenge and placebo throat lozenge respectively. Table 11.4.35 summarises these data and more detailed information is presented in Table 14.2.86.

Table 11.4.35 Consumer questionnaire: At two hours post-dose, how deep down within the throat do you think this throat lozenge coats the throat – Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	73	74
Mean±sd	3.70±2.61	3.93±2.51	2.11±2.24
LS mean[a]	3.31	3.57	1.71
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	1.60	0.81,2.39	<0.0001 ***
Strepsils Cool throat lozenge vs Placebo	1.86	1.05,2.66	<0.0001 ***

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.86

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

Both Strepsils throat lozenges gave statistically significantly higher scores than the placebo throat lozenge (p≤0.0001 in both cases) with respect to the question asked at two hours concerning "how deep down the throat was the comforting felt" recorded on an 11-point scale where 0 = Not at all deep in the throat and 10 = Very deep in the throat. The LS mean scores estimated from the ANCOVA model were 3.54, 4.12 and 1.89 for the Strepsils Warm throat lozenge, Strepsils Cool throat lozenge and placebo throat lozenge respectively. Table 11.4.36 summarises these data and more detailed information is presented in Table 14.2.87.

Table 11.4.36 Consumer questionnaire: At two hours post-dose, how deep down within the throat was the comforting felt – Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	73	74
Mean±sd	3.94±2.74	4.48±2.37	2.28±2.57
LS mean[a]	3.54	4.12	1.89
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge vs Placebo	1.65	0.83,2.48	0.0001 ***
Strepsils Cool throat lozenge vs Placebo	2.23	1.40,3.07	<0.0001 ***

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.87
Measured on a 11-point scale where 0 = Not at all deep in the throat, 10 = Very deep in the throat

The Strepsils Warm throat lozenge produced a warming sensation in the throat which lasted statistically significantly longer than that reported for the placebo throat lozenge (p<0.0001). The number of subjects who reported a warming sensation lasting beyond 30 minutes was 19 (25%) for the Strepsils Warm throat lozenge, nine (12%) for the Strepsils Cool throat lozenge and six (8%) for the placebo throat lozenge. The comparison between the Strepsils Cool throat lozenge and placebo was not statistically significant (p=0.09). Table 11.4.37 summarises these data.

Table 11.4.37 Consumer questionnaire: At two hours post-dose, how long did the warming sensation of the throat lozenge last in your throat - Full analysis set

	Strepsils Warming throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	74	74
Did not feel any warming sensation	5 (6.5%)	31 (41.9%)	34 (45.9%)
Less than 5 minutes	4 (5.2%)	8 (10.8%)	14 (18.9%)
Between 5 and 10 minutes	21 (27.3%)	6 (8.1%)	12 (16.2%)
Between 10 and 20 minutes	18 (23.4%)	13 (17.6%)	1 (1.4%)
Between 20 and 30 minutes	10 (13.0%)	7 (9.5%)	7 (9.5%)
Between 30 and 60 minutes	16 (20.8%)	7 (9.5%)	4 (5.4%)
Between 60 and 90 minutes	2 (2.6%)	1 (1.4%)	1 (1.4%)
Between 90 and 120 minutes	1 (1.3%)	1 (1.4%)	1 (1.4%)
Parameter estimates	Odds ratio[b]	95% CI	p
Strepsils Warm throat lozenge vs. Placebo	0.16	0.09,0.30	<0.0001 ***
Strepsils Cool throat lozenge vs. Placebo	0.60	0.33,1.09	0.09

a Estimated from proportional odds model with factors for treatment and centre and a covariate for baseline throat soreness
b A value < 1 indicates the first treatment had a longer duration of effect
*** Comparison statistically significant at 0.1% level
Source: Table 14.2.88

The Strepsils Cool throat lozenge produced a cooling sensation in the throat which lasted statistically significantly longer than that reported for the placebo throat lozenge (p<0.0001). The number of subjects who reported a cooling sensation lasting beyond 30 minutes was six (8%) for the Strepsils Warm throat lozenge, 17 (23%) for the Strepsils Cool throat lozenge and eight (11%) for the placebo throat lozenge. The comparison between the Strepsils Warm throat lozenge and the placebo throat lozenge was not statistically significant (p=0.44). Table 11.4.38 summarises these data.

Table 11.4.38 Consumer questionnaire: At two hours post-dose, how long did the cooling sensation of the throat lozenge last in your throat - Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
N	77	73	74
Did not feel any cooling sensation	48 (62.3%)	11 (15.1%)	52 (70.3%)
Less than 5 minutes	11 (14.3%)	7 (9.6%)	4 (5.4%)
Between 5 and 10 minutes	4 (5.2%)	6 (8.2%)	4 (5.4%)
Between 10 and 20 minutes	5 (6.5%)	12 (16.4%)	5 (6.8%)
Between 20 and 30 minutes	3 (3.9%)	20 (27.4%)	1 (1.4%)
Between 30 and 60 minutes	5 (6.5%)	12 (16.4%)	6 (8.1%)
Between 60 and 90 minutes	1 (1.3%)	3 (4.1%)	2 (2.7%)
Between 90 and 120 minutes	0 (0.0%)	2 (2.7%)	0 (0.0%)
Parameter estimates	Odds ratio[b]	95% CI	p
Strepsils Warm throat lozenge vs. Placebo	0.77	0.40,1.49	0.44
Strepsils Cool throat lozenge vs. Placebo	0.11	0.06,0.21	<0.0001 ***

[a] Estimated from proportional odds model with factors for treatment and centre and a covariate for baseline throat soreness
[b] A value < 1 indicates the first treatment had a longer duration of effect
*** Comparison statistically significant at 0.1% level
Source: Table 14.2.89

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 some evidence of non-normality for the analyses involving the primary endpoint for the full analysis set. Subject number 213 in the placebo group had a baseline sore throat severity of 2 with the next lowest score of 5 at 15 minutes post-dose, and, as a consequence, the value for the AUC for the change from baseline in throat soreness was 5.525 which was a gross outlier; the next highest value being 1.992. Given the very clear superiority of the two Strepsils formulations over placebo, it was decided to appeal to the robustness of the F-test rather than perform additional non-parametric analyses. Nineteen subjects with baseline scores of less than 6 were excluded from the associated per-protocol analysis for this variable. In this analysis, although there was still some evidence of non-normality, there were no gross outliers.

There was also some evidence of non-normality for several of the secondary endpoints. However, given that the degree of non-normality was minor it was decided again that these 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, centre and a covariate for baseline throat soreness and the baseline score for the relevant variable of interest if appropriate.

For the time to moderate pain relief, differences between the treatment groups were assessed using a Cox regression analysis with factors for treatment and centre and a covariate for baseline throat soreness.

In general, the terms for baseline scores were statistically significant in the analyses performed. Patients with more severe symptoms had a greater scope for improvement and therefore mean reductions for these subjects tended to be greater. The term for centre was not found to be statistically significant in any of the analyses.

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 UNK or NA it was replaced by the first day of the month or January respectively, provided this does not contradict any other dates recorded. For missing adverse events and medications dates during the trial, the worst-case date was used (e.g. the end of the month for a stop date, the randomisation date for start of AE).

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

Because there was no missing data, 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-centre Studies

The study utilised three referral centres where patients were directed to CPS Research for their study assessments. If it was more convenient for the patient to be seen at the referral centre then the study assessments were performed there instead of at CPS Research. The referral centres used were Rutherglen, Waverley and Chapelhall GP practices.

The statistical analysis models included centre as a factor. Because the Waverley and Chapelhall centres recruited only seven and three subjects respectively, these two centres will be combined as a single centre within the formal statistical analysis. There was no evidence to suggest that the results differed significantly between centres.

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 Subjects

The use of the Per Protocol (PP) 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 baseline to 2 hours) and the total sum of pain relief ratings. Twenty-two patients were excluded from the PP 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

Exploratory subgroup analyses of the primary efficacy endpoint were performed for several key baseline characteristics. For each characteristic, the main effect and treatment-by-subgroup interaction terms were added to the model used in the primary endpoint analysis. Key variables of interest were centre (Table 14.2.90), baseline throat soreness severity (≤median, >median; Table 14.2.91), age at study entry (≤median, >median; Table 14.2.92), gender (Table 14.2.93), total score from tonsillo-pharyngitis assessment at baseline (≤median, >median; Table 14.2.94) and baseline VAS for difficulty in swallowing (≤median, >median; Table 14.2.95).

The analysis to explore the gender effect revealed a statistically significant treatment-by-gender group interaction at the 10% level (p=0.09). For male subjects the most effective treatment in reducing sore throat severity was the Strepsils Warm throat lozenge whereas for females, the most effective treatment was the Strepsils Cool throat lozenge. For male subjects the difference in LS means between the two Strepsils throat lozenges was -0.36 (95% confidence interval -1.11 to 0.38) while for female subjects the difference was 0.71 (95% confidence interval 0.10 to 1.32). For females the difference between active treatments was statistically significant (p=0.02). Furthermore, for male subjects both Strepsils throat lozenge formulations performed statistically significantly better than the placebo throat lozenge (p<0.05), whereas for female subjects, only the Strepsils Cool throat lozenge was statistically significant better at reducing throat soreness compared to the placebo throat lozenge

(p<0.05). Further details are presented in Table 11.4.39. There are no obvious reasons for this qualitative interaction and it is thought that this is spurious outcome.

Table 11.4.39 AUC from baseline to two hours post dose for the change from baseline in throat soreness by gender - Full analysis set

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
MALES			
N	32	29	31
Mean±sd	-2.11±1.58	-1.73±0.98	-1.06±1.24
LS mean[a]	-2.11	-1.75	-0.98
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warming throat lozenge – Placebo	-1.13	-1.86,-0.40	0.003 **
Strepsils Cooling throat lozenge – Placebo	-0.76	-1.51,-0.01	0.047 *
FEMALES			
N	45	45	43
Mean±sd	-1.63±1.43	-2.29±1.69	-0.96±1.85
LS mean[a]	-1.57	-2.29	-1.01
Parameter estimates	LS mean[b]	95% CI	p
Strepsils Warm throat lozenge – Placebo	-0.56	-1.18,0.05	0.07
Strepsils Cool throat lozenge – Placebo	-1.28	-1.89,-0.66	<0.0001 ***

a Estimated from ANCOVA model with factors for treatment, centre, gender and treatment-by-gender interaction and a covariate for baseline throat soreness
b A negative difference favours the first treatment against second treatment
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.93

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

None of the other exploratory subgroup analyses of the primary efficacy endpoint revealed treatment-by-subgroup interactions which were statistically significant at the 10% level.

Exploratory analyses of two of the secondary efficacy endpoints, the assessment of cooling relief at both the first moment of swallowing and two hours post-dose were also performed. (Details of the analysis of these parameters for the Full Analysis set are given in Table 14.2.58 and further summarised in Table 11.4.15). Table 11.4.40 summarises the incidence of cooling relief at the first moment of swallowing and two hours post-dose for the subgroup of subjects who reported a burning sore throat at the pre-dose assessment. At both time points statistically significantly more cooling relief (p<0.0001 in both cases) was reported for subjects who received the Strepsils Cool throat lozenge compared to placebo. The comparison between the Strepsils Warm throat lozenge and placebo was not significant at either assessment. These results are qualitatively identical to those for the Full Analysis set. Further details are given in Table 14.2.96.

Table 11.4.40 Did the throat lozenge provide cooling relief at the first moment you swallowed it and at two hours post-dose – Subjects suffering from burning sore throat at the pre-dose assessment

	Strepsils Warm throat lozenge	Strepsils Cool throat lozenge	Placebo throat lozenge
AT THE FIRST MOMENT OF SWALLOWING			
N	37	44	37
Number (%) reporting	4 (10.8%)	30 (68.2%)	5 (13.5%)
Parameter estimates	Odds ratio[b]	95% CI	P
Strepsils Warm throat lozenge vs. Placebo	0.80	0.19,3.29	0.76
Strepsils Cool throat lozenge vs. Placebo	14.83	4.64,47.38	<0.0001 ***
TWO HOURS POST-DOSE			
N	37	44	37
Number (%) reporting	3 (8.1%)	34 (77.3%)	4 (10.8%)
Parameter estimates	Odds ratio[b]	95% CI	P
Strepsils Warm throat lozenge vs. Placebo	0.78	0.16,3.82	0.76
Strepsils Cool throat lozenge vs. Placebo	32.45	8.80,119.6	<0.0001 ***

[a] Estimated from a logistic regression model with factors for treatment and centre and a covariate for baseline throat soreness
[b] A value > 1 indicates the first treatment is favoured over the second treatment
*** Comparison statistically significant at 0.1% level
Source: Tables 14.2.96

11.4.3 Tabulation of Individual Response Data

In addition to tables giving group data for efficacy variables, relevant individual subject data are presented in by-subject tabular listings in Appendix 16.2.

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-subject Displays

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

11.4.7 Efficacy Conclusions

The superiority of Strepsils Cool throat lozenges and Strepsils Warm throat lozenges over the placebo throat lozenge was apparent with highly statistically significant differences for the vast majority of efficacy variables including all variables related to sore throat relief, throat soreness, difficulty in swallowing, throat numbness and overall treatment rating. The results were robust with identical conclusions drawn from the equivalent per-protocol analyses (where performed).

For the primary efficacy endpoint, the area under the change from baseline curve (AUC) in severity of throat soreness from 0 to 2 hours (using the 11-point Throat Soreness Scale), LS mean reductions of –2.06, –1.78 and -0.98 were obtained for the Strepsils Cool throat lozenge, Strepsils Warm throat lozenge and placebo throat lozenge respectively. The Strepsils Cool throat lozenge and Strepsils Warm throat lozenge produced a 29% and 25% mean change from baseline respectively in severity of throat soreness at 2 hours compared to 10% for the placebo throat lozenge.

Statistically significant pain relief was evident by 1 minute for Strepsils Cool throat lozenges and by 5 minutes for Strepsils Warm throat lozenges and lasted for at least 2 hours with both. Results for throat soreness, pain relief, difficulty in swallowing all implied that peak effect was achieved at 15 minutes for the Strepsils Cool throat lozenge. For the Strepsils Warm Throat lozenge peak pain relief effect was seen at 15 minutes while peak throat soreness and difficulty swallowing effects were achieved at 30 minutes. The duration of effect for all efficacy parameters for both throat lozenges was at least 2 hours with the exception of difficulty swallowing for the Strepsils Warm throat lozenge. Throat numbness was evident by 1 minute for both Strepsils throat lozenges with peak effect seen at 10 minutes for the Strepsils Cool throat lozenge and 15 minutes for the Strepsils Warm throat lozenge. The throat numbness lasted 2 hours for the Strepsils Cool throat lozenge and 45 minutes for the Strepsils Warm throat lozenge.

The pain relief element of the consumer questionnaire completed after the first dose supported the findings of the subjective rating scales. At one minute post dose subjects treated with Strepsils Cool throat lozenge / Strepsils Warm throat lozenge perceived greater cooling relief / warming relief (as appropriate) compared to the placebo throat lozenge group. These differences were statistically significant for both

Strepsils throat lozenges (p<0.0001 in each case). At one minute post dose the incidence of soreness, burning and soothing relief in the Strepsils Cool throat lozenge group was statistically significantly greater than that with the placebo throat lozenge and the incidence of general pain relief in both active treatment groups at 2 hours was statistically significantly higher than that for the placebo throat lozenge group.

For the functional element of the consumer questionnaire statistically significant differences in favour of both Strepsils throat lozenges compared with the placebo throat lozenge were obtained for the area most impaired at baseline; swallowing (p=0.018 Strepsils Warm throat lozenges and p=0.011 Strepsils Cool throat lozenge). Furthermore patients began to feel more like their best at 2 hours for both Strepsils throat lozenges.

12 SAFETY EVALUATION

All subjects 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 225 randomised patients received one dose of study medication. Seventy seven subjects received a single Strepsils Warm throat lozenge, 74 subjects received a Strepsils Cool throat lozenge and 74 subjects received a placebo throat lozenge.

12.2 Adverse Events (AEs)

All treatment emergent adverse events for each subject are listed in Appendix 16.2, Listings 16.2.7.1 and 16.2.7.2, giving both preferred terms according to MedDRA (Version 12.0) 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 subjects reported a total of 23 treatment emergent adverse events. The largest numbers of events were reported by subjects in the placebo throat lozenge group with ten (14%) subjects reporting 11 treatment emergent events, while four (5%) subjects in the Strepsils Warm throat lozenge group reported a total of eight events and four (5%) subjects in the Strepsils Cool throat lozenge group reported one event each. The majority of events were of mild severity (20 events (87%)), and none were considered to be definitely, probably and 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 eight reports (three in each of the Strepsils Warm throat lozenge and placebo throat lozenge groups and two in the Strepsils Cool throat lozenge group) and respiratory, thoracic and mediastinal disorders with six reports (three in the placebo throat lozenge group, two in the Strepsils Cool throat lozenge group and one in the Strepsils Warm throat lozenge group).

Table 14.3.4 reports the number of subjects reporting each preferred term. The most common treatment emergent adverse event reported was headache with seven reports during the study involving seven subjects; this involved three (4%) subjects in the placebo throat lozenge group and two subjects in each of the Strepsils throat lozenge groups.

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. No adverse events were considered to be definitely, probably and possibly related to the study medication or as severe.

More details about the severity of events and the relationships of treatment emergent adverse events to study medication are given in Table 12.2.2 below.

Table 12.2.2 Severity and relationship of treatment emergent adverse events to therapy

	Strepsils Warm throat lozenge (n=77)		Strepsils Cool throat lozenge (n=74)		Placebo throat lozenge (n=74)	
	Number of subjects reporting	Number of reports (% of total)	Number of subjects reporting	Number of reports (% of total)	Number of subjects reporting	Number of reports (% of total)
Total	4 (5%)	8	4 (5%)	4	10 (14%)	11
Severity:						
Mild	4 (5%)	6 (75%)	4 (5%)	4 (100%)	9 (12%)	10 (91%)
Moderate	1 (1%)	2 (25%)	-	-	1 (1%)	1(9%)
Severe	-	-	-	-	-	-
Relationship:						
Definite	-	-	-	-	-	-
Probable	-	-	-	-	-	-
Possible	-	-	-	-	-	-
Unlikely	3 (4%)	5 (63%)	3 (4%)	3 (75%)	7 (9%)	8 (73%)
None	3 (4%)	3 (37%)	1 (1%)	1 (25%)	3 (4%)	3 (27%)

Source: Appendix 16.2. Listings 16.2.7.1 and 16.2.7.2

Two events were reported during follow-up (i.e. more than 24 hours after dosing); 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 were no statistically significant pairwise treatment differences between the treatment groups in the proportion of subjects reporting treatment emergent adverse events. For the Strepsils Warm throat lozenge group, four (5%) subjects reported eight adverse events. For the Strepsils Cool throat lozenge group, four (5%) subjects reported four adverse events. Within the placebo throat lozenge group, 10 (14%) subjects reported 11 events.

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

No serious adverse events or other significant adverse events were reported.

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

No other safety evaluations were performed in this study.

12.6 Safety Conclusions

There were no safety issues within this study.

There were no significant differences between the treatment groups in relation to the proportion of patients reporting AEs. There were no SAEs. The majority of AEs were mild with no treatment emergent events classified as severe. Most AEs were events related to the patient's upper respiratory tract infection such as headache, cough and congestion. By far the most common treatment emergent adverse event reported was headache with 7 (3%) patients reporting 7 headaches across the treatment groups all classified as unlikely or not related to treatment.

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

The primary objective of this study was to determine the analgesic properties of Strepsils Cool and Strepsils Warm throat lozenges in patients with sore throat due to URTI. The superiority of both Strepsils throat lozenges over the placebo throat lozenge was clearly apparent with highly statistically significant differences for all the analgesic variables related to sore throat relief, throat soreness, throat numbness

and difficulty in swallowing. The results were robust with qualitatively identical conclusions drawn from the equivalent per-protocol analyses (where performed).

The variability observed for the primary efficacy endpoint in this study was 1.47 (the root mean square error from the ANCOVA model of the full analysis set), which was somewhat higher than the value observed in the previous study (1.09) and used in the sample size assessment for the current study. However the analysis of the area under the change from baseline curve (AUC) in severity of throat soreness from 0 to 2 hours (using the 11-point Throat Soreness Scale) in the current study revealed LS mean reductions from baseline of –2.06 , –1.78 and -0.98 for Strepsils Cool throat lozenge, Strepsils Warm throat lozenge and placebo throat lozenge respectively, and LS mean differences of 1.08 (95%CI -1.56, -0.60) for the comparison of Strepsils Cool throat lozenge and placebo throat lozenge and 0.80 (95%CI -1.27, -0.33) for the comparison of Strepsils Warm throat lozenge and placebo throat lozenge. These active-placebo differences were also somewhat larger than those observed previously (0.77) and used as a guide in the sample size assessment. The study was therefore adequately powered to meet its objectives.

Other analgesic studies have concluded that a reduction of 1 - 2 points on an 11 point ordinal scale represented clinically important differences[16, 17, 18]. The magnitude of the changes observed in the present study both in terms of changes from baseline and between each of the Strepsils throat lozenges and the placebo throat lozenge are therefore clinically meaningful.

Throat soreness, pain relief, difficulty in swallowing and throat numbness single dose data indicated that effects are evident from between 1 minute and 5 minutes for the Strepsils Cool and Strepsils Warm throat lozenge respectively. These early analgesic effects are supported by the consumer questionnaire. At one minute post dose both the Strepsils Cool throat lozenge and Strepsils Warm throat lozenges provided warming/cooling relief compared to the placebo throat lozenge this difference was highly significant for both Strepsils throat lozenges ($p<0.0001$). At one minute post dose the Strepsils Cool throat lozenge provided soreness, burning and soothing relief ($p<0.01$) and general pain relief was still being provided by both throat lozenges at 2 hours ($p<0.01$). At 2 hours post dose the relief experienced by the patients taking the Strepsils throat lozenges was felt significantly deeper in the throat than the placebo throat lozenge ($p<0.0001$).

The single dose data implied that peak effect was achieved by 15 and 30 minutes for the Strepsils Cool and Strepsils Warm throat lozenge respectively after initial dosing and lasted for up to 2 hours. This is reassuring as it indicates that relief provided by both Strepsils throat lozenges is not confined to the time the throat lozenge remains in the mouth and relief is felt long after the throat lozenge is gone.

In addition the consumer questionnaire indicated that at two hours post dose patients taking both Strepsils throat lozenges were happier in relation to their throat and began to feel more like their best overall, and over 50% of patients felt better than before they took the throat lozenge. The sensorial experience of a cooling sensation

was clearly evident with over 60% of patients feeling a cooling sensation within 5 seconds from the Strepsils Cool throat lozenge. Similarly the Strepsils Warm throat lozenge provided a warming sensation that over 60% of patients felt within 30 seconds. Both throat lozenges were significantly superior to the placebo throat lozenge ($p<0.001$) in terms of their perceived ability to sooth, coat and provide comfort to the throat.

Not unsurprisingly for patients with a sore throat the two functional areas which were considered to be most impaired at baseline were swallowing and talking. What was interesting to note was the analgesic benefit reported by the patients translated into a functional benefit, with statistically significant differences in favour of the Strepsils Warm throat lozenge seen for both talking and swallowing.

There were no safety issues highlighted by this study. There were no significant differences between the treatment groups in relation to the proportion of patients reporting AEs. There were no SAEs. The majority of AEs were mild with no treatment emergent events classified as severe. Most AEs were events related to the patient's upper respiratory tract infection such as headache, cough and congestion. By far the most common treatment emergent adverse event reported was headache with 7 (3%) patients reporting 7 headaches across the treatment groups all classified as unlikely or not related to treatment.

13.2 Conclusion

Strepsils Cool throat lozenges and Strepsils Warm throat lozenges provide fast, safe and effective relief for sore throats due to upper respiratory tract infections. Following a single dose, relief is evident from 1 minute post dose and lasts for at least 2 hours with maximal effects from 15 minutes post dose. Patients can feel relief as soon as they swallow and feel better at 2 hours.

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

Table Number	Table Title
14.1.1	Details of withdrawal – Safety set (1 page)
14.1.2	Demographics – Full analysis set (5 pages)
14.1.3	Relevant previous medical history – Full analysis set (1 page)
14.1.4	Relevant ongoing medical history – Full analysis set (1 page)
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15 REFERENCE LIST

1) The Boots Company PLC 1989. Research Report No M88082.

2) Boots Healthcare International 1996. Research Report No BH5013R

3) Reckitt Benckiser 2008. Research Report Number TH0705.

4) Gaspar L, Turi J, Toth-Bagi Z, Suri C and Vago P. Possibilities of the administration of Benzyl-Alcohol and the Amyl-m-Cresol (Strepsils) in the Oral Cavity. Dentist Review 91. 1998; 143-150.

5) Gaspar L, Szmryka A, Turi J, Toth-Bagi Z, Suri C, Vago P, Sefer A and Chadi AH. Clinical Experiences with Benzyl-Alcohol and Amyl-m-Cresol in the application of oral antiseptic tablets (Strepsils) in stomatological diseases. Dentist Journal 93. 2000; 83-90.

6) Schachtel BP, Cleves G S, Konerman JP, Brown AT and Markham AO. A placebo-controlled model to assay the onset of action of non-prescription-strength analgesic drugs. Clin Pharmacol Ther 1994; 55: 464-70.

7) Schachtel BP, Fillingham KM, Beiter DJ, Lane AC and Schwartz LA. Subjective and Objective Features of Sore Throat. Arch Inter Med 1984; 144: 497-500.

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

9) Watson N, Nimmo WS, Christian J, Charlesworth A, Speight J and 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. International Journal of Clinical practice 2000; 54(8): 490-496.

10) Benrimoj SI, Langford JH, Christian J, Charlesworth A and 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.

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

12) Edwards C, Stillman P. (2000) Minor illness or major disease? Responding to symptoms in the pharmacy. 3rd Edition. Pharmaceutical Press, p38

13) Wade AG, Marshall LE, Simpson M, Shephard A. Bioavailability and efficacy of active throat lozenges in the relief of sore throat pain. Poster at Annual Scientific Meeting of the British Pain Society. Glasgow 24 – 27 April 2007.

14) Hartung-Brooks L. (1990) Sore Throat. On Continuing Practice, 17(1): 2–6

15) Matthews JNS, Altman DG, Campbell MJ, Royston P Analysis of serial measurements in medical research. BMJ 1990; 300: 230-235.

16) Interactive Textbook on Clinical Symptom Research. http//symptomresearch.nih.gov. Chapter 1: The Design of Clinical Trials for Treatment of Pain (Mitchell B. Max, MD, National Institute of Dental and Craniofacial Research, NIH).

17) Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimum clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. Eur J Pain 2004; 8(4): 283-291.

18) Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole M. Clinical importance of changes in chronic pain intensity measured on an 11 point numerical pain rating scale. Pain 2001; 94(2): 149-158.

19) Farrar JT, Berlin JA, Strom BL. Clinically important changes in acute pain outcome measures: a validation study. J Pain Sympt Man 2003; 25(5): 406-411

20) SAS Institute Inc. The SAS System, Version 9.1.3. Cary, NC, SAS Institute Inc. 2004.

21) S-PLUS 6.2 User's Guide, Data Analysis Division, Mathsoft, Seattle, WA, 2002.