Reckitt Benckiser

1 STUDY REPORT TITLE PAGE

EudraCT Number:	2007-004375-19
Study Number:	TH0705
Protocol Title:	A multi-centre, randomised, double-blind, parallel-group, placebo-controlled, multiple dose study of the efficacy of Strepsils Original throat lozenges in the relief of sore throat due to upper respiratory tract infection
Study Phase:	IV
Date First Patient Enrolled:	06 November 2007
Date Last Patient Completed:	19 February 2008
Report Date:	17 July 2008
Chief Investigator:	Dr Moyra Anderson BSc MB MCh BAO MRCGP, Old School Surgery, 54 Station Road, Greenisland, Carrickfergus, BT38 8TP, Northern Ireland
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

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Insight Clinical Consulting Ltd

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Reckitt Benckiser Healthcare International Ltd

Study Sponsor: Reckitt Benckiser Healthcare International Limited, Dansom Lane, Hull, England, HU8 7DS

2 SYNOPSIS

Name of Sponsor/ Company: Reckitt Benckiser Healthcare International Ltd	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority use only)**
Name of Finished Product: Strepsil Original Lozenges	**Volume:**	
Name of Active Ingredient(s): 2, 4 –dichlorobenzylalcohol, amylmetacresol,	**Page:**	

Title of Trial: A multi-centre, randomised, double-blind, parallel-group, placebo-controlled, multiple dose study of the efficacy of Strepsils Original throat lozenges in the relief of sore throat due to upper respiratory tract infection

Investigator(s): Dr M Anderson, Dr P Steele, Dr J McBride, Dr D McNally, Dr P Conn, Dr H McGoldrick, Dr N Lavin, Dr M Redmond.

Trial Centre(s): Multi-centre study in 8 Primary Care Investigational Sites in Northern Ireland.

Publication (reference): None

Studied Period: 3.5 months **Date first patient enrolled:** 06 November 2007 **Date last patient completed:** 19 February 2008	**Phase of Development:** IV

Objectives: The primary objective of this study was to determine the analgesic properties of Strepsils Original 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 Strepsils Original throat lozenges or placebo. In addition to the analgesic endpoints, a functional measure, difficulty in swallowing, was also assessed.

The secondary objective of this study was to determine additional patient/consumer benefits associated with Strepsils Original by measuring freedom from symptoms and by the responses to a consumer questionnaire.

Methodology: Patients with a sore throat due to URTI, either presented opportunistically or following response to advertisements for patients in local doctors' surgeries and community pharmacies were referred to their nearest investigative site.

Patients were screened at primary care investigative sites in Northern Ireland. Eligible patients (those that met the study inclusion criteria and not the exclusion criteria) were randomised. 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 dosed with the assigned trial medication according to their randomisation number (active or placebo lozenge). At 5, 10, 15, 30, 45, 60, 75, 90, 105, 120 minutes post first dose, at the end of Day 1, 24 hours post first dose, and at the end of Days 2 and 3 patients completed the throat soreness and difficulty in swallowing scales along with a 7 – point categorical sore throat relief scale. One question of the consumer questionnaire concerning pain relief was completed at 5 minutes with other pain relief questions completed at 120 minutes. The second part of the consumer questionnaire concerning functional impairments was completed at baseline and repeated at the end of Day 3. In addition an overall treatment rating was completed at 120 minutes post first dose and at the end of Day 3. The first two-hour assessment period was completed under supervision in a designated area within the investigative site. No food, drink or smoking was permitted during this 2-hour period.

Following completion of the two-hour assessment, patients left the investigative site with their trial medication, paracetamol (rescue medication) and patient diaries. At the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3, the patient was asked to complete the rating scales in their diary. Between one and four days after completing the study, patients returned to the investigative site with their completed diaries, unused trial medication and rescue medication. Any adverse events (AEs) and changes in concomitant medication were

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recorded in the patient's CRF and any ongoing AEs were followed-up. If the patient's sore throat resolved before Day 3, they discontinued their trial medication and the reason for discontinuation i.e. no further need for study medication, was recorded at the follow-up assessment.

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

Number of Patients:	**Planned:**	310 to complete first 2 hour assessment
	Analysed:	314 Screened, 310 Randomised
		Full Analysis 310, Per Protocol 250, Safety 310

Diagnosis and main Criteria for Inclusion: Male and female patients aged between 18 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 5 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 including the rescue medication.

Test Product: Strepsils Original Throat Lozenges containing 1.2 mg, 2, 4 – dichlororbenzyl alcohol and 0.6 mg amylmetacresol. Batch No. BN0126986.

Each patient was provided with the first lozenge in the investigational site with instructions to suck it slowly, moving the lozenge around the mouth until dissolved and not to chew or crunch the lozenge. Following discharge patients could take one lozenge every 2 – 3 hours as required for up to 3 days.

In addition patients were supplied with 500 mg paracetamol tablets as rescue medication if needed (Panadol®, UK Product Licence No. PL00071/5074R). Batch No. BN700413.

Duration of Treatment: Up to 3 days

Reference Therapy: Shape and colour matched non-medicated sugar-based lozenge. Batch No. BN0126989

Criteria for Evaluation:

Efficacy: Efficacy was assessed by subjective rating scales. The primary efficacy variable was the mean change from baseline in severity of throat soreness (using the 11 point Throat Soreness Scale) for the Strepsils Original Group versus the placebo group at two hours post first dose.

There were a number of secondary endpoints including AUCs from baseline to two hours post first dose for the change from baseline in throat soreness and difficulty in swallowing, and for sore throat relief. Sore throat relief and changes from baseline in throat soreness and difficulty in swallowing at the end of Day 1, 24 hours post first dose and at the end of Days 2 and 3 were also assessed. Onset of analgesia defined as time to first reporting moderated pain relief, time taken to be symptom free, overall treatment rating, overall lozenge and rescue medication consumption were also included as secondary efficacy measures.

Safety: Safety and tolerability were assessed in terms of the overall proportion of patients with

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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 two 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 tested 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 nonparametric approach could be used instead.

Centres recruiting less than eight patients were pooled for any formal statistical analysis model that involved centre as a factor.

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

The primary efficacy variable and key secondary efficacy variables were analysed by an 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. Differences between treatment groups in the proportion of patients reporting treatment emergent adverse events were compared via 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 11.0 of MedDRA.

SUMMARY AND CONCLUSIONS

EFFICACY RESULTS: In general the treatment groups were well balanced for the demographic variables. Overall patient ages ranged from 18 to 76 years with a mean age of 36.1 years. The majority of patients, 303 (98%) were Caucasian and there were more females than males. The superiority of Strepsils Original throat lozenges over placebo was clearly apparent with highly statistically significant differences for all the analgesic variables related to sore throat relief, throat soreness and difficulty in swallowing. The results were robust with identical conclusions drawn from the equivalent per-protocol analyses. Results for the primary efficacy variable are summarised in Table 1.

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Table 1 Primary Efficacy Variable – Change from baseline in severity of throat soreness at two hours post first dose

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

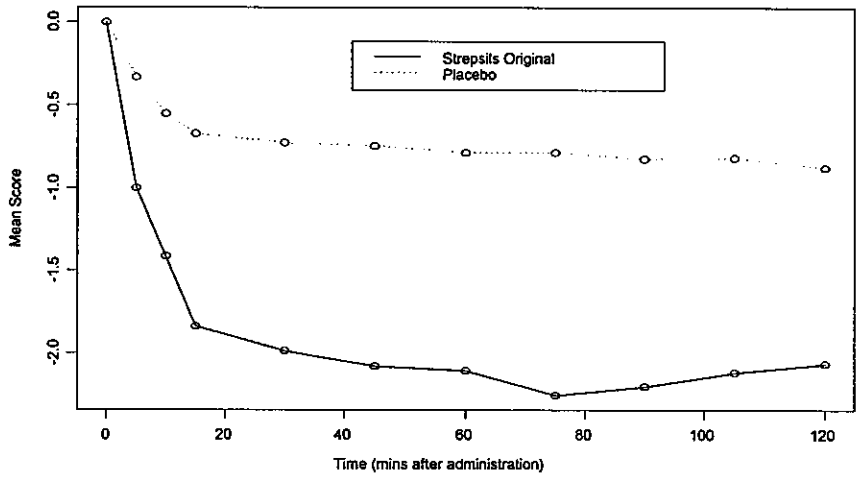
	Full Analysis Set		Per Protocol Set	
	Strepsils	Placebo	Strepsils	Placebo
N	153	154	127	123
Mean (sd) Baseline Throat Soreness Score	7.13 (1.05)	7.17 (1.15)	7.03 (1.05)	6.98 (1.12)
Mean (sd) 2 hours Throat Soreness Score	5.07 (2.11)	6.29 (1.83)	5.27 (2.02)	6.23 (1.58)
Mean (sd) Change from BSL	-2.07 (2.02)	-0.88 (1.50)	-1.76 (1.78)	-0.76 (1.27)
LS Mean Change[a]	-2.06	-0.85	-1.87	-0.86
Difference between LS means[b]	-1.21		-1.01	
SE	0.20		0.19	
95% CI	-1.59, -0.82		-1.38, -0.63	
p-value for treatment	<0.0001		<0.0001	

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

[b] Strepsils Original minus placebo. A negative difference favours Strepsils Original

Figure 1: Mean change from baseline in throat soreness from 5 to 120 minutes post first dose – Full Analysis Set

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



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Key secondary efficacy variable data are summarised in Table 2.

Table 2 Summary of Key Secondary Efficacy Variables – Full Analysis Set

Variable	Strepsils Original n	Strepsils Original LS mean[a]	Placebo n	Placebo LS mean[a]	Diff.[b]	95% CI	p
Throat Soreness (measured on a 11 point scale where 0 = not sore, 10 = very sore)							
AUC from baseline to 2 hours for change from baseline in throat soreness	154	-1.94	154	-0.69	-1.26	-1.54, -0.97	<0.0001
Change from baseline in throat soreness at end of Day 3	148	-4.02	150	-2.15	-1.87	-2.40, -1.34	<0.0001
Sore Throat Relief (measured on 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)							
AUC from baseline to 2 hours for sore throat relief	154	1.99	154	0.72	1.28	1.04, 1.52	<0.0001
Sore throat relief at 2 hours	153	1.93	154	0.84	1.09	0.78, 1.40	<0.0001
Sore throat relief at end of Day 3	148	3.37	152	1.79	1.58	1.15, 2.01	<0.0001
Difficulty in Swallowing (measure on 100 mm VAS where 0mm = not difficult, 100mm = very difficult)							
AUC from baseline to 2 hours for change from baseline in difficulty in swallowing	151	-14.4	152	-3.8	-10.6	-13.4, -7.8	<0.0001
Change from baseline in difficulty in swallowing at 2 hours	150	-15.0	149	-3.8	-11.1	-15.0, -7.3	<0.0001
Change from baseline in difficulty in swallowing at end of Day 3	142	-33.1	147	-15.9	-17.2	-22.4, -12.0	<0.0001
Overall Treatment Rating (measured on 11 point scale where 0 = poor, 10 = excellent)							
Overall Treatment Rating – 2 hours	153	5.49	153	2.75	2.74	2.15, 3.32	<0.0001
Overall Treatment Rating – end of Day 3	148	5.72	151	2.89	2.83	2.23, 3.43	<0.0001

[a] Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness For variables related to difficulty in swallowing there was an additional covariate for baseline score for difficulty in swallowing

[b] Strepsils Original minus placebo, all differences favour Strepsils Original

Pain relief was evident by 5 minutes and lasted for at least 2 hours with the Strepsils Original Lozenges. Throat soreness, pain relief and difficulty in swallowing all implied that peak effect was 75 minutes after initial dosing.

The pain relief element of the consumer questionnaire completed after the first dose supported the findings of the subjective rating scales: at five minutes post-dose, 101/154 (66%) patients

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this difference was highly statistically significant ($p<0.0001$). There were differences highly in favour of Strepsils Original for the patients' opinion on pain relief, what the relief felt like (e.g. soothing, coating, site of action of the lozenge within the mouth, how fast acting the product was, duration of action, how satisfied the patient was with the pain relief attained).

Changes in sore throat severity, difficulty in swallowing and sore throat relief were also highly statistically significant in favour of Strepsils Original at the end of day 1, 24 hours post initial dose, at the end of day 2 and the end of day 3. Differences between Strepsils Original and placebo gradually increased over the three day study period for all parameters measured.

For the functional element of the consumer questionnaire statistically significant differences in favour of Strepsils Original were obtained for the three areas most impaired at baseline; swallowing ($p=0.0007$), eating a meal ($p=0.005$), and talking ($p=0.0015$).

The number of patients achieving freedom of symptoms (defined as the patient reporting complete sore throat relief and no throat soreness) were low. However the difference between treatment groups was highly statistically significant with more patients in the Strepsils Original group (13%) being symptom free compared to placebo (2%) by the end of Day 3.

There was a statistically significant treatment-by-centre interaction ($p<0.0001$) for the primary endpoint, the mean change from baseline in severity of throat soreness. Investigation revealed that the treatment effect ranged from substantially in favour of Strepsils Original in two large centres, through marginally in favour of Strepsils Original in the two other large centres, to marginally in favour of placebo at the two smallest centres. This pattern of variation in treatment effect was not considered to critically affect the overall interpretation of the results.

SAFETY RESULTS:

There were no safety issues within this study. There was no difference between the treatment groups in relation to the proportion of patients reporting adverse events. There were no treatment emergent serious adverse events (SAEs). The majority of adverse events were mild with only five treatment emergent events classified as severe. Most adverse events were events related to the patient's upper respiratory tract infection such as headache, cough, chills, and pyrexia. By far the most common adverse event reported was headache with 13 (8%) patients reporting 17 headaches in the Strepsils Original group and 9 (6%) reporting 9 events in the placebo group.

Five of the six events considered to be possibly or probably related to the lozenges were related to effects in the mouth; mouth ulceration and tongue disorders (wounds on tongue). Two patients in the Strepsils Original group and one patient in the placebo group reported mouth ulcers, possibly or probably related to the lozenges. The reports of tongue disorders (wounds on tongue) were reported in the placebo group.

CONCLUSION:

Strepsils Original Throat Lozenges provide fast, safe and effective relief for sore throats due to upper respiratory tract infections. Following a single dose, relief is evident at 5 minutes post dose and lasts for at least 2 hours with maximal effects at 75 minutes post dose. Patients can feel the lozenge working as soon as they swallow and feel better at 2 hours. Analgesic effects continue over the 3 day study period with additional functional benefits in swallowing, eating and talking evident at 3 days.

Date of the report: 17 July 2008

3 TABLE OF CONTENTS

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

3.2 List of Appendices

16.1.10 Documentation of inter-laboratory standardisation methods and Quality assurance procedures if used. Laboratories were not used for analyses in this study, so this appendix is not present

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

16.1.12 Important publications referenced in the report. None of the publications referenced in the report are appended, so this appendix is not present

16.2 PATIENT DATA LISTINGS

16.2.1 Discontinued Patients

16.2.2 Protocol Deviations

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 CRFs for deaths, other serious adverse events and withdrawals for adverse events. No subjects died. CRFs for Patients 03 – 195, 07 – 519, and 07 – 520 who withdrew from the study due to an adverse event and Patient 03 – 247 who experienced a serious adverse event are appended.

16.3.2 Other CRFs submitted – no other CRFs are appended, so this appendix is not present

16.4 INDIVIDUAL PATIENT DATA LISTINGS (US ARCHIVAL LISTINGS)

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Abbreviation in Full
AE	Adverse Event
AMC	Amylmetacresol BP
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomic Therapeutic Class
AUC	Area under the curve
BSL	Baseline
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organisation
CV	Curriculum Vitae
DCBA	2,4-Dichlorobenzyl alcohol
EC	Ethics Committee
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMSU	Investigational Medicinal Supplies Unit
IRB	Institutional Review Board
ITT	Intention-To-Treat
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Authorities
OTC	Over-The-Counter
PP	Per Protocol
RBHI	Reckitt Benckiser Healthcare International
SAE	Serious Adverse Event
SDV	Source Data Verification
SE	Standard Error

SPID	Sum of the Pain Intensity Differences
TOTPAR	Total sum of pain relief
TPA	Tonsillopharyngitis Assessment
URTI	Upper Respiratory Tract Infection
VAS	Visual Analogue Scale
WHO	World Health Organisation

5 ETHICS

5.1 Independent Ethics Committee (IEC)

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 11 October 2007 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 Research Ethics Committee 2 of The Office for Research Ethics Committees Northern Ireland on 26 October 2007. Protocol Administrative Change 01 was sent to the IEC for information and acknowledged on 2 November 2007. The original consent form was amended to refer to the correct Participant Information Sheet on 15 November 2007, sent to the IEC for information and acknowledged on 5 December 2007.

5.2 Ethical Conduct of the Study

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

5.3 Patient Information and Consent

Copies of the representative Participant Information Sheet dated 22 October 2007 and a blank consent form version 1 dated 15 November 2007 are provided in Appendix 16.1.3. The original consent form dated 19 September 2007 was signed by 53 patients before it was noted that the consent form referred to the previous version of the Participant Information Sheet, the consent form was updated to Version 1 dated 15 November 2007, sent to the IEC for information and implemented for the rest of the participants in the study.

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 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 M Anderson and principal investigator at each site are also included in the Appendix.

The study was carried out at eight Primary Care Investigational Sites in Northern Ireland under the guidance of the Principal Investigator at each site. Some study related activities were delegated to medically qualified sub-investigators and other suitably qualified site personnel. The study was managed by personnel from the Contract Research Organisation (CRO) Medevol Ltd. Data management and the statistical analyses were performed by Nottingham Clinical Research Limited.

Strepsils Original throat lozenges and placebo lozenges were manufactured by Reckitt Benckiser Healthcare International Ltd (Nottingham, UK). The study drug supplies were packed and shipped to the Investigational Sites, Northern Ireland by the Investigational Medicinal Supplies Unit (IMSU), Reckitt Benckiser Healthcare International (RBHI). RBHI study project management and report writing were contracted out to Insight Clinical Consulting Ltd. RBHI was 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 Strepsils Original throat lozenges.

Strepsils Original throat lozenges contain the active antimicrobial ingredients amylmetacresol BP (0.6 mg) and 2,4-dichlorobenzyl alcohol (1.2 mg) (AMC/DCBA). The lozenges are indicated for the symptomatic relief of mouth and throat infections and are the leading sore throat relief brand in many markets around the world. Previous studies support the efficacy of AMC/DCBA and Strepsils lozenges[1,2,3,4] but additional work is required to develop the brand and further support the analgesic efficacy of the product.

This study examined the effect of Strepsils Original throat lozenges versus a non-medicated sugar-based placebo in patients with sore throat over a period of three days. 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 a previous study in sore throat (BH5013)[2] with Strepsils Original throat lozenges. In the previous study (BH5013) only twenty-five percent of the planned number of patients were recruited in to the study due to seasonal factors (i.e. the decrease in the incidence of sore throats at the end of winter season) and the study being single centre only. Despite the reduced numbers, the study demonstrated a statistically significant difference in favour of Strepsils Original throat lozenges compared with placebo (non-medicated sugar based lozenge) on one of the secondary endpoints, and approached statistical difference for the primary endpoint. However, due to the failure to recruit sufficient patients, the study was not adequately powered. Therefore, RBHI wished to conduct a study of similar design commencing early in the sore throat 'season' and with multiple centres to ensure that the required number of patients was recruited. The methodology utilised was based on that used in the previous study with the addition of a consumer questionnaire to provide consumer acceptability data.

8 STUDY OBJECTIVES

The primary objective of this study was to determine the analgesic properties of Strepsils Original throat lozenges in patients with sore throat due to upper respiratory tract infection (URTI). The analgesic properties were assessed by comparing throat soreness in patients treated with Strepsils Original throat lozenges or placebo. In addition to the primary endpoint, sore throat relief and a functional measure, difficulty in swallowing, were also assessed.

The secondary objective of this study was to determine additional patient/consumer benefits associated with Strepsils Original throat lozenges. These benefits were assessed by measuring freedom from symptoms and also by a consumer questionnaire. The questionnaire included opinions on pain relief, what the relief felt like e.g. soothing, site of action of the lozenge within the mouth, how fast acting the product was, duration of action, how satisfied the patient was with the pain relief attained and how their sore throat affected their daily activities.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan – Description

The study protocol and protocol administrative change 01 (dated 22 October 2007) are included as Appendix 16.1.1. The case report form (CRF) is included as Appendix 16.1.2.

This was a multi-centre, randomised, double-blind, parallel-group, placebo-controlled, multiple-dose study of the efficacy of Strepsils Original throat lozenges in the relief of sore throat due to upper respiratory tract infection (URTI).

Patients were those with a sore throat due to URTI. Patients either presented opportunistically or following response to advertisements for patients in local doctors'

surgeries and community pharmacies where they were referred to their nearest investigative site.

Patients were screened at the primary care investigative sites in Northern Ireland. Eligible patients (those that met the study inclusion and not the exclusion criteria) were randomised. Following the baseline assessments, patients were dosed with the assigned trial medication according to their randomisation number (active or placebo lozenge) and completed the two-hour assessment period under supervision in a designated area within the investigative site. No food, drink or smoking was permitted during the 2-hour assessment period.

Following completion of the two-hour assessment, patients left the investigative site with their trial medication, paracetamol (rescue medication) and their patient diaries. At the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3, the patient was asked to complete their patient diary. Between one and four days after completing the study, patients returned to the investigative site with their completed patient diaries, unused trial medication and rescue medication. Any adverse events (AEs) and changes in concomitant medication were recorded in the patients CRF and any ongoing AEs were followed-up. If the patient's sore throat resolved before Day 3, they discontinued their trial medication and the reason for discontinuation i.e. no further need for study medication, was recorded at the follow-up assessment.

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

Three hundred and ten patients (155 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 first 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[5, 6, 7]. The methodology has been previously used in a study (BH5013)[2] 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[8, 9, 10].

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 5 points was required to confirm the presence of tonsillopharyngitis and permit entry into the study.

As with the previous Strepsils Original throat lozenges study (BH5013), a non-medicated sugar-based placebo lozenge was used as a control. A 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 lozenge helps to increase saliva production[11, 12] and the mucosa remains lubricated[13]. In order to control for the contribution of the lozenge formulation on the efficacy a non-medicated sugar based lozenge was used. This placebo control was the same colour, size and shape as the Strepsils Original throat lozenge and provided the appropriate control.

Paracetamol was provided to patients to be used as rescue medication. Rescue medication was not to be used until after completion of the 2-hour post-dose assessment and therefore would not affect assessment of the primary endpoint.

9.3 Selection of Study Population

Patients were those with a sore throat due to URTI who attended their GP or community pharmacy. Patients either presented opportunistically to the investigative sites or in response to advertisements in local GP surgeries and community pharmacies. For patients that rang a surgery in response to advertising, some initial screening took place over the telephone according to a pre-determined script.

9.3.1 Inclusion Criteria

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

1) Age: ≥18 - ≤75.
2) Both male and female patients were included.
3) Primary diagnosis: Patients with sore throat of onset within the past 4 days (i.e. ≤ 4 days) due to URTI.
4) Patients who had a sore throat (≥6) on the Throat Soreness Scale at baseline.
5) Objective findings that confirmed the presence of tonsillopharyngistis (≥5 points on the expanded Tonsillopharyngitis Assessment).
6) Patients who had given written informed consent.

9.3.2 Exclusion Criteria

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

1) Any previous history of allergy or known intolerance to the study drug or the following formulation constituents, AMC/DCBA, anise oil, peppermint oil, menthol natural or menthol synthetic, tartaric acid gran 571 GDE, ponceau 4R edicol E124, carmoisine edicol E122, sugar, glucose.
2) Any previous history of allergy or known intolerance to the study rescue drug (paracetamol) or the following formulation constituents, maize starch, potassium sorbate, purified talc, stearic acid, polvidone, starch pre-gelatinised, hypromellose, triacetin, ethanol, propylene glycol, shellac, brilliant blue FCF (E133), sodium lactate, dimethylpolysiloxane.
3) Those whose sore throat had been present for more than 4 days.
4) Those who had evidence of mouth breathing.
5) Those who had evidence of severe coughing.
6) Those who had any disease that could compromise breathing e.g. bronchopneumonia.
7) Those who had taken any medicated confectionary, throat pastille, spray, or any products with demulcent properties such as boiled sweets, within the previous 2 hours.
8) Those who had used any sore throat medication containing a local anaesthetic within the past 4 hours.
9) Those who had used any analgesic, antipyretic or 'cold' medication (e.g. decongestant, antihistamine, antitussive, or throat lozenge) within the previous 8 hours.
10) Those who had used a longer acting or slow release analgesic during the previous 24 hours e.g. piroxicam.
11) Those taking antibiotics during the previous 14 days.
12) Those with any painful condition that may have distracted attention from sore throat pain e.g. mouth ulcers, etc.
13) Those with a history of severe renal impairment.
14) Those with a history of severe hepatic impairment.
15) Those taking warfarin and other coumarin.
16) Those taking carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes in the 14 days before enrolment into the study (i.e. before first dosing day).
17) Those with a history of alcohol abuse or who stated that they regularly consumed alcohol in excess of the recommended amounts (excessive alcohol: >21 units per week for females and >28 units per week for males).
18) Those who were glutathione-deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.
19) Those with any painful condition that required regular analgesic usage.
20) Those unable to refrain from smoking during their stay in the investigative site.
21) Women of childbearing potential, who 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, an intrauterine device). A woman of childbearing potential was defined as any female who was less than 2 years post-menopausal or had not undergone an

hysterectomy or surgical sterilisation, e.g. bilateral tubal ligation, bilateral ovariectomy (oophorectomy).

22) Those previously randomised into the study.
23) Those who had participated in a clinical trial in the previous 30 days. Thirty days were calculated from time of last dosing in the previous trial to the time of anticipated dosing in this trial.
24) Those unable in the opinion of the Investigator to comply fully with the study requirements, e.g. such as those who could not comprehend or correctly use the pain rating scales.

9.3.3 Removal of Patients from Therapy or Assessment

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

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

The primary reason for withdrawal was documented as one of the following: AE; lack of efficacy; withdrew consent; lost to follow-up; no further need for study medication; protocol violation; death/SAE; Investigator decision or other. The Investigator had to make reasonable attempts to contact patients who were lost to follow-up - a minimum of two documented telephone calls or a letter was considered reasonable.

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

- recording and review of all AEs
- recording and review of any concomitant therapy changes
- female patients were asked if they were pregnant. Pregnancies were recorded and followed up as detailed in the protocol
- review of the patient diary and check for completeness
- collection of any unused trial and rescue medication
- any other clinical assessment deemed appropriate for the clinical care of the patient

9.4 Treatments

9.4.1 Treatments Administered

The following medications were administered:

i. Strepsils Original Throat Lozenges, containing 1.2 mg DCBA and 0.6 mg AMC
ii. Non-medicated sugar-based placebo lozenges

Each patient was provided with the first lozenge in the investigational site with instructions to suck it slowly, moving the lozenge around the mouth, until it had dissolved. Patients were instructed not to chew or crunch the lozenges. Patients were supplied with enough trial medication to take at home during the study period and instructed to take one lozenge every 2-3 hours as required.

Patients were also supplied with rescue medication (paracetamol 500mg tablets). Patients were instructed not to take any paracetamol in the investigational site (ie before completing the 2-hour post-dose assessments), but once they had been discharged, they were allowed to take paracetamol if required. Two tablets of paracetamol up to four times a day were permitted as required, and patients were instructed not to take other paracetamol-containing products concurrently during the study. Patients were requested to return all unused medication at the follow-up visit.

9.4.2 Identity of Investigational Product(s)

The identity of the medications supplied in the study were:

i. Strepsils Original Throat Lozenges, containing 1.2 mg DCBA and 0.6 mg AMC; (Formulation Reference Number FR07/032). Batch No. BN0126986.
ii. Non-medicated sugar-based placebo lozenges (Formulation Reference Number FR07/031). Batch No. BN0126989.
iii. Rescue Medication: Paracetamol 500 mg tablets (Panadol ®, UK Product Licence No. PL 00071/5074R). Batch No. 700413.

Paracetamol 500 mg tablets (Panadol) were the commercial product marketed by GlaxoSmithKline Consumer Healthcare, Brentford, TW8 9GS, UK and were sourced in the UK. Supplies remained in their packaging and were only secondary packed and labelled for the study.

Strepsils Original Throat Lozenges and the non-medicated sugar-based placebo lozenges were manufactured and primary packed to Good Manufacturing Practice by RBHI, Nottingham NG90 2DB.

All drug supplies, including rescue medication, 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 Patients to Treatment Groups

The randomisation code is presented in Appendix 16.1.7. Randomisation was generated for 350 patients in blocks of 4. The last 2 patients were randomised in a block of 2.

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 and is summarised in Table 9.4.1. Further details of the initial allocation of randomisation numbers/study supplies to centre and their ultimate re-distribution between centres is provided in Section 9.8.1. Patient (screening) number is quoted throughout the listings in Appendix 16.2 and in the body of the report.

Table 9.4.1 Allocation of Patient Numbers and Randomisation Numbers to Study Centres

Centre No	Investigator	Pt (Screening) Nos Allocated	Randomisation Nos Allocated
Centre 01	Dr P Steele	001-090	001-039
Centre 02	Dr J McBride	091-170	053-054
Centre 03	Dr D McNally	171-250	057-068
		621-624	084-140
			154-157
			239-240
			249-257
Centre 04	Dr P Conn	251-310	141-153
Centre 05	Dr H McGoldrick	311-410	173-228
			241-248
			258-263
Centre 06	Dr N Lavin	411-470	229-231
Centre 07	Dr M Redmond	471-530	069-083
			265-300
Centre 08	Dr M Anderson	531-620	301-348

9.4.4 Selection of Doses in the Study

The doses selected in this study represent the normal non-prescription unit doses for Strepsils Original Lozenges. The unit dose of 1000 mg paracetamol for the rescue medication is consistent with product labelling.

9.4.5 Selection of Timing of Dose for Each Patient

The timing of dosing for each patient varied as required. First dose was administered in the investigational site.

9.4.6 Blinding

RBHI IMSU held the master code for the randomisation schedule and supplied each Investigator 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 treatment group the patients had been randomised in order to ascertain which study drug was taken in order that the SAE could be treated appropriately. 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 18 April 2008, only after all data queries had been answered and the database had been locked.

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 rescue medication that the patient received during the course of the study.

The Investigator recorded any medications given in treatment of AEs on the concomitant medication page in the patient's CRF. If patients required medication before the completion of the 2-hour assessments they were withdrawn from the study. Any medication taken by the patient during the course of the study was also recorded in the CRF.

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

The use of the following treatments was not permitted during the study:

- 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);
- carbamazpine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes in the 14 days 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 first lozenge administration was monitored by site staff. The staff watched the patients put the lozenge in their mouths and checked compliance by conducting a mouth inspection. The returned medication was counted and checked by study staff against the patient diary. The diary contained a record of when (time and date) the lozenges were taken each day.

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.

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; height (cm); weight (kg); body mass index (kg/m^2); 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 the current medication use and therapy history in the previous 30 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.

Table 9.5.1 Table of Study Procedures

Study Period	Screening	Treatment Period		Treatment Period				Follow-up
	Pre-dose	Time (mins) after 1st dose (Day 1)		End of each treatment day (incl. a 24hr post 1st dose)				(1-4 days after Day 3)
Study Day	N/A	0	5, 10, 15, 30, 45, 60, 75, 90, 105, 120	Day 1	24 hr post-first dose	Day 2	Day 3	
Demographics	X							
Medical History	X							
Concomitant Medication	X			X		X	X	X
Females: Pregnancy, fertility, contraceptive precaution questions.	X							X*
Tonsillopharyngitis Score	X							
Eligibility	X							
Time of first dose		X						
Adverse Events		X (Pre-dose)	X (120 mins)	X	X	X	X	X
Lozenge usage/counts				X	X	X	X	X
Paracetamol usage				X	X	X	X	X
Returned medications collected								X
Throat Soreness	X	X	X	X	X	X	X	
Difficulty in swallowing		X	X	X	X	X	X	
Sore Throat Relief			X	X	X	X	X	
Treatment Rating			X (120 mins)				X	
Consumer Questionnaire		X	X (5, 120 mins)					X†

* Pregnancy question only

† Functional Impairment only

Throat soreness: At screening, 1 minute pre first dose (time 0), 5, 10, 15, 30, 45, 60, 75, 90, 105, 120 minutes post first dose, at the end of Day 1, 24 hours post first dose, and at the end of days 2 and 3 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), 5, 10, 15, 30, 45, 60, 75, 90, 105, 120 minutes post first dose, at the end of Day 1, 24 hours post first dose, and at the end of days 2 and 3 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.

Sore Throat Relief: 5, 10, 15, 30, 45, 60, 75, 90, 105, 120 minutes post first dose, at the end of Day 1, 24 hours post first dose, and at the end of days 2 and 3 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').

Overall treatment rating: At 120 minutes post-dose and at the end of Day 3, patients completed the overall treatment rating. Patients were asked 'How would you rate this 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.

Consumer Questionnaire: The consumer questionnaire was in two different parts. 1 minute pre first dose (time 0) and at the end of Day 3 patients completed the 'Functional Impairment Scale'. At 5 minutes post first dose patients completed Question 1 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 (Q2-Q15).

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 to 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 the variability in the application of the analgesic rating scales and consumer questionnaire in this multi-centre study, 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 three rating scales at each time point within 15 seconds. To ensure accurate completion of the assessments, each patient was to be 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 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 experience 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 experience 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 is 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 a categorical scale. Throat soreness, pain relief and difficulty in swallowing over the first 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 variable for this study was the mean change from baseline in severity of throat soreness (using the 11 point Throat Soreness Scale) for the Strepsils Original group versus the placebo group at 2 hours post first dose.

The secondary efficacy endpoints were:

- AUC from baseline to two hours for the change from baseline in throat soreness.
- AUC from baseline to two hours post first dose for sore throat relief.
- Onset of analgesia defined as time to first reporting 'moderate pain relief' (which is the mid-point on the 7-point sore throat relief scale).
- Sore throat relief at two hours post first dose and at the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3.
- The change from baseline in severity of throat soreness at the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3.
- AUC from baseline to two hours for the change from baseline in difficulty in swallowing.
- The change from baseline in difficulty in swallowing at two hours post first dose and at the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3.
- Overall treatment rating at two hours and at the end of Day 3.
- Whether the patient was symptom free at the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3. Freedom of symptoms was defined as the patient reporting complete sort throat relief and no throat soreness.
- The time taken for patients to be free from symptoms for the first time.
- Overall lozenge consumption as recorded in the patient diary up to the end of Day 3.
- Overall rescue medication (paracetamol) consumption as recorded in the patient diary up to the end of Day 3.

- The proportion of patients that discontinued trial medication due to resolution of sore throat.

- Response to questions from the consumer questionnaire, including opinion on pain relief, what the relief feels like e.g. soothing, site of action of the lozenge within the mouth, how fast acting the product is, duration of action, how satisfied the patient is with the pain relief attained and how their sore throat affects their daily activities.

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

9.5.4 Drug Concentration Measurements

Drug concentrations were not measured in this study.

9.6 Data Quality Assurance

The protocol, participant information sheet and CRFs were subject to Quality Control checks and several reviews during their development, by RB and CRO study staff, including the data management staff.

All data were entered onto the Nottingham Clinical Research Limited (NCRL) 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[1] edit checks were used for consistency checks.

Before database lock, a database audit was performed which had three components. For the components 1 and 2, 16 patients (including three NSAE and 16 concomitant medications) were randomly selected from those cases that had been entered and checked.

Audit component 1: Consistency checking and query generation

Patients were selected to undergo full consistency checking where an error would be a failure to issue a query when current procedure called for a data enquiry to be raised, or a failure to appropriately respond to a consistency check. No errors were found on any of the 16 cases.

Audit component 2: Transcription and annotation procedures

Patients were selected for full audit where errors could be either transcription or other failures with respect to standard procedures for annotating working copies etc.

Two different members of the study team, compared every field in each of the cases manually with the NODES database, and all errors were noted. The total error rate was 0.05%. The error rate for 'significant data errors' was 0.01%. The acceptance level for the error rate in the final audit was the default error rate of 0.1%.

Audit component 3: Critical data fields

Due to the potential number of fields to be checked, it was agreed with RBHI that a random sample of 25% of the total number of patients would be selected for component 3. This equated to 78 patients.

The Study Statistician determined the critical fields, which were:

- Randomisation number
- Date and time of initial lozenge
- Time 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 AE data

One experienced member of the data management department compared each of the critical fields on the working copy of the CRF manually against SAS listings and all errors were to be noted and corrected. No errors were found on any of the 78 patients.

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

- 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

9.7.1 Statistical and Analytical Plans

The statistical analysis was conducted by NCRL on behalf of RBHI. A copy of the final statistical analysis plan is presented in Appendix 16.1.9.

All statistical tests were performed using a two-tailed 5% overall significance level, unless otherwise stated. The null hypothesis at all times was that the two 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. 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 tested 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 nonparametric approach could be used instead.

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

All the AUC analyses were based on actual rather than scheduled timings and were calculated using the trapezoidal rule. Patients who withdrew prior to the two-hour assessment had their last recorded post-baseline score carried forward to two hours for the AUC calculation. For ease of interpretation the AUC value obtained was divided by the total time the scale was assessed.

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

There were several instances of patients scoring the item related to "Driving a car" as not applicable for the functional impairment scale. In these cases, a score of zero was assumed for this item in terms of calculating the total score; however, the score was assumed as missing for the summary statistics produced for this item.

Centres recruiting less than eight patients were pooled for any formal statistical analysis model that involved centre as a factor.

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

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

All calculations and figures were produced using SAS Version 9.1 or S-PLUS 6.2[2].

The comparability of treatment groups with respect to patient demographics and baseline characteristics were 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 March 2007 Version.

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 endpoint was the change from baseline in severity of throat soreness (using the 11-point Throat Soreness Scale) at two hours post first dose. This was analysed 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.

Secondary endpoints

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

- The AUC from baseline to two hours post first dose for the change from baseline in throat soreness.
- AUC from baseline to two hours post first dose for sore throat relief.
- Sore throat relief at two hours post first dose and at the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3.
- The change from baseline in severity of throat soreness at the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3.
- Overall treatment rating at two hours post first dose and at the end of Day 3.
- Overall lozenge consumption as recorded in the patient diary up to the end of Day 3. (Patients who failed to return their patient diaries were omitted from this analysis).
- Overall rescue medication (paracetamol) consumption as recorded in the patient diary during the first 24 hours post initial dose and up to the end of Day 3. (Patients who failed to return their patient diaries were omitted from this analysis).

The AUC for change from baseline to two hours post first dose in difficulty in swallowing and the change from baseline in difficulty swallowing at two hours post first dose, at the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3 were analysed by ANCOVA with factors for treatment group and centre and covariates for the baseline value from difficulty in swallowing and baseline throat soreness severity.

The remaining data for sore throat relief, severity of throat soreness and for the VAS score for difficulty of swallowing at the assessments not mentioned above were tabulated but not formally analysed.

Freedom of symptoms was defined as the patient reporting complete sore throat relief and no throat soreness. The proportion of patients who had freedom of symptoms at the end of Days 2 and 3 was analysed using logistic regression with factors for treatment group and centre and a covariate for baseline throat soreness

severity. The odds ratio between Strepsils Original and placebo was reported. The proportion of patients who were symptom free at the end of day 1 and at 24 hours post first dose and the proportion of patients who discontinued trial medication due to resolution of sore throat was to be similarly analysed. In the event no patients withdrew due to sore throat resolution, no patient was symptom free at day 1 and only one patient was symptom free at 24 hours post first dose and these analyses were not performed.

The time taken for patients to report at least moderate sore throat relief (on a 7-point scale) 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 (not including the post study follow-up assessment) or the time of rescue, whichever was the earlier. Patients reporting the use of rescue medication prior to reporting at least moderate sore throat relief were censored at the time the first rescue medication was taken.

The time taken for patients to be free from symptoms for the first time was compared between treatment groups using a Cox proportional hazards model with factors for treatment group and centre and a continuous covariate for baseline throat soreness severity. Patients not reporting freedom of symptoms were censored at the time of their last recorded follow-up assessment (not including the post study follow-up assessment).

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. The change from pre-dose to the end of Day 3 in the functional impairment scale (each component and overall total score) were analysed by ANCOVA with factors for treatment group, centre and covariates for the baseline throat soreness and the relevant baseline functional impairment score. The other non-binary responses were analysed using the same ANCOVA model as the primary efficacy endpoint. Questions where the patients could select multiple responses and the question concerning the duration of action of the lozenge in the throat 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.

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 (≤7, >7), age at study entry (≤35, >35), gender, total score from tonsillopharyngitis assessment at baseline (≤8, >8), functional impairment score at baseline (≤30, >30) and baseline VAS for difficulty in swallowing (≤65, >65). Any interactions that seemed noteworthy had their nature described. These models were used to estimate treatment comparisons within the subgroups that corresponded 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.

An alternative definition of being symptom free was explored where it was defined as a sore throat score of either 0 or 1. The rationale for the alternative definition was that sore throat relief is not a symptom of a sore throat and the primary measure of interest was throat soreness and that a score of 1 was not considered high enough to warrant self-medication. This endpoint was considered to be more sensitive to being able to detect treatment group differences.

The time taken for patients to first report at least mild sore throat relief (on a 7-point scale) 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 mild sore throat relief were censored at the time of their last recorded follow-up assessment (not including the post study follow-up assessment) or the time of rescue, whichever was the earlier. Patients reporting the use of rescue medication prior to reporting at least mild sore throat relief were censored at the time the first rescue medication was taken.

9.7.1.2 Safety

All randomised patients who took a dose of study medication were included in the analysis of safety.

Exposure to study drug

Extent of exposure was described by whether the patient took any trial medication. The number of doses of study lozenges taken on each of the study days and over the whole study period (based on information recorded in the patient diary) were also tabulated along with the number of days exposure to study test product (last date of dosing minus first day of dosing + 1). As some patients recorded dosing information on days 4 and 5, overall lozenge consumption up to the end of day 3 was also tabulated.

Adverse events

All AEs were listed and tabulated by treatment, severity, relationship to therapy and primary system organ class according to Version 11.0 of MedDRA. 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 with the worst recorded severity; non-continuous AEs reported several times by the same patient were counted as multiple events. Events present immediately prior to first dose of study medication that did not worsen in severity were not included. Events with start dates during follow-up (between end of Day 3 and post study follow-up visit) were not considered treatment emergent and were listed separately. In deriving the tabulation relating to preferred term reporting, the severity of a recurrent AE was taken to be the most severe and the relationship to therapy as the most probable. Differences between treatment groups in the proportion of patients reporting treatment emergent AEs were compared using the chi-square test.

Laboratory variables

No laboratory tests were recorded during this study.

Withdrawals

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

Concomitant medications

Concomitant medications commencing during the study were coded using the ATC level 2 categories from the WHO dictionary Enhanced Version March 2007.

9.7.2 Determination of Sample Size

In a previous study the difference between Strepsils Original and the placebo in the mean change from baseline in the severity of throat soreness at two hours (using the 11-point Throat Soreness Scale) was 0.7, with a standard deviation of 1.9. Assuming that the variability in the mean change from baseline in the severity of throat soreness in this study was of a similar magnitude as before, 155 patients per group were required to provide 90% power to detect a difference in mean change from baseline of 0.7 using a two sample t-test at the 5% significance level. The actual variability observed during the study was 1.7 (root mean square error from the ANCOVA model of the full analysis set), which was slightly lower than predicted and the observed mean difference between treatments much higher, namely 1.2

9.8 Changes in the Conduct of the Study or Planned Analysis

9.8.1 Changes in the Conduct of the Study

Due to uneven recruitment at the Study Sites, study supplies (IMP, rescue medication, CRFs and patient diaries) were transferred across sites. Table 9.8.1 summarises the original supplies allocated to each site by randomisation number and details of additional supplies provided to sites.

Table 9.8.1 Reallocation of Study Supplies

Site No.	Investigator	Original Allocation		Additional Supplies		
		Randomisation Nos	Total	Randomisation Nos	Total	Date of Reallocation
01	Dr P Steele	1 to 52	52			
02	Dr J McBride	53 to 96	44			
03	Dr D McNally	97 to 140	44	84 – 89	6	21 Jan 08 (from Site 02)
				90 – 96	7	24 Jan 08 (from Site 02)
				57 – 68	12	29 Jan 08 (from Site 02)
				239 – 240, 249	3	29 Jan 08 (from Site 06)
				250 – 257	8	04 Feb 08 (from Site 06)
				154 - 157	4	14 Feb 08 (from Site 04)
04	Dr P Conn	141 to 172	32			
05	Dr H McGoldrick	173 to 228	56	241 – 248	8	14 Jan 08 (from Site 06)
				258 - 263	6	06 Feb 08 (from Site 06)
06	Dr N Lavin	229 to 264	36			
07	Dr M Redmond	265 to 300	36	69 - 83	15	18 Jan 08 (from Site 02)
08	Dr M Anderson	301 to 348	48			

In the redistribution of supplies block size was apparently overlooked leading to part-blocks being re-allocated. Although this was less than ideal it is unlikely to have lead to any untoward treatment allocation biases.

9.8.2 Changes in the Planned Statistical Analysis of the Study

It was decided that an analysis of the AUC from baseline to two hours for the change from baseline in throat soreness was also to be performed using the per-protocol set.

The protocol stated that the change from pre-dose to the end of Day 3 in the functional impairment scale would be analysed using an ANCOVA model with factors for treatment group and centre and a covariate of baseline sore throat severity. This analysis was performed with the relevant baseline functional impairment score as a further covariate.

There were conflicting definitions of what constitutes "freedom of symptoms" within the study protocol. On protocol pages 25 and 43 it was defined as the patient reporting complete sort throat relief, no throat soreness and a VAS of less than 10mm for difficulty in swallowing. Whereas on protocol page 12 no mention was made of the VAS criterion. The statistical analysis used the less restrictive definition. In addition an alternative definition of freedom of symptoms was also adopted as an exploratory analysis where it was defined as a sore throat score of either 0 or 1. The rationale for the alternative definition was that sore throat relief is not a symptom of a sore throat and the primary measure of interest was throat soreness and that a score of 1 was not considered high enough to warrant self-medication. This endpoint was considered to be more sensitive to being able to detect treatment group differences.

Overall rescue medication (paracetamol) consumption as recorded in the patient diary was also analysed during the first 24 hours post initial dose in addition to over the whole study period.

The proportion of patients who were symptom free at the end of day 1 and at 24 hours post first dose and the proportion of patients who discontinued trial medication due to resolution of sore throat were to be analysed using logistic regression. In the event no patients withdrew due to sore throat resolution, no patients were symptom free at day 1 and only one patient was symptom free at 24 hours post first dose and these analyses were not performed.

10 STUDY PATIENTS

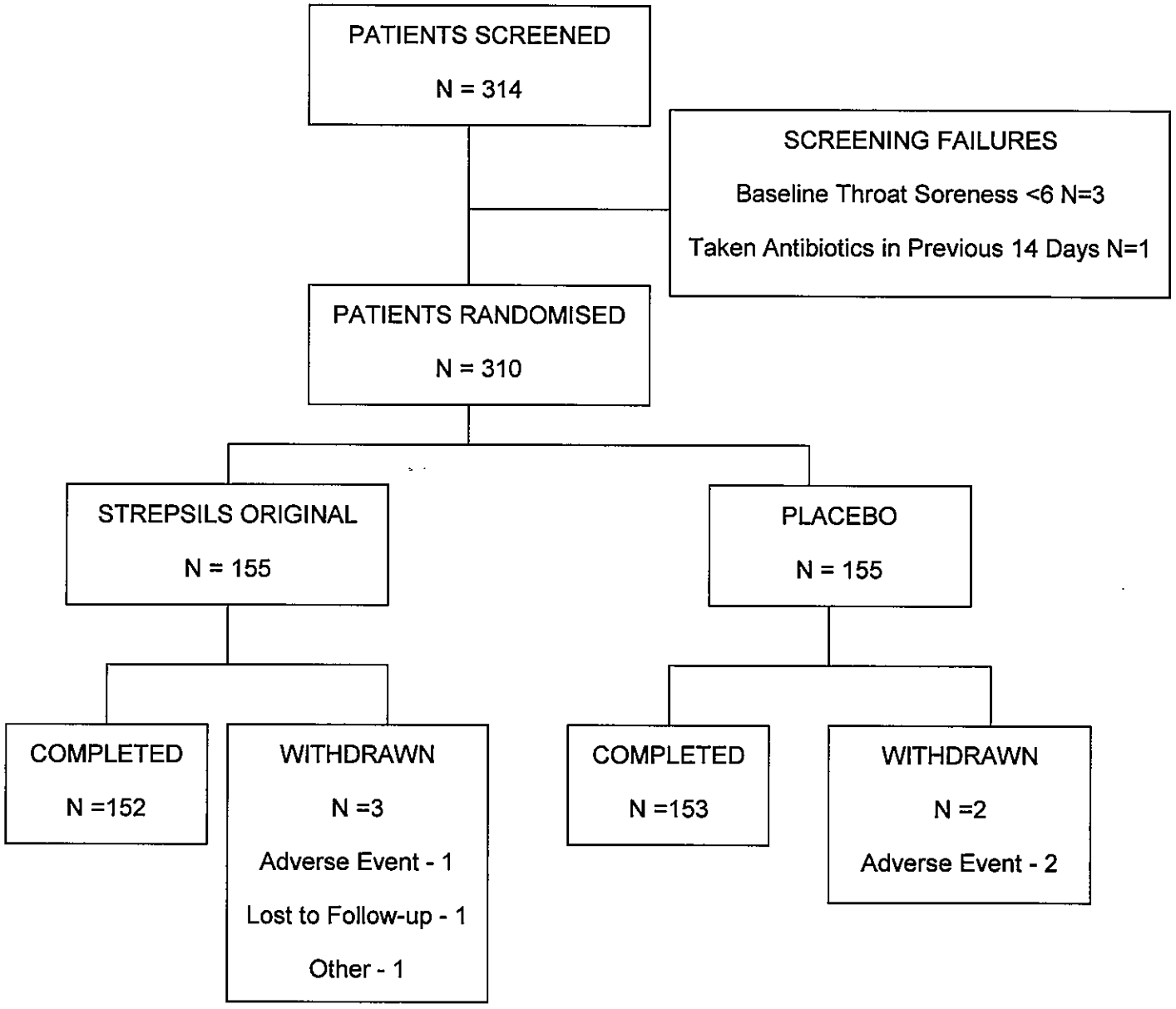
10.1 Disposition of Patients

A listing of all patients discontinued from the study after enrolment is provided in Appendix 16.2.1.

A total of 314 patients were screened for the study with 310 patients randomised between 6th November 2007 and 15th February 2008, 155 patients received Strepsils Original throat lozenges and 155 patients received placebo. Three patients withdrew from the study in the Strepsils Original Group, one (07 – 519 (numbers given are the centre number followed by the patient number)) due to an AE (mouth ulcer experienced 46.1 hours after first dose), one (03 – 197) was lost to follow-up and one (03 – 211) withdrew for other reasons (the patient could not stay in the clinic and only provided data up to the 45 minute assessment and withdrew one hour post dosing). Two patients withdrew from the study in the placebo group, both due to AEs, 03 – 195 due to vomiting 25.3 hours post first dose and 07 – 520 due to increasing

severity of sore throat 44.4 hours post first dose. Further details are presented in Table 14.1.1 and Appendix 16.2; Listing 16.2.1.1 and summarised in Figure 10.1.1.

Figure 10.1.1 Disposition of Patients



Patients were recruited in eight centres. Table 10.1.1 summarises recruitment by centre. The largest centre (site 03) recruited 84 patients. Centres 02 and 06 recruited two and three patients respectively. As specified in the statistical plan, centres recruiting less than eight patients were pooled for any formal statistical analysis model.

Table 10.1.1 Recruitment by Centre

Centre No.	Investigator	Strepsils Original	Placebo	Total
Centre 01	Dr P Steele	19 (12.3%)	20 (12.9%)	39 (12.6%)
Centre 02	Dr J McBride	1 (0.6%)	1 (0.6%)	2 (0.6%)
Centre 03	Dr D McNally	43 (27.7%)	41 (26.5%)	84 (27.1%)
Centre 04	Dr P Conn	7 (4.5%)	6 (3.9%)	13 (4.2%)
Centre 05	Dr H McGoldrick	34 (21.9%)	36 (23.2%)	70 (22.6%)
Centre 06	Dr N Lavin	1 (0.6%)	2 (1.3%)	3 (1.0%)
Centre 07	Dr M Redmond	26 (16.8%)	25 (16.1%)	51 (16.5%)
Centre 08	Dr M Anderson	24 (15.5%)	24 (15.5%)	48 (15.5%)
Total		155 (100.0%)	155 (100.0%)	310 (100.0%)

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.

Sixty (19%) patients had major protocol deviations and were therefore excluded from the per-protocol set. Of the major protocol deviations 46/60 (77%) were due to a painful condition that could have distracted attention from sore throat pain (exclusion criterion 12) or that required regular analgesic use (exclusion criterion 19). The majority of these patients 29/46 (63%) were recruited from Centre 08.

Three patients, two in the Strepsils Original group (03 – 211 and 05 – 357) and one in the placebo group (05 – 328) did not provide data for the primary efficacy endpoint and therefore 307 patients were included in the full analysis set for this variable.

One patient in the placebo group (05 – 340) took a second dose of study medication 39 minutes after the initial dose; patients were not allowed to receive a second dose of study medication during the first two hours of the study.

Table 10.2.1 Protocol Deviations – Full Analysis Set

	Strepsils Original N (%)	Placebo N (%)	Overall N (%)
N	155	155	310
Number not included in the full analysis set for primary efficacy endpoint	2 (1)	1 (1)	3 (1)
Number excluded from PP population	28 (18)	32 (21)	60 (19)
Number with minor protocol deviations	69 (45)	91 (59)	160 (52)
Reasons for exclusion from PP population (not mutually exclusive)			
Reported a painful condition that could have distracted attention from sore throat pain or that required regular analgesic use	22 (14)	24 (15)	46 (15)
Inadmissible timing of assessments	4 (3)	4 (3)	8 (3)
No data for primary endpoint	2 (1)	1 (1)	3 (1)
Inadmissible concomitant medication	-	3 (2)	3 (1)
Study medication within the first two hours after first dose	-	1 (1)	1 (0.3)
Minor study protocol deviations (not mutually exclusive)			
Missing some assessment data	35 (23)	58 (37)	93 (30)
Less than four hours between doses of rescue medication	26 (17)	37 (24)	63 (20)
Day 2 and 3 assessments one day late	8 (5)	12 (8)	20 (6)
Inadmissible concomitant medication commencing more than two hours after first dose of study medication	9 (6)	11 (7)	20 (6)
More than eight rescue medication tablets in 24-hour period	5 (3)	11 (7)	16 (5)
No diary data	6 (4)	2 (1)	8 (3)
More than 12 doses of study lozenges on any study day	1 (1)	2 (1)	3 (1)
Day 3 assessment one day late	3 (2)	-	3 (1)
Inadmissible concomitant medication taken throughout study that potentially induces liver enzymes	-	1 (1)	1 (0.3)
Inadmissible age	1 (1)	-	1 (0.3)

Source: Appendix 16.2, Listings 16.2.2.1 to 16.2.2.3

Rating scale assessments within the 2 hours post first dose were due at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes. Inadmissible assessments were as follows:

- 5,10 and 15 minute assessments not performed within +/- 1 minutes of the scheduled times
- 30, 45, 60, 75, 90, 105 and 120 minute assessments not performed within +/- five minutes of the scheduled times.

Eight patients from Centre 05 (four in each treatment group) had at least one inadmissible timing for an assessment within the first two hours of the study and were excluded from the per-protocol set.

Three patients (all in the placebo group) were taking inadmissible concomitant medication either immediately prior to study entry or during the first two hours after randomisation. Further details of the patients excluded from the per-protocol set are given in Appendix 16.2, Listings 16.2.2.1 and 16.2.2.3.

A total of 160 (52%) patients had at least one minor protocol deviation, including 91 (59%) of placebo-treated patients and 69 (45%) of Strepsils Original-treated patients. These minor protocol deviations were not considered sufficient to exclude the patients form the per-protocol set. The primary reasons for minor protocol deviations were missing assessment data or less than 4 hours between rescue medication doses.

Twenty (6%) patients commenced prohibited concomitant medication following completion of the two-hour clinic phase of the study; all these patients took analgesics. Additionally, one patient took carbamazepine throughout the study for epilepsy.

Eight (3%) patients failed to provide any diary data. Reasons for no diary data included patient withdrawal after an hour, lost to follow-up and lost diaries.

Three (1%) patients had an occurrence of taking more than 12 lozenges on one of the study days.

Finally, one patient (08 – 568) was aged 76 at the time of study entry, a year over the permitted maximum age. Further details of the patients with minor protocol deviations are given in Appendix 16.2, Listings 16.2.2.2 and 16.2.2.3.

11 EFFICACY EVALUATION

11.1 Data Sets Analysed

Appendix 16.2.3.1 contains a tabular listing of the patients included in each of the analysis populations. The strategy for the inclusion/exclusion criteria for each of the data sets analysed was included in the statistical analysis plan for the study and finalised following discussions of evaluability held after the database had been locked and prior to the blind being broken.

Three analysis sets were used in the analysis. The primary efficacy analysis population was the full analysis set. The per-protocol (PP) set was used for the analysis of the primary efficacy endpoint (the mean change from baseline in severity of throat soreness (using the 11 point Throat Soreness Scale)), the AUC from baseline to two hours post first dose for pain relief and the change from baseline in throat soreness only. All safety analyses were completed using the safety analysis set. These populations were defined as follows:

Full analysis set

The full analysis set consisted of all patients who were randomised to the study and who took at least one dose of study medication. Any patients with treatment administration errors were analysed according to the treatment to which they were randomised. The full analysis set was the primary efficacy analysis population. This analysis set included 310 patients (155 in each treatment group). Two patients (one in each treatment group) failed to provide any post-dose data for the two-hour clinic period but did provide diary data. One Strepsils Original treated patient withdrew from the study having only provided data up to 45-minute post-dose assessment, therefore 307 patients (154 in the placebo group and 153 in the Strepsils Original group) were included in the analysis of the primary efficacy endpoint.

Per-protocol set

This 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 two hour assessment post first-dose. All protocol deviations were assessed and documented on a case-by-case basis prior to the database lock, and major deviations, i.e. those considered to have the potential to seriously impact the efficacy results, led to the relevant patient being excluded from the set.

The only variables assessed using the per-protocol set were the primary efficacy endpoint (the mean change from baseline in severity of throat soreness (using the 11 point Throat Soreness Scale)), the AUC from baseline to two hours post first dose for pain relief and the change from baseline in throat soreness. This analysis set included 250 patients, 127 patients in the Strepsils Original group and 123 in the placebo group.

Safety set

All patients who took at least one dose of study medication were included in the analysis of safety. The safety set was analysed as treated. This set included 310 patients.

11.2 Demographic and Other Baseline Characteristics

A summary of patient demographics is presented in Tables 14.1.2 to 14.1.5 and listed by patient number in Appendix 16.4. 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, patient ages ranged from 18 to 76 years, with a mean age of 36.1 years. The majority of patients, 303 (98%), were Caucasian and there were more females than males (68% to 32%).

Mean height was 167.5 cm (range 148 to 195 cm), mean weight was 75.7 kg (range 49.0 to 161.2 kg) and mean BMI 26.9 kg/m^2 (range 17.6 to 55.7 kg/m^2). A total of 203 (66%) drank alcohol, 84 (27%) were current smokers and 33 (11%) were former smokers. Table 14.1.2 presents full summary statistics of demographic variables.

Table 11.2.1 Demographics – Full Analysis Set

Variable	Strepsils Original	Placebo	Overall
Number of patients	155	155	310
Age (yr) (Mean (sd))	36.3 (14.0)	35.9 (14.2)	36.1 (14.1)
Gender (% male)	32.3%	32.3%	32.3%
Race (% Caucasian)	100.0%	95.5%	97.7%
Height (cm) (Mean (sd))	167.3 (9.2)	167.7 (9.0)	167.5 (9.1)
Weight (kg) (Mean (sd))	74.5 (16.5)	77.0 (18.9)	75.7 (17.8)
BMI (kg/m^2) (Mean (sd))	26.6 (5.4)	27.3 (6.0)	26.9 (5.7)

Source: Table 14.1.2

A total of 87 (28%) patients reported a previous medical condition (Table 14.1.3) and 174 (56%) patients reported an ongoing medical condition of which 66 (21%) patients had conditions within the psychiatric system and 65 (21%) had conditions of the gastrointestinal system (Table 14.1.4). Forty-six (15%) patients reported a painful condition that could have distracted attention from sore throat pain or that required regular analgesic use that violated the protocol exclusion criteria; all these patients were excluded from the per-protocol set.

To be eligible for study entry patients had to have a TPA score of 5 or above and had to score at least 6 on the 11-point throat soreness scale where 0 = 'not sore' and 10 = 'very sore'. A summary of these screening assessments is presented in Table 11.2.2.

Table 11.2.2 Screening Assessments – Full Analysis Set

Variable	Strepsils Original	Placebo	Overall
Number of patients	155	155	310
TPA Score (mean (sd))	8.8 (2.8)	9.1 (2.6)	9.0 (2.7)
TPA (min, max)	5.0, 17.0	5.0, 18.0	5.0, 18.0
Throat Soreness (mean (sd))	7.1 (1.0)	7.2 (1.1)	7.1 (1.0)
Throat Soreness (min, max)	6.0, 10.0	6.0, 10.0	6.0, 10.0

Source: Table 14.1.5

Table 14.1.6 presents a summary of the mean values of the efficacy variables recorded immediately prior to dosing with the first dose. Table 11.2.3 summarises these data.

Table 11.2.3 Mean (SD) For Pre-Dose Efficacy Variables – Full Analysis Set

Variable	Strepsils Original	Placebo	Overall
Functional Impairment Scale (How sore throat affected) *Each activity measured on a 11-point scale where 0 = Would not interfere at all, 10 = Would completely interfere*			
Number of patients	154	155	309
Eating a meal	5.5 (2.2)	5.8 (2.5)	5.6 (2.4)
Driving a car	0.9 (1.7)	1.0 (2.0)	0.9 (1.8)
Sleeping	4.4 (3.1)	4.2 (3.3)	4.3 (3.2)
Reading	1.2 (2.0)	1.8 (2.4)	1.5 (2.2)
Working	3.7 (3.1)	4.2 (3.2)	4.0 (3.2)
Talking	5.8 (2.4)	6.2 (2.3)	6.0 (2.4)
Swallowing	7.1 (1.8)	7.4 (1.8)	7.2 (1.8)
Concentrating	2.8 (2.6)	3.1 (2.9)	2.9 (2.7)
Total score (0 to 80)	31.3 (13.1)	33.6 (14.4)	32.5 (13.8)
Throat Soreness (mean (sd)) (0=not sore, 10=very sore)	7.1 (1.0) (n=155)	7.2 (1.2) (n=155)	7.1 (1.1) (n=310)
Difficulty in Swallowing (mean (sd)) 100mm VAS (0mm=not difficult, 100mm=very difficult)	62.6 (19.6) (n=152)	62.5 (20.3) (n=153)	62.5 (19.9) (n=305)

Source: Table 14.1.6

With respect to the functional impairment scale, of the eight activities referenced, patients experienced most impairment with swallowing (mean score 7.22), talking (mean score 5.99) and eating a meal (mean score 5.64). The mean scores for throat soreness and difficulty in swallowing pre-first dose were 7.15 and 62.5 mm respectively. Five patients failed to provide a pre-dose VAS for difficulty in swallowing and there was a large range in scores from 5 to 98 mm.

Details of concomitant medication ongoing at time of randomisation are presented in Table 14.1.7, 173 (56%) patients reported the use of at least one concomitant medication at study entry. In terms of WHO ATC level 2 categories, the most commonly reported concomitant medication categories were sex hormones and modulators of the genital system, and psychoanaleptics with 61 (20%) patients and 36 (12%) receiving these medications respectively.

Twenty-five (8%) patients were reported to be using analgesic drugs at the time of entry that may have interfered with the study assessments. Of the 25 patients taking concomitant analgesics, 14 patients were using aspirin as an antiplatelet therapy, 5 were taking various anti-migraine preparations (rizatriptan, pizotifen, sumatriptan and zolmitriptan) and 6 were recorded as having ongoing analgesic medications (paracetamol and codeine combinations and tramadol). However, since these medications were not taken in the eight hours prior to randomisation, or during the two hours after dosing, the patients were not regarded as violating the study protocol.

Seven (2%) patients had ongoing anti-inflammatory and anti-rheumatic products (glucosamine, diclofenac and misoprostol, diclofenac, ibuprofen and naproxen).

Glucosamine was allowable by the study protocol and as the other medications were not taken in the eight hours prior to randomisation or during the two hours after dosing, these were also not considered as protocol violators.

One patient took carbamazepine throughout the study for epilepsy. This was contrary to exclusion criterion 16, which was included due to the provision of paracetamol as rescue medication and the potential effects of carbamazepine on liver enzymes. This was regarded as a minor protocol deviation as the use of concomitant medication would not interfere with the study assessments.

11.3 Measurements of Treatment Compliance

Listing of lozenge consumption is presented in Appendix 16.2.5 and summarised in Table 14.3.1. All patients took their initial dose under supervision at the investigative sites. Subsequent doses were recorded by the patients in their patient diaries. Lozenge returns and diary entries were checked by study staff when the patient returned to the clinic three to seven days after their initial appointment. Seven patients, including one patient lost to follow-up, failed to return their diaries so had no exposure data available. The majority of patients, 286/310 (92%), were compliant with the treatment regime; one lozenge every 2 – 3 hours as required, no more than 8 lozenges in any 24 hours period. Twenty-four patients (8%) exceeded this recommended daily intake of lozenges on 30 occasions with one patient (07 – 523) taking 17 lozenges on Day 2. Further details of exposure data based on the diary information are presented in Section 12.1.

11.4 Efficacy Results

Efficacy data are presented in Section 14.2 Tables and summarised here.

11.4.1 Analysis of Efficacy

11.4.1.1 Primary Endpoint

The primary endpoint was the change from baseline in severity of throat soreness (using the 11-point Throat Soreness Scale) at two hours post first dose. Primary endpoint analyses for the Full Analysis Set and Per Protocol (PP) Set are presented in Tables 14.2.1.1 and 14.2.1.2 respectively and summarised in Table 11.4.1.

Table 11.4.1 Primary Efficacy Endpoint: Change from Baseline in Severity of Throat Soreness at Two Hours Post First Dose

		Strepsils Original	Placebo
FULL ANALYSIS SET			
N		153	154
Baseline	Mean (sd)	7.13 (1.05)	7.17 (1.15)
Two hours	Mean (sd)	5.07 (2.11)	6.29 (1.83)
Change from baseline	Mean (sd)	-2.07 (2.02)	-0.88 (1.50)
	LS mean[a]	-2.06	-0.85
	Difference between LS means[b]	-1.21	
	SE	0.20	
	95% CI	-1.59, -0.82	
	p-value for treatment[a]	<0.0001	
PER-PROTOCOL SET			
N		127	123
Baseline	Mean (sd)	7.03 (1.05)	6.98 (1.12)
Two hours	Mean (sd)	5.27 (2.02)	6.23 (1.58)
Change from baseline	Mean (sd)	-1.76 (1.78)	-0.76 (1.27)
	LS mean[a]	-1.87	-0.86
	Difference between LS means[b]	-1.01	
	SE	0.19	
	95% CI	-1.38, -0.63	
	p-value for treatment[a]	<0.0001	

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b Strepsils Original minus placebo. A negative difference favours Strepsils Original
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

Three patients failed to provide 2-hour data so 307 patients rather than 310 patients were included in the Full Analysis Set analysis of the primary efficacy variable. Least squares (LS) mean reductions of –2.06 (Strepsils Original) and –0.85 (placebo) were observed; the LS mean difference of –1.21 (95% CI –1.59, -0.82) was highly statistically significant (p<0.0001) in favour of Strepsils Original. The term for centre was also statistically significant in the ANCOVA model (p=0.0002) whereas the covariate for baseline throat soreness severity was not statistically significant (p=0.22; Table 14.2.1.1).

Sixty (19%) patients were excluded from the equivalent per-protocol analysis due to major protocol violations or missing data (see Section 10.2). The statistical conclusions were qualitatively identical to those obtained with the full analysis set as described above. The LS mean reductions from baseline were –1.87 and –0.86 for Strepsils Original and placebo respectively; the LS mean difference was –1.01 (95% CI –1.38, -0.63, p<0.0001: Table 14.2.1.2).

11.4.1.2 Secondary Endpoints

AUC from baseline to two hours post first dose for the change from baseline in throat soreness

The analyses for AUC from baseline to two hours post first dose for the change from baseline in throat soreness for the Full Analysis Set and Per Protocol Set are presented in Tables 14.2.2.1 and 14.2.2.2 respectively and summarised in Table 11.4.2.

Table 11.4.2 AUC from Baseline to two hours Post First Dose for the Change from Baseline in Throat Soreness

	Strepsils Original	Placebo
FULL ANALYSIS SET		
N	154	154
Mean (sd)	-1.97 (1.49)	-0.73 (1.14)
LS mean[a]	-1.94	-0.69
Difference between LS means[b]	-1.26	
Se	0.15	
95% CI	-1.54, -0.97	
p-value for treatment[a]	<0.0001	
PER-PROTOCOL SET		
N	127	123
Mean (sd)	-1.79 (1.37)	-0.69 (1.00)
LS mean[a]	-1.85	-0.74
Difference between LS means[b]	-1.11	
Se	0.14	
95% CI	-1.40, -0.83	
p-value for treatment[a]	<0.0001	

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b Strepsils Original minus placebo. A negative difference favours Strepsils Original

Source: Tables 14.2.2.1 and 14.2.2.2

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

For the Full Analysis Set (n=308), the terms for treatment and centre in the ANCOVA model were both highly statistically significant (p<0.0001) whereas the term for baseline throat soreness severity did not attain statistical significance (p=0.06). The difference in LS mean reductions of –1.94 (Strepsils Original) and –0.69 (placebo), was highly statistically significant in favour of Strepsils Original (p<0.0001, Table 14.2.2.1).

For the equivalent Per-Protocol analysis (n=250), all three terms in the ANCOVA model were statistically significant: treatment (p<0.0001), centre (p=0.0001) and baseline throat soreness severity (p=0.048). The LS mean reductions estimated from the model were –1.85 and –0.74 for Strepsils Original and placebo respectively (Table 14.2.2.2).

Full summary statistics of change in throat soreness at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post dose for the Full Analysis Set are presented in Tables 14.2.1.1 and 14.2.11. These data are summarised in Table 11.4.3 and graphically represented in Figure 11.4.1.

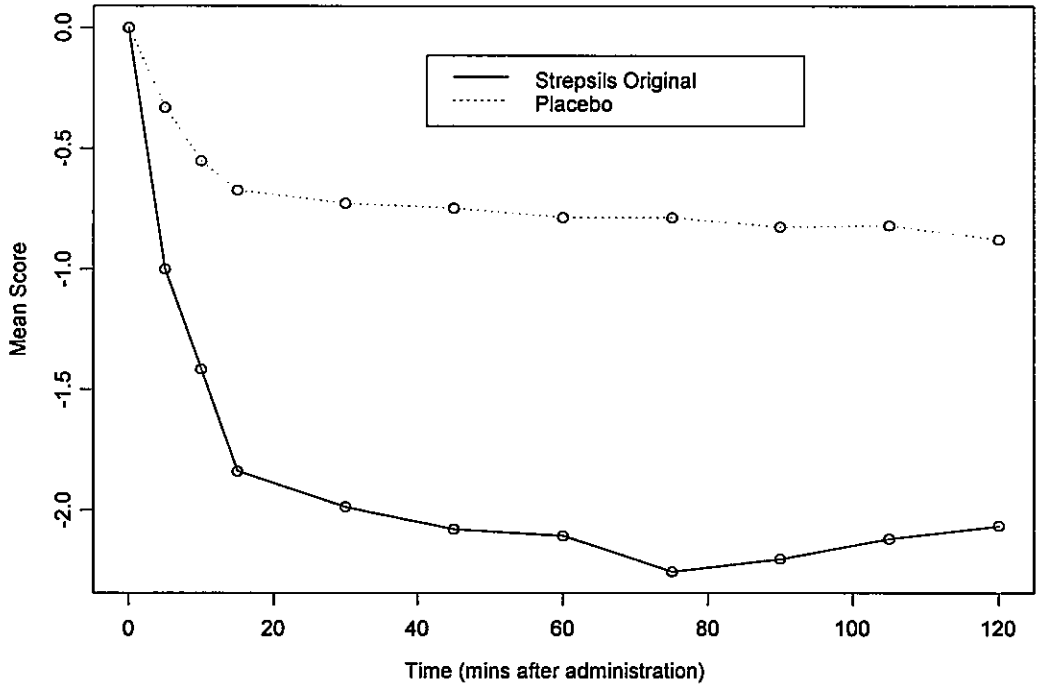
Table 11.4.3 Mean (SD) for Change from Baseline in Throat Soreness at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes Post Dose – Full Analysis Set

Minutes post-dose	Strepsils Original		Placebo	
	Mean (SD)	N	Mean (SD)	N
Baseline	7.13 (1.05)	155	7.16 (1.15)	155
5	-1.00 (1.46)	154	-0.33 (0.88)	154
10	-1.42 (1.44)	154	-0.55 (1.01)	154
15	-1.84 (1.48)	154	-0.67 (1.16)	153
30	-1.99 (1.55)	154	-0.73 (1.19)	154
45	-2.08 (1.60)	154	-0.75 (1.22)	154
60	-2.11 (1.74)	152	-0.79 (1.30)	154
75	-2.25 (1.83)	153	-0.79 (1.33)	154
90	-2.20 (1.90)	153	-0.82 (1.38)	154
105	-2.12 (1.91)	153	-0.82 (1.44)	154
120	-2.07 (2.02)	153	-0.88 (1.50)	154

Source: Tables 14.1.6, 14.2.1.1 and 14.2.11 *Throat soreness measured on a 11-point scale where 0 = Not sore, 10 = Very sore*

For all assessments, mean changes from baseline were much larger for Strepsils Original than for the placebo group. Maximum mean reduction from baseline following administration of Strepsils Original was achieved at 75 minutes post dose.

Figure 11.4.1 Mean change from baseline in throat soreness from 5 to 120 minutes post first dose – Full Analysis Set



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

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

The analyses for AUC from baseline to two hours post first dose for sore throat relief for the Full Analysis Set and Per Protocol Set are presented in Tables 14.2.3.1 and 14.2.3.2 respectively and summarised in Table 11.4.4.

Table 11.4.4 AUC from Baseline to Two Hours Post First Dose for Sore Throat Relief

	Strepsils Original	Placebo
FULL ANALYSIS SET		
N	154	154
Mean (sd)	1.99 (1.36)	0.72 (0.90)
LS mean[a]	1.99	0.72
Difference between LS means[b]	1.28	
Se	0.12	
95% CI	1.04, 1.52	
p-value for treatment[a]	<0.0001	
PER-PROTOCOL SET		
N	127	123
Mean (sd)	1.85 (1.33)	0.70 (0.79)
LS mean[a]	1.96	0.80
Difference between LS means[b]	1.17	
Se	0.13	
95% CI	0.91, 1.42	
p-value for treatment[a]	<0.0001	

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b Strepsils Original minus placebo. A positive difference favours Strepsils Original

Source: Tables 14.2.3.1 and 14.2.3.2

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

For the Full Analysis Set, the LS mean AUC for pain relief from the ANCOVA model was 1.99 for Strepsils Original and 0.72 for placebo; the mean difference of 1.28 (95% CI 1.04, 1.52) was highly statistically significantly ($p<0.0001$) in favour of Strepsils Original. The terms for centre ($p<0.0001$) and baseline throat soreness severity ($p=0.001$) were also statistically significant (Table 14.2.3.1). The equivalent Per-Protocol analysis had qualitatively identical statistical conclusions. The LS means were 1.96 and 0.80 for Strepsils Original and placebo respectively.

Full summary statistics and frequency distributions of sore throat relief at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post dose for the Full Analysis Set are presented in Tables 14.2.4 and 14.2.5. These data are summarised in Table 11.4.5 and graphically represented in Figure 11.4.2.

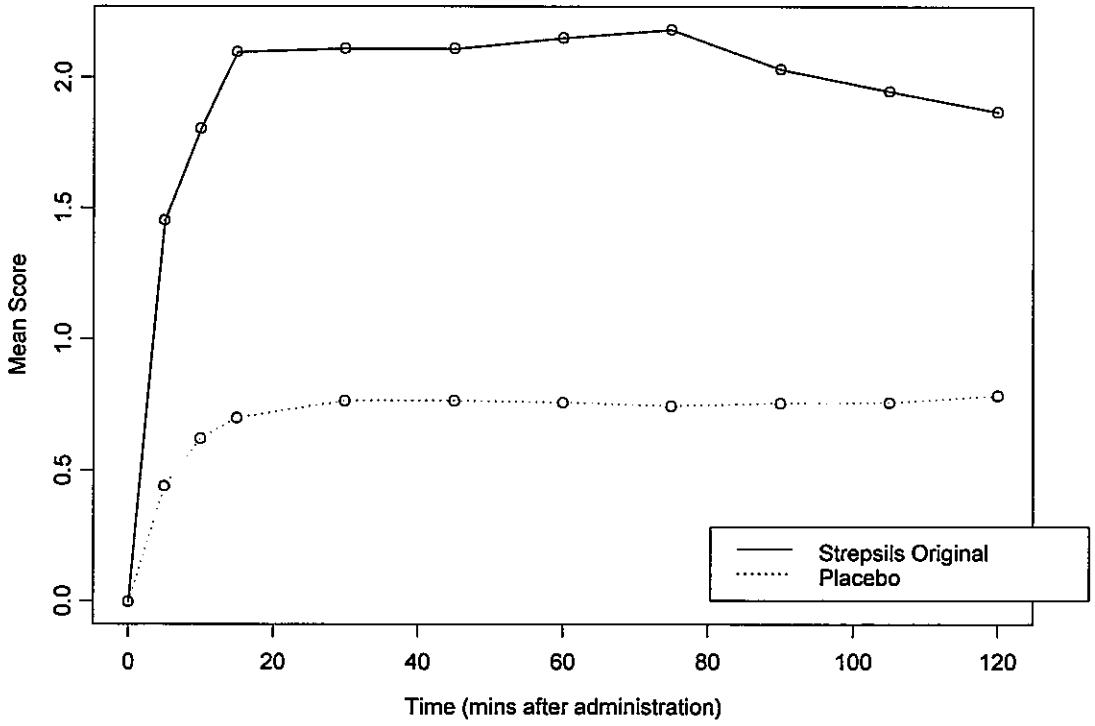
For all these assessments mean relief values were much higher for Strepsils Original compared with the placebo group. As with change in throat soreness, maximum relief following administration of Strepsils Original was achieved at 75 minutes post dose.

Table 11.4.5 Mean (SD) for Sore Throat Relief at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes Post First Dose – Full Analysis Set

Minutes post-dose	Strepsils Original		Placebo	
	Mean (SD)	n	Mean (SD)	n
5	1.45 (1.13)	154	0.44 (0.70)	154
10	1.81 (1.20)	154	0.62 (0.81)	154
15	2.10 (1.31)	154	0.70 (0.86)	154
30	2.11 (1.42)	153	0.77 (1.00)	154
45	2.11 (1.51)	154	0.77 (1.00)	154
60	2.15 (1.60)	152	0.76 (1.05)	154
75	2.18 (1.67)	153	0.75 (1.05)	154
90	2.03 (1.64)	153	0.76 (1.12)	153
105	1.95 (1.68)	153	0.76 (1.17)	154
120	1.87 (1.63)	153	0.79 (1.20)	154

Source: Tables 14.2.4 and 14.2.5 *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*

Figure 11.4.2 Mean sore throat relief from 5 to 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

Sore throat relief at two hours post first dose and at the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3.

The analysis for sore throat relief at two hours post first dose for the Full Analysis Set are presented in Table 14.2.5 and summarised in Table 11.4.6.

Table 11.4.6 Sore Throat Relief at Two Hours Post Dose – Full Analysis Set

	Strepsils Original	Placebo
N	153	154
0 No relief	42 (27.5%)	87 (56.5%)
1 Slight relief	29 (19.0%)	39 (25.3%)
2 Mild relief	30 (19.6%)	13 (8.4%)
3 Moderate relief	26 (17.0%)	9 (5.8%)
4 Considerable relief	13 (8.5%)	2 (1.3%)
5 Almost complete relief	11 (7.2%)	3 (1.9%)
6 Complete relief	2 (1.3%)	1 (0.6%)
Mean (sd)	1.87 (1.63)	0.79 (1.20)
LS mean[a]	1.93	0.84
Difference between LS means[b]	1.09	
Se	0.16	
95% CI	0.78, 1.40	
p-value for treatment[a]	<0.0001	

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b Strepsils Original minus placebo. A positive difference favours Strepsils Original
Source: Table 14.2.5

All three terms in the ANCOVA model were statistically significant: treatment and centre ($p<0.0001$) and baseline throat soreness severity ($p=0.006$). At 2 hours post first dose more patients on the Strepsils Original group reported some relief compared with the placebo group. The LS mean sore throat scores were 1.93 and 0.84 for Strepsils Original and placebo respectively. The difference between the LS means of 1.09 (95% CI 0.78, 1.40) was highly statistically significant ($p<0.0001$).

The analyses for sore throat relief at the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3 for the Full Analysis Set are presented in Tables 14.2.6 to 14.2.9 respectively and summarised in Table 11.4.7.

Table 11.4.7 Sore Throat Relief at the End of Day 1, 24 hours post first dose and at the end of Days 2 and 3 – Full Analysis Set

	n	Mean (sd)	LS mean[a]	Difference between LS means[b]	se	95% CI	p-value for treatment[a]
END OF DAY 1							
Strepsils Original	147	1.95 (1.31)	1.97	0.95	0.14	0.67,1.23	<0.0001
Placebo	152	1.00 (1.18)	1.01				
24 HOURS POST FIRST DOSE							
Strepsils Original	149	2.44 (1.61)	2.42	1.14	0.17	0.81,1.48	<0.0001
Placebo	151	1.29 (1.38)	1.28				
END OF DAY 2							
Strepsils Original	148	2.82 (1.78)	2.84	1.35	0.19	0.97,1.73	<0.0001
Placebo	150	1.49 (1.57)	1.49				
END OF DAY 3							
Strepsils Original	148	3.37 (1.93)	3.37	1.58	0.22	1.15,2.01	<0.0001
Placebo	152	1.81 (1.86)	1.79				

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b Strepsils Original minus placebo. A positive difference favours Strepsils Original

Source: Tables 14.2.6 to 14.2.9

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

At all four of these assessments the superiority of Strepsils Original was clearly apparent with highly statistically significant differences against placebo (p<0.0001; Tables 14.2.6 to 14.2.9). The difference between treatments gradually increased over the three day study period.

Table 14.2.10 shows details of the analysis of time to first reporting of "moderate pain relief". In total, 97/155 (63%) reported moderate pain relief in the Strepsils Original group compared to 34/155 (22%) in the placebo group. The Kaplan-Meier median time to reporting moderate pain relief in the Strepsils group was 45 minutes (95% CI 15, 780 minutes), the equivalent median value for the placebo group was non-estimable, but in excess of 3600 minutes. All terms in the Cox regression analysis were statistically significant i.e. treatment (p<0.0001), centre (p<0.0001) and baseline sore throat severity (p=0.007). The hazard ratio from the Cox model was 5.73 (95% CI 3.74, 8.78) indicating the superiority of Strepsils Original.

The change from baseline in severity of throat soreness at the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3.

The analyses for the change from baseline in throat soreness at the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3 for the Full Analysis Set are presented in Tables 14.2.12 to 14.2.15 respectively and summarised in Table 11.4.8.

Table 11.4.8 Change from Baseline in Throat Soreness at the end of Day 1, 24 hours post First Dose and at the end of Days 2 and 3 – Full Analysis Set

	n	Mean (sd)	LS mean[a]	Difference between LS means[b]	SE	95% CI	p-value for treatment[a]
END OF DAY 1							
Strepsils Original	148	-1.61 (1.76)	-1.57	-0.83	0.19	-1.21, -0.46	<0.0001
Placebo	152	-0.82 (1.58)	-0.74				
24 HOURS POST FIRST DOSE							
Strepsils Original	149	-2.54 (2.05)	-2.43	-1.25	0.22	-1.69, -0.82	<0.0001
Placebo	151	-1.32 (1.92)	-1.17				
END OF DAY 2							
Strepsils Original	147	-3.18 (2.27)	-3.06	-1.45	0.25	-1.93, -0.96	<0.0001
Placebo	152	-1.80 (2.16)	-1.61				
END OF DAY 3							
Strepsils Original	148	-4.11 (2.32)	-4.02	-1.87	0.27	-2.40, -1.34	<0.0001
Placebo	150	-2.31 (2.48)	-2.15				

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b Strepsils Original minus placebo. A negative difference favours Strepsils Original
Source: Tables 14.2.12 to 14.2.15 *Throat soreness measured on a 11-point scale where 0 = Not sore, 10 = Very sore*

At all four of these assessments the superiority of Strepsils Original was clearly apparent with highly statistically significant differences against placebo (p<0.0001; Tables 14.2.12 to 14.2.15). As with pain relief, the difference between treatments in change from baseline in throat soreness gradually increased over the three day study period.

AUC from baseline to two hours for the change from baseline in difficulty in swallowing.

The analysis for AUC from baseline to two hours post first dose for the change from baseline in difficulty in swallowing for the Full Analysis Set is presented in Table 14.2.18 and summarised in Table 11.4.9.

Table 11.4.9 AUC from Baseline to two Hours Post First Dose for the Change from Baseline in Difficulty in Swallowing – Full Analysis Set

	Strepsils Original	Placebo
N	151	152
Mean (sd)	-14.0 (15.9)	-3.4 (11.3)
LS mean[a]	-14.4	-3.8
Difference between LS means[b]	-10.6	
Se	1.4	
95% CI	-13.4, -7.8	
p-value for treatment[a]	<0.0001	

a Estimated from ANCOVA model with factors for treatment and centre and a covariates for baseline throat soreness and baseline score for difficulty in swallowing
b Strepsils Original minus placebo. A negative difference favours Strepsils Original
Source: Tables 14.2.18

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

All four terms in the ANCOVA model were statistically significant, namely treatment, baseline throat soreness severity and baseline difficulty swallowing score (p<0.0001) and centre (p=0.004). The LS mean reductions of –14.4 mm (Strepsils Original) and -3.8 mm (placebo) highly favoured Strepsils Original (Table 14.2.18).

Full summary statistics of change in difficulty in swallowing at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post dose for the Full Analysis Set are presented in Tables 14.2.16 and 14.2.17. These data are summarised in Table 11.4.10 and graphically represented in Figure 11.4.3.

Table 11.4.10 Mean (SD) for Change from Baseline in Difficulty in Swallowing at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post dose – Full Analysis Set

Minutes post-dose	Strepsils Original		Placebo	
	Mean (SD)	N	Mean (SD)	N
Baseline	62.6 (19.6)	152	62.5 (20.3)	153
5	-7.1 (13.6)	150	-0.2 (9.2)	149
10	-10.4 (13.5)	151	-1.9 (9.8)	152
15	-13.8 (15.3)	150	-2.3 (11.0)	152
30	-14.5 (15.9)	150	-3.3 (11.5)	149
45	-14.4 (16.3)	151	-3.7 (12.1)	152
60	-15.1 (18.1)	148	-3.8 (12.9)	152
75	-15.6 (20.0)	150	-3.5 (14.0)	151
90	-15.3 (21.6)	148	-3.8 (14.9)	152
105	-15.3 (20.8)	150	-4.8 (14.8)	151
120	-15.0 (21.6)	150	-3.6 (14.8)	149

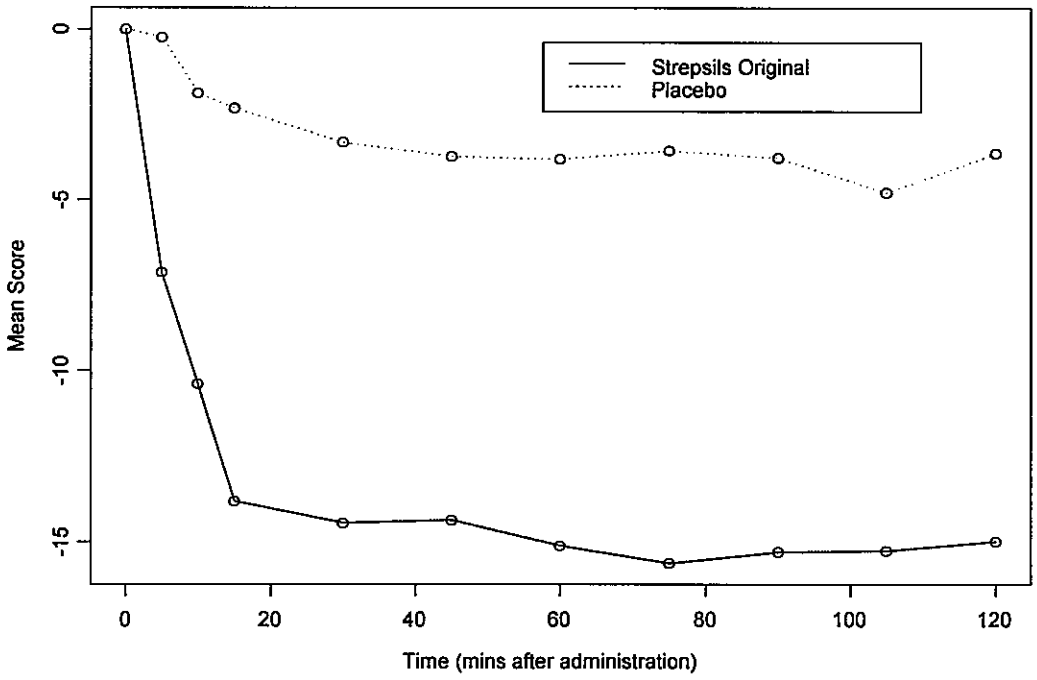
Source: Tables 14.1.6, 14.2.16 and 14.2.17

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

At each time point post first dose, mean changes from baseline in difficulty in swallowing were much larger for Strepsils Original compared with the placebo group. As with pain relief and changes in throat soreness the maximum mean reduction

from baseline in difficulty in swallowing following administration of Strepsils Original was achieved at 75 minutes post dose.

Figure 11.4.3 Mean change from baseline in difficulty in swallowing from 5 to 120 minutes post first dose – Full analysis set



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

The change from baseline in difficulty in swallowing at two hours post first dose and at the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3.

The analysis for the change from baseline in difficulty in swallowing at two hours post first dose for the Full Analysis Set is presented in Table 14.2.17 and summarised in Table 11.4.11.

Table 11.4.11 Change from Baseline in Difficulty in Swallowing at Two Hours Post Dose – Full Analysis Set

	Strepsils Original	Placebo
N	150	149
Baseline (mean(sd))	62.5 (19.7)	62.4 (20.5)
Two hours post-dose (mean (sd))	47.5 (22.7)	58.8 (22.1)
Change from baseline (mean (sd))	-15.0 (21.6)	-3.6 (14.8)
LS mean[a]	-15.0	-3.8
Difference between LS means[b]	-11.1	
Se	2.0	
95% CI	-15.0, -7.3	
p-value for treatment[a]	<0.0001	

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

b Strepsils Original minus placebo. A negative difference favours Strepsils Original

Source: Tables 14.2.17 *Difficulty in swallowing measured on 100mm VAS where 0mm = Not difficult, 100mm = Very difficult*

LS mean reductions of –15.0 mm (Strepsils Original) and –3.8 mm (placebo) were observed; the LS mean difference of –11.1 mm (95% CI –15.0, -7.3) was highly statistically significantly (p<0.0001) in favour of Strepsils Original. All other terms in the ANCOVA model were statistically significant namely: centre (p=0.003), baseline throat soreness severity (p=0.0001) and baseline score for difficulty in swallowing (p<0.0001; Table 14.2.17).

The analyses for the change from baseline in difficulty in swallowing at the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3 for the Full Analysis Set are presented in Tables 14.2.19 to 14.2.22 respectively and summarised in Table 11.4.12.

Table 11.4.12 Change from baseline in difficulty in swallowing at the end of Day 1, 24 hours post first dose and at the end of days 2 and 3 – Full analysis set

	n	Mean (sd)	LS mean[a]	Difference between LS means[b]	se	95% CI	p-value for treatment[a]
END OF DAY 1							
Strepsils Original	144	-10.8 (18.2)	-10.7	-6.9	1.8	-10.6, -3.3	0.0002
Placebo	150	-4.1 (16.0)	-3.8				
24 HOURS POST FIRST DOSE							
Strepsils Original	145	-18.6 (20.6)	-17.9	-9.0	2.1	-13.2, -4.9	<0.0001
Placebo	147	-9.8 (18.4)	-8.9				
END OF DAY 2							
Strepsils Original	144	-24.0 (23.4)	-23.5	-11.9	2.4	-16.7, -7.1	<0.0001
Placebo	147	-12.0 (21.2)	-11.6				
END OF DAY 3							
Strepsils Original	142	-33.4 (24.2)	-33.1	-17.2	2.6	-22.4, -12.0	<0.0001
Placebo	147	-16.6 (24.7)	-15.9				

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

b Strepsils Original minus placebo. A negative difference favours Strepsils Original

Source: Tables 14.2.19 to 14.2.22

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

At all four of these assessments the superiority of Strepsils Original was clearly apparent with statistically significant differences against placebo ($p \leq 0.0002$; Tables 14.2.19 to 14.2.22). As with pain relief and change in throat soreness, the difference between treatments in change from baseline in difficult in swallowing gradually increased over the three day study period.

Overall treatment rating at two hours and at the end of Day 3.

The analyses for the overall treatment rating at two hours and at the end of Day 3 Full Analysis Set are presented in Table 14.2.23 and summarised in Table 11.4.13.

Table 11.4.13 Overall treatment rating at two hours and at the end of day 3 – Full analysis set

	Strepsils Original		Placebo
TWO HOURS			
N	153		153
Mean (SD)	5.46 (2.40)		2.71 (2.82)
LS mean[a]	5.49		2.75
Difference between LS means[b]		2.74	
Se		0.30	
95% CI		2.15, 3.32	
p-value for treatment[a]		<0.0001	
END OF DAY 3			
N	148		151
Mean (SD)	5.68 (2.58)		2.85 (2.74)
LS mean[a]	5.72		2.89
Difference between LS means[b]		2.83	
Se		0.31	
95% CI		2.23, 3.43	
p-value for treatment[a]		<0.0001	

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b Strepsils Original minus placebo. A positive difference favours Strepsils Original

Source: Tables 14.2.23

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

The rating was graded on an 11-point scale where 0 = poor, 10 = excellent. At two hours, 306 (99%) patients provided data. The LS mean scores were 5.49 for Strepsils Original and 2.75 for placebo, the LS mean difference of 2.74 (95% CI 2.15, 3.32) was highly statistically significant (p<0.0001) in favour of Strepsils Original. The covariate for baseline throat soreness severity was also statistically significant (p=0.002), but the term for centre was not significant (p=0.51). By the end of day 3, the LS mean scores for both treatments increased slightly; the scores were 5.72 and 2.89 for the Strepsils Original and placebo treatment groups respectively. The LS mean difference between treatments had increased to 2.83 (95% CI 2.23, 3.43; p<0.0001). Once again, the baseline covariate for throat soreness was statistically significant (p=0.012) and centre was not statistically significant (p=0.50). At the end of Day 3, 299 (96%) patients provided data.

Whether the patient was symptom free at the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3. Freedom of symptoms was defined as the patient reporting complete sort throat relief and no throat soreness

The analyses for the number of patients who were symptom free at the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3 for the Full Analysis Set are presented in Table 14.2.24 and summarised in Table 11.4.14.

Table 11.4.14. Number (%) of patients who were symptom free at the end of Day 1, at 24 hours post first dose and at the ends of Day 2 and 3 – Full analysis set

	Strepsils Original	Placebo	Treatment p-value[a]
End of day 1	0/147 (0%)	0/152 (0%)	-
24 hours post first dose	1/149 (0.7%)	0/151 (0%)	-
End of day 2	5/147 (3.4%)	1/150 (0.7%)	0.12
End of day 3	19/148 (12.8%)	3/150 (2.0%)	0.0007

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

Source: Tables 14.2.24

Freedom of symptoms was defined as the patient reporting complete sore throat relief and no throat soreness

No patients reported freedom of symptoms by the end of day 1 and only one patient (in the Strepsils Original group) reported freedom of symptoms by 24 hours post first dose. By the end of day 2, six patients were symptom free, five in the Strepsils Original group and one in the placebo group. At the end of day 3, 19/148 (13%) patients in the Strepsils Original group and 3/150 (2%) in the placebo group were symptom free. At this assessment the difference between treatment groups in the logistic regression model was statistically significant (p = 0.0007); the terms for centre (p=0.02) and baseline throat soreness severity (p=0.03) were also statistically significant.

The time taken for patients to be free of symptoms for the first time

The analyses for the time taken for patients to be free symptoms for first time for the Full Analysis Set are presented in Table 14.2.25.

In total, 21/155 (14%) became symptom free in the Strepsils Original group compared to 3/155 (2%) in the placebo group. The terms for treatment (p=0.0008) and baseline sore throat severity (p=0.02) were statistically significant in the Cox model. The factor for centre was not statistically significant (p=0.08). The hazard ratio from the Cox model was 7.89 (95% CI 2.35, 26.52) indicating the superiority of Strepsils Original.

Overall Lozenge Consumption as recorded in the patient diary up to the end of Day 3

The analysis for the overall lozenge consumption as recorded in the patient diary up to the end of Day 3 for the Full Analysis Set is presented in Table 14.2.26 and summarised in Table 11.4.15.

Table 11.4.15 Overall lozenge consumption as recorded in the patient diary up to the end of Day 3 – Full analysis set

	Strepsils Original		Placebo
N	150		153
Mean (sd)	11.39 (5.58)		12.58 (6.13)
LS mean[a]	11.73		12.91
Difference between LS means[b]		-1.18	
SE		0.67	
95% CI		-2.50, 0.14	
p-value for treatment[a]		0.08	

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b Strepsils Original minus placebo. A negative difference favours Strepsils Original

Source: Tables 14.2.26

Excludes the seven patients who failed to return their patient diaries

Seven patients (five in the Strepsils Original group and two in the placebo group) failed to return their diaries so were omitted from this analysis. The LS mean overall lozenge consumption up to the end of Day 3 estimated from the ANCOVA model was 11.73 for Strepsils Original compared to 12.91 for placebo; this difference did not achieve statistical significance (p=0.08). The terms for centre (p=0.18) and baseline throat soreness severity (p=0.46) were also not statistically significant for this variable.

Overall Rescue Medication (paracetamol) consumption as recorded in the patient diary during the first 24 hours post initial dose and up to the end of Day 3.

The analyses for the overall rescue medication (paracetamol) consumption as recorded in the patient diary during the first 24 hours post initial dose and up to the end of Day 3 for the Full Analysis Set are presented in Table 14.2.27 and summarised in Table 11.4.16.

Table 11.4.16 Overall rescue medication (paracetamol) consumption as recorded in the patient diary – Full analysis set

	Strepsils Original		Placebo
DURING FIRST 24 HOURS POST INITIAL DOSE			
N	150		153
Mean (sd)	2.16 (2.81)		2.58 (3.04)
LS mean[a]	2.31		2.71
Difference between LS means[b]		-0.39	
Se		0.32	
95% CI		-1.01,0.23	
p-value for treatment[a]		0.21	
UP TO THE END OF DAY 3			
N	150		153
Mean (sd)	4.86 (6.57)		5.44 (6.53)
LS mean[a]	5.17		5.74
Difference between LS means[b]		-0.56	
Se		0.69	
95% CI		-1.92,0.79	
p-value for treatment[a]		0.41	

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b Strepsils Original minus placebo. A negative difference favours Strepsils Original
Source: Tables 14.2.27

Excludes the seven patients who failed to return their patient diaries

An ANCOVA model was fitted on the consumption during the first 24 hours post dose. The terms for baseline throat soreness severity (p=0.0001) and centre (p<0.0001) were statistically significant whereas the term for treatment was not statistically significant (p=0.21). The LS mean rescue medication consumption in the first 24 hours was 2.31 tablets in the Strepsils Original group compared to 2.71 tablets in the placebo group. The statistical conclusions were the same when investigating paracetamol consumption over the whole study; treatment group effect was not statistically significant (p=0.41), whereas centre (p<0.0001) and baseline throat soreness severity (p=0.0002) were highly statistically significant. The LS mean consumptions for paracetmaol usage over the whole study estimated from the ANCOVA were 5.17 for Strepsils Original and 5.74 for placebo.

The proportion of patients that discontinued trial medication due to resolution of sore throat

No patients discontinued trial medication due to resolution of sore throat (Table 14.2.28).

Consumer Questionnaire Responses – Part 1

The results obtained from Part 1 of the consumer questionnaire for the Full Analysis Set are summarised in Table 14.2.29. The questions included in Part 1 related to the relief experienced with the lozenges. Due to the different nature of the questions, some questions are described below and others are summarised in Tables 11.4.17 to

11.4.20. All questions asked on ordinal scales were analysed via ANCOVA with factors for treatment group and centre and a covariate for baseline throat soreness.

At five minutes post-dose, 101/154 (66%) patients in the Strepsils Original group reported relief compared to 23/147 (16%) in the placebo group; this difference was highly statistically significant (Q1; p<0.0001). At two hours, 98/151 (65%) patients in the Strepsils Original group felt better than before they took the lozenge compared to 40/152 (26%) placebo-treated patients (Q2; p<0.0001).

The results for Q3 "How can you describe the type of relief this lozenge gave you?" are summarised in Table 11.4.17.

Table 11.4.17 Results from the Consumer Questionnaire Q 3: How can you Describe the Type of Relief this Lozenge Gave You? – Full Analysis Set

	Strepsils Original N=155	Placebo N=155
Soothing Relief	97 (63%)	42 (27%)
Soreness Relief	63 (41%)	19 (12%)
Coating Relief	48 (31%)	24 (15%)
Pain Relief	47 (30%)	6 (4%)
Relief from Burning	22 (14%)	8 (5%)
No Relief	17 (11%)	80 (52%)
Relief from Swelling	11 (7%)	1 (1%)

Source Table 14.2.29

The most popular terms for describing the type of relief obtained with the Strepsils Original Lozenge were soothing relief, soreness relief and coating relief. More patients in the Strepsils Original Lozenge group selected these three types of relief than those on placebo. When asked (Q13) the majority of patients in the study 228/308 (74%) rated soothing action as being very or extremely important to them.

Table 11.4.18 Results from the Consumer Questionnaire Q 4-7: Proportion of Patients Very Satisfied and Quite Satisfied – Full Analysis Set

Consumer Questionnaire Question	Proportion of Patient n (%) Very Satisfied / Quite Satisfied	
	Strepsils Original	Placebo
Overall, how satisfied are you with the speed with which the lozenge began to give you any relief?	96/154 (62%)	21/154 (14%)
Overall, how satisfied are you with any soothing relief that the lozenge gave you?	92/154 (60%)	26/154 (17%)
Overall, how satisfied are you with the length of time of pain relief that the lozenge gave you?	62/154 (40%)	17/154 (11%)
Overall, how satisfied are you with the strength of pain relief with which the lozenge began to give you relief?	69/153 (45%)	16/154 (10%)

Source Table 14.2.29 *Questions answered on 5 point rating scale where 1 = Very satisfied, 2 = Quite satisfied, 3 = Average, 4 = Not very satisfied, 5 = Not at all satisfied*

For all four parameters, patients in the Strepsils Original group were more satisfied with the relief they obtained than those in the placebo group. In each case the difference in satisfaction rating was highly statistically significant ($p<0.0001$).

Table 11.4.19 Results from the Consumer Questionnaire Q 9-12, Q15: 10 point ordinal scale Questions – Full Analysis Set

	n	Mean (sd)	LS mean[a]	Difference between LS means[b]	se	95% CI	p-value for treatment[a]
How deep down within the throat was the relief felt? (Measured on 10 point scale 1= not at all deep, 10 = very deep in the throat)							
Strepsils Original	153	5.03 (2.09)	5.00	2.17	0.24	1.70,2.64	<0.0001
Placebo	154	2.86 (2.10)	2.83				
How deep down within the throat do you think this lozenge coats the throat? (Measured on 10 point scale 1= not at all deep, 10 = very deep in the throat)							
Strepsils Original	153	5.01 (2.12)	4.89	2.29	0.24	1.83,2.76	<0.0001
Placebo	154	2.71 (2.02)	2.60				
Please tell us your overall opinion of how moisturising/lubricating this lozenge is (Measured on 10 point scale 1= not moisturising/lubricating at all, 10 = very moisturising/lubricating)							
Strepsils Original	153	5.41 (2.10)	5.53	1.85	0.27	1.32,2.38	<0.0001
Placebo	154	3.56 (2.59)	3.68				
How soothing do you think this lozenge is? (Measured on 10 point scale 1= not at all soothing, 10 = very soothing)							
Strepsils Original	153	5.56 (1.99)	5.74	2.24	0.25	1.74,2.74	<0.0001
Placebo	154	3.32 (2.46)	3.49				
How much do you think this lozenge coats the throat? (Measured on 10 point scale 1= not at all coating, 10 = very coating)							
Strepsils Original	154	5.13 (1.97)	5.03	2.26	0.23	1.81,2.71	<0.0001
Placebo	154	2.86 (2.03)	2.77				

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 Strepsils Original minus placebo.

Source: Tables 14.2.29

Scores for Strepsils Original lozenge were consistently higher than those obtained for the placebo lozenge. Strepsils Original lozenges were considered to provide relief deeper within the throat and be more moisturising/lubricating, soothing and coating than the placebo lozenges. All differences were highly statistically significant ($p<0.0001$).

Table 11.4.20 Results from the Consumer Questionnaire Q16: 5 point ordinal scale Question – Full Analysis Set

	n	Mean (sd)	LS mean[a]	Difference between LS means[b]	se	95% CI	p-value for treatment[a]
Please tell us your overall opinion of the lozenge in terms of each attribute: Speed of Action (1= very fast acting, 5 = very slow acting)							
Strepsils Original	153	2.72 (1.15)	2.64	-0.91	0.15	-1.20,-0.62	<0.0001
Placebo	152	3.64 (1.45)	3.56				
Please tell us your overall opinion of the lozenge in terms of each attribute: Soothing Action (1= not very soothing, 5 = very soothing)							
Strepsils Original	154	3.43 (1.01)	3.56	1.18	0.13	0.92,1.45	<0.0001
Placebo	151	2.25 (1.35)	2.38				
Please tell us your overall opinion of the lozenge in terms of each attribute: Duration of Action (1= not very long lasting, 5 = very long lasting)							
Strepsils Original	154	2.84 (1.09)	2.89	0.73	0.14	0.46,1.00	<0.0001
Placebo	151	2.11 (1.28)	2.16				
Please tell us your overall opinion of the lozenge in terms of each attribute: Strength (1= not very strong, 5 = very strong)							
Strepsils Original	154	3.07 (1.12)	3.00	1.24	0.13	0.99,1.49	<0.0001
Placebo	153	1.83 (1.12)	1.76				

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 Strepsils Original minus placebo.
Source: Tables 14.2.29

All four attributes were highly statistically significantly in favour of Strepsils Original ($p<0.0001$) with Strepsils Original considered to be faster and longer acting, more soothing and stronger than placebo lozenges.

Consumer Questionnaire Responses – Part 2

The analyses for the change from pre-dose to the end of Day 3 in the functional impairment scale for each separate component and overall total score for the Full Analysis Set are presented in Table 14.2.30 and summarised in Table 11.4.21.

Table 11.4.21 Change from pre-dose to the end of Day 3 in the functional impairment scale (each component and overall total score) – Full Analysis Set

	n	Mean (sd)	LS mean[a]	Difference between LS means[b]	se	95% CI	p-value for treatment[a]
EATING A MEAL							
Strepsils Original	145	-1.92 (2.76)	-2.12	-0.86	0.30	-1.45,-0.26	0.005
Placebo	151	-1.28 (2.95)	-1.26				
DRIVING A CAR							
Strepsils Original	138	-0.18 (1.65)	-0.26	-0.06	0.17	-0.41,0.28	0.71
Placebo	146	-0.21 (1.89)	-0.20				
SLEEPING							
Strepsils Original	144	-1.53 (2.50)	-1.67	-0.24	0.30	-0.82,0.34	0.42
Placebo	151	-1.23 (3.50)	-1.43				
READING							
Strepsils Original	144	-0.29 (1.97)	-0.55	-0.16	0.21	-0.57,0.25	0.44
Placebo	150	-0.51 (2.35)	-0.39				
WORKING							
Strepsils Original	144	-0.85 (2.89)	-1.12	-0.26	0.30	-0.86,0.33	0.38
Placebo	150	-0.90 (3.05)	-0.86				
TALKING							
Strepsils Original	145	-2.11 (2.86)	-2.39	-1.00	0.31	-1.61,-0.39	0.002
Placebo	151	-1.35 (2.88)	-1.39				
SWALLOWING							
Strepsils Original	145	-2.52 (3.06)	-2.84	-1.11	0.32	-1.75,-0.47	0.0007
Placebo	151	-1.66 (2.87)	-1.73				
CONCENTRATING							
Strepsils Original	145	-0.87 (2.38)	-0.90	-0.30	0.27	-0.82,0.23	0.27
Placebo	151	-0.77 (2.79)	-0.60				
TOTAL OF ALL EIGHT RESPONSES							
Strepsils Original	145	-10.3 (14.6)	-11.9	-3.9	1.7	-7.3,-0.5	0.03
Placebo	151	-7.9 (17.3)	-8.0				

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 Strepsils Original minus placebo. A negative difference favours Strepsils Original

Source: Tables 14.2.30

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

LS mean reductions for all eight activities favoured Strepsils Original with statistically significant differences for the three areas most impaired by sore throat at baseline; swallowing (p=0.0007), eating a meal (p=0.005), and talking (p=0.002), and the total score summing up all eight responses (p=0.03).

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; the AUC for the change from baseline in throat soreness and AUC for pain relief with the Shapiro-Wilk tests being statistically significant for both treatment groups. However on inspection of the residual plots, there appeared to be no gross outliers. Given the very clear superiority of Strepsils Original over placebo, it was decided to appeal to the robustness of the F-test rather than perform additional non-parametric analyses.

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

11.4.2.1 Adjustments for Covariates

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

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

In general, the terms for centre and baseline scores were statistically significant in the statistical models. Patients with more severe symptoms had a greater scope for improvement and therefore mean reductions tended to be greater.

11.4.2.2 Handling of Dropouts or Missing Data

One patient who withdrew prior to the two-hour assessment had their last recorded post-baseline score carried forward to two hours for all three AUC analyses.

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

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 ANCOVA and Cox regression models included centre as a factor. Centres 02 and 06 who recruited less than eight patients were pooled for any formal statistical

analysis model that involved centre as a factor. There was a statistically significant treatment-by-centre interaction for the primary endpoint, see Section 11.4.2.8 for a detailed discussion.

11.4.2.5 Multiple Comparison/Multiplicity

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

11.4.2.6 Use of an "Efficacy Subset" of Patients

The use of the Per Protocol (PP) population (defined in Section 11.1) was restricted to the primary efficacy endpoint (the mean change from baseline in severity of throat soreness (using the 11 point Throat Soreness Scale)), the AUC for the change from baseline up to two hours post first dose in throat soreness and AUC for pain relief. Sixty patients were excluded from the PP set but the statistical conclusions drawn from this subset were qualitatively identical to those 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 and Other Exploratory Analyses

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 ($\leq$7, >7), age at study entry ($\leq$35, >35), gender, total score from tonsillopharyngitis assessment at baseline ($\leq$8, >8), functional impairment score at baseline ($\leq$30, >30) and baseline VAS for difficulty in swallowing ($\leq$65, >65 mm).

The treatment by centre subgroup analysis for the primary endpoint is presented in Table 14.2.31 and summarised in Table 11.4.22. There was a statistically significant treatment-by-centre interaction ($p<0.0001$) for the primary endpoint. The greatest influence on this significant interaction term probably comes from Sites 05 and 08, large recruiters with large mean differences and Sites 03 and 07 large recruiters with only intermediate mean differences. These four sites account for over 80% of the patient population but show markedly different trends. Although both trends favour Strepsils Original, the magnitude of the difference between the LS means vary. This interaction is therefore primarily quantitative not qualitative and is not considered a great concern. The highest recruiting site was centre 03 which had 83 patients in the ANCOVA model, although differences favoured Strepsils Original, the difference was not statistically significant ($p=0.50$). Centre 03 differed from the other centres in that it recruited a large number of patients not registered with the GP, these were mainly

students who were younger with less medical history and ongoing concomitant medication than the patient populations at the other sites.

Table 11.4.22 Primary Efficacy Endpoint - Change from baseline in severity of throat soreness at two hours post first dose by centre – Full analysis set

Centre	Strepsils Original LS mean (N)	Placebo LS mean (N)	Difference between LS means[b] (95% CI)	p-value for treatment[a]
01	-1.59 (19)	-0.69 (20)	-0.90 (-1.91, 0.12)	0.08
03	-1.34 (42)	-1.10 (41)	-0.24 (-0.94, 0.46)	0.50
04	-1.41 (7)	-1.44 (6)	0.03 (-1.74, 1.80)	0.97
05	-3.08 (33)	-0.99 (35)	-2.09 (-2.86, -1.32)	<0.0001
07	-0.89 (26)	-0.62 (25)	-0.27 (-1.16, 0.62)	0.55
08	-3.88 (24)	-0.51 (24)	-3.37 (-4.29, -2.45)	<0.0001
02/06 combined	-1.07 (2)	-1.57 (3)	0.50 (-2.41, 3.41)	0.73

a Estimated from ANCOVA model with factors for treatment, centre and treatment-by-centre interaction and a covariate for baseline throat soreness

b Strepsils Original minus placebo. A negative difference favours Strepsils Original

Source: Tables 14.2.31

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

Treatment by baseline throat soreness severity subgroup analysis for the primary endpoint is presented in Table 14.2.32. There was a statistically significant treatment-by-baseline throat soreness severity interaction (p=0.015). This interaction was quantitative rather than qualitative in nature i.e. treatment group differences highly favoured Strepsils Original in both subgroups but the magnitudes of the treatment differences were substantially different. For those patients with throat soreness ≤7, the treatment group LS mean reductions in the primary measure were –1.71 (Strepsils Original) and –0.88 (placebo), a mean difference of –0.83 (p=0.0009). Those with higher baseline scores had more scope for improvement so LS mean reductions were much larger for active group i.e. –2.66 (Strepsils Original) and –0.86 (placebo), a mean difference of –1.80 (p<0.0001; Table 14.2.32).

Treatment by baseline age subgroup analysis for the primary endpoint is presented in Table 14.2.33. There was a statistically significant treatment-by-age group interaction (p=0.03). As for baseline throat soreness this interaction was quantitative rather than qualitative in nature. For those patients whose age was 35 years or under at screening, the treatment group LS mean reductions in the primary measure were –1.87 (Strepsils Original) and –1.07 (placebo), a mean difference of –0.80 (p=0.003). For those patients aged greater than 35 years the LS mean reductions were much larger for active group i.e. –2.25 (Strepsils Original) and –0.59 (placebo), a mean difference of –1.66 (p<0.0001).

The remaining subgroup analyses are presented in Tables 14.2.34 to 14.2.37. The treatment-by-subgroup interaction terms for gender (p=0.21), total score from tonsillopharyngitis assessment at baseline (p=0.46), functional impairment score at

baseline (p=0.32) and baseline VAS for difficulty in swallowing (p=0.22) were not statistically significant.

An alternative definition of being symptom free was explored where it was defined as a sore throat score of either 0 or 1. The rationale for the alternative definition was that sore throat relief is not a symptom of a sore throat and the primary measure of interest was throat soreness and that a score of 1 was not considered high enough to warrant self-medication. This endpoint was considered to be more sensitive to being able to detect treatment group differences earlier. Using this alternative definition and fitting a logistic regression model, statistically significantly more Strepsils Original-treated patients were symptom free versus placebo at the end of days 2 and 3 (p=0.004 and p<0.0001 respectively) as detailed in Table 11.4.23. The term for centre was also statistically significant at these two assessments. Further information is given in Table 14.2.38.

Table 11.4.23 Number (%) of patients who were symptom free (alternative definition) at the end of Day 1, at 24 hours post first dose and at the ends of Day 2 and 3 – Full analysis set

	Strepsils Original	Placebo	Treatment p-value[a]
End of day 1	3/148 (2%)	2/152 (1%)	0.66
24 hours post first dose	12/149 (8%)	5/151 (3%)	0.08
End of day 2	24/147 (16%)	9/152 (6%)	0.004
End of day 3	52/148 (35%)	15/150 (10%)	<0.0001

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

Source: Tables 14.2.38

Freedom of symptoms was defined as the patient reporting a throat soreness score of either 0 or 1

Table 14.2.39 presents details of the analysis relating to the time taken for patients to be free from symptoms for the first time using the alternative definition as detailed above. In total, 57/155 (37%) became symptom free in the Strepsils Original group compared to 17/155 (11%) in the placebo group. The terms for treatment (p<0.0001), centre (p=0.03) and baseline sore throat severity (p=0.006) were all statistically significant in the Cox model. The hazard ratio from the Cox model was 4.32 (95% CI 2.50, 7.47).

Table 14.2.40 shows details of the analysis of time to first reporting "mild pain relief". In total, 125/155 (81%) reported mild pain relief in the Strepsils Original group compared to 63/155 (41%) in the placebo group. The Kaplan-Meier median time to reporting mild pain relief in the Strepsils group was 10 minutes (95% CI 10, 15 minutes) the equivalent median value for the placebo group was non-estimable but was in excess of 3600 minutes. The terms for treatment (p<0.0001) and baseline sore throat severity (p=0.009) in the Cox regression analysis were statistically significant. The hazard ratio from the Cox model was 3.57 (95% CI 2.59, 4.93).

11.4.3 Tabulation of Individual Response Data

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

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

11.4.4 Drug Dose, Drug Concentration and Relationships to Response

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

11.4.5 Drug-Drug and Drug-Disease Interactions

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

11.4.6 By-patient Displays

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

11.4.7 Efficacy Conclusions

The superiority of Strepsils Original over placebo 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 and overall treatment rating. The results were robust with identical conclusions drawn from the equivalent per-protocol analyses.

For the primary efficacy endpoint, the change from baseline to two hours post first dose in throat soreness (using the 11-point Throat Soreness Scale), LS mean reductions of –2.06 and –0.85 were obtained for Strepsils Original and placebo respectively.

Pain relief was evident by 5 minutes and lasted for at least 2 hours with the Strepsils Original Lozenges. Throat soreness, pain relief and difficulty in swallowing all implied that peak effect was 75 minutes after initial dosing.

The pain relief element of the consumer questionnaire completed after the first dose supported the findings of the subjective rating scales, at five minutes post-dose, 101/154 (66%) patients in the Strepsils Original group reported relief from the moment they swallowed compared to 23/147 (16%) in the placebo group, this difference was highly statistically significant ($p<0.0001$). There were differences highly in favour of Strepsils Original for the patients' opinion on pain relief, what the relief felt like (e.g. soothing, coating, site of action of the lozenge within the mouth,

how fast acting the product was, duration of action, how satisfied the patient was with the pain relief attained).

Changes in sore throat severity, difficulty in swallowing and sore throat relief were also highly statistically significant in favour of Strepsils Original at the end of day 1, 24 hours post initial dose, at the end of day 2 and the end of day 3. Differences between Strepsils Original and placebo gradually increased over the three day study period for all parameters measured.

For the functional element of the consumer questionnaire statistically significant differences in favour of Strepsils Original were obtained for the three areas most impaired by sore throat at baseline; swallowing (p=0.0007), eating a meal (p=0.005), and talking (p=0.002).

The number of patients achieving freedom of symptoms (defined as the patient reporting complete sore throat relief and no throat soreness) was low. However the difference between treatment groups was highly statistically significant with more patients in the Strepsils Original group (13%) being symptom free compared to placebo (2%) by the end of Day 3.

12 SAFETY EVALUATION

All patients who took at least one dose of study medication were included in the analysis of safety. The safety set was analysed as treated.

12.1 Extent of Exposure

Lozenge consumption data is presented in Table 14.3.1 and summarised in Tables 12.1.1 and 12.1.2.

All 310 patients randomised to study medication received at least one dose of study medication with 155 patients receiving Strepsils Original and the same number receiving placebo. Seven patients (five in the Strepsils Original Group and two in the placebo) failed to return their patient diaries and apart from their initial dose within the clinic, no other dosing information was available. These patients have been omitted from Tables 12.1.1 and 12.1.2. Over the whole study, the mean number of lozenges taken was 11.8 for the Strepsils Original group (maximum taken 38) and 13.2 for the placebo group (maximum taken 42). Mean number of days of exposure was 2.68 and 2.88 days for the Strepsils Original and placebo groups respectively.

Table 12.1.1 Extent of exposure, Mean Number of Lozenges Taken on Each Study Day – Safety set

Variable	Strepsils Original		Placebo		Overall	
Number of lozenges taken	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
Day 1	4.39 (1.71)	150	4.08 (1.80)	153	4.24 (1.76)	303
Day 2	4.38 (2.70)	149	4.98 (2.81)	153	4.68 (2.77)	302
Day 3	2.69 (2.78)	148	3.56 (2.76)	151	3.13 (2.80)	299
Day 4	2.64 (1.87)	22	3.04 (2.21)	27	2.86 (2.05)	49
Day 5	5.00 (5.66)	2	1.75 (0.96)	4	2.83 (3.13)	6
Whole Study	11.8 (6.1)	150	13.2 (6.8)	153	12.5 (6.5)	303
Up to the end of Day 3	11.4 (5.6)	150	12.6 (6.1)	153	12.0 (5.9)	303

Source: Table 14.3.1

Excludes the seven patients who failed to return their patient diaries

Table 12.1.2 Extent of exposure, Number of Days Exposure to Study Medication – Safety set

Variable	Strepsils Original	Placebo	Overall
N	150	153	303
Mean (SD)	2.68 (0.89)	2.88 (0.87)	2.78 (0.89)
Median	3.00	3.00	3.00

Source: Table 14.3.1

Excludes the seven patients who failed to return their patient diaries

12.2 Adverse Events (AEs)

All treatment emergent AEs are listed by patient in Appendix 16.2, Listings 16.2.7.1 and 16.2.7.2, giving both preferred terms according to MedDRA (Version 11.0) and the original term used by the investigator.

12.2.1 Brief Summary of Events

Adverse event data are presented in Tables 14.3.2 – 14.3.5 and summarised here. The same number of patients within each treatment group, 25/155 (16%) reported at least one treatment emergent AE (Table 14.3.2). A total of 43 events were reported in the Strepsils Original group and 41 events in the placebo group. There was one SAE during the study but this was considered to have no relationship to the study medication and was not classified as being treatment emergent, further details of this SAE is given in Section 12.3. The majority of AEs were mild with only five treatment emergent events classified as severe. Most AEs were events related to the patients' upper respiratory tract infection such as headache, cough, chills, and pyrexia.

12.2.2 Display of Adverse Events

Table 14.3.3 presents a summary of treatment emergent AEs by primary system organ class. The most common classes for events reported were nervous system disorders with 29 reports (17 in the Strepsils Original group and 12 in the placebo group) and respiratory, thoracic and mediastinal disorders with 21 reports (12 in the Strepsils Original group and 9 in the placebo group). Of the 13 gastrointestinal disorders reported, 10 involved patients in the placebo group.

Table 14.3.4 reports the number of patients reporting each preferred term. By far the most common treatment emergent AE reported was headache with 26 reports during the study; this involved 13 (8%) patients reporting 17 headaches in the Strepsils Original group and 9 (6%) reporting 9 events in the placebo group. There were six separate reports of cough (four in the Strepsils Original group and two in the placebo group).

Table 14.3.5 presents a summary of treatment emergent AEs by primary system organ class, preferred term, severity and relationship to study medication. The data are summarised in Table 12.2.3. The severity of a recurrent AE for any patient was taken to be the most severe and the relationship to therapy as the most probable. The majority of events were mild, only five treatment emergent events were graded as severe: two in the Strepsils Original group namely mouth ulceration (07 – 519) and pharyngolaryngeal pain (07 – 518) and three in the placebo group namely headache (01 – 028), pharyngolaryngeal pain (07 – 520) and toothache (07 – 506).

No events of definite relationship were reported, one event of probable relationship occurred the severe mouth ulceration reported by patient 07 - 519 in the Strepsils Original group. A further five events of possible relationship were reported four in the placebo group (two reports of tongue disorder (01 – 031, 03 – 203), one report of nausea (01 – 031) and one report of tongue ulceration (03 – 224)) and one in the Strepsils group (mouth ulceration (03 – 201)).

One AE (ear pain – 07-492) was reported prior to initial dosing of study medication. A further four events; two in the Strepsils Group (tooth abscess - 01-025 and throat infection – 03-247) and two in the placebo group (exacerbation of sore throat – 04-258 and migraine 07 – 471) were reported during follow-up (between the end of Day 3 and post study follow-up). These events were not considered treatment emergent as defined by the statistical analysis plan (SAP) and are listed separately in Appendix 16.2, Listings 16.2.7.3 to 16.2.7.6.

Table 12.2.3 Severity and relationship of treatment emergent adverse events to therapy

	Strepsils Original (n=155)		Placebo (n=155)	
	Number of patients reporting	Number of reports (% of total)	Number of patients reporting	Number of reports (% of total)
Total	25 (16%)	43	25 (16%)	41
Severity:				
Mild	18 (12%)	35 (81%)	19 (12%)	32 (78%)
Moderate	5 (3%)	6 (14%)	4 (3%)	6 (15%)
Severe	2 (1%)	2 (5%)	3 (2%)	3 (7%)
Relationship:				
Definite	-	-	-	-
Probable	1 (1%)	1 (2%)	-	-
Possible	1 (1%)	1 (2%)	3 (2%)	4 (10%)
Unlikely	10 (6%)	20 (47%)	9 (6%)	11 (27%)
None	14 (9%)	21 (49%)	16 (10%)	26 (63%)

Source: Appendix 16.2. Listings 16.2.7.1 and 16.2.7.2

12.2.3 Analysis of Adverse Events

There was no statistically significant difference between treatment groups in the proportion of patients reporting treatment emergent AEs.

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

One SAE was reported, patient number 03 - 247 reported a throat infection that required hospitalisation. The event, which occurred during the follow-up period and was therefore not classified as treatment emergent, started on study day 5 and lasted three days. The event was graded as severe with no relationship to study medication. The patient received clarithromycin intravenously and recovered without sequalae.

12.3.1 Narratives of Deaths, other Serious Adverse Events and certain other Significant Adverse Events

Patient 03 – 247 a 27 year old male Caucasian was randomised into the study on 8 February 2008 and received Strepsils Original throat lozenges. The patient continued in the study for 3 days taking a total of 6 Strepsils lozenges in this time. On 12 February 2008, 2 days after Study Day 3, the patient was hospitalised with a severe throat infection diagnosed as left sided tonsillitis. The event was due to significant exacerbation of the URTI from which the patient was already suffering. The patient was hospitalised for intravenous antibiotics (clarithromycin) and analgesia. The event was considered to have no relationship to the study medication, the patient was discharged on 15 February 2008 when he was eating and drinking. The patient had previously suffered two non serious AEs on Study Day 2 (9 February 2008); intermittent pyrexia and shivering. The patient was a non smoker who in June 2005 had previously been hospitalised for an episode of "acute tonsillitis". There was

no other relevant medical history and the patient was not taking any concomitant medication.

12.4 Clinical Laboratory Evaluation

No laboratory data was recorded in this study.

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

In total, 11/155 (7%) patients in the placebo group and 9/155 (6%) in the Strepsils Original group reported starting concomitant medication after baseline. Twelve (4%) patients started to use antibacterials for systemic use and 5 (2%) started using analgesics (Table 14.3.6 and Listing 16.2.4.5).

12.6 Safety Conclusions

There were no safety issues within this study.

There was no difference between the treatment groups in relation to the proportion of patients reporting AEs. There were no treatment emergent SAEs. The majority of AEs were mild with only five treatment emergent events classified as severe. Most AEs were events related to the patient's upper respiratory tract infection such as headache, cough, chills, and pyrexia. By far the most common adverse event reported was headache with 13 (8%) patients reporting 17 headaches in the Strepsils Original group and 9 (6%) reporting 9 events in the placebo group.

Five of the six events considered to be possibly or probably related to the lozenges were related to effects in the mouth; mouth ulceration and tongue disorders (wounds on tongue). Two patients in the Strepsils Original group and one patient in the placebo group reported mouth ulcers, possibly or probably related to the lozenges. The reports of tongue disorders (wounds on tongue) were reported in the placebo group.

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

The primary objective of this study was to determine the analgesic properties of Strepsils Original throat lozenges in patients with sore throat due to URTI. The superiority of Strepsils Original over placebo was clearly apparent with highly statistically significant differences for all the analgesic variables related to sore throat relief, throat soreness and difficulty in swallowing. The results were robust with qualitatively identical conclusions drawn from the equivalent per-protocol analyses.

For the primary efficacy endpoint, the change from baseline to two hours post first dose in throat soreness (using the 11-point Throat Soreness Scale), there were LS

mean reductions of –2.06 (Strepsils Original) and –0.85 (placebo). The difference between the LS means for the treatments at 2 hours of -1.21 (95%CI -1.59, -0.82, p<0.0001) was greater than the difference of -0.7 observed in the previous study[2]. While the mean difference in treatment effect in this study (-1.21) was larger than that reported in the previous study (-0.7)[2], given that the earlier study recruited only 50 patients in total, the 95% confidence interval for the underlying mean difference based on the results of the previous study was (-1.5 to 0.2) and hence the current results are not completely unexpected.

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 the difference between Strepsils Original and placebo are therefore clinically meaningful.

Throughout the study the ANCOVA covariates of centre and throat soreness were consistently statistically significant indicating that, as expected from a subjective painful condition, patients from different centres with different baseline characteristics assessed their response to treatment to different degrees. These effects are real effects but do not affect the interpretation of the observed treatment effect. There was a statistically significant treatment-by-centre interaction (p<0.0001) for the primary endpoint in the present study. Although the treatment groups were well balanced for demographic variables overall there were differences across the centres which may have contributed to the different treatment responses observed at the different centres. From the exploratory sub-group analyses there were statistically significant treatment-by-baseline throat soreness severity interaction (p=0.015). This was not unexpected as the greater the initial pain rating the greater potential for change, with small changes at the upper end of the rating scales being more clinically meaningful to patients than changes at the middle and lower end of the rating scale[16]. This is why baseline throat soreness rating was included as a covariate in the ANCOVA. In addition there was a statistically significant treatment-by-age interaction (p=0.03) for the primary endpoint. For those patients aged greater than 35 years the LS mean reductions were much larger for the active group and smaller for the placebo group. Given that centres differed in their mean baseline throat soreness scores and the age of their patients and that these treatment-subgroup interactions were identified, it is probable that these factors contributed to the treatment-by-centre interaction. The treatment-by-centre interaction is primarily quantitative, not qualitative in nature and therefore is not considered a great concern.

Throat soreness, pain relief and difficulty in swallowing single dose data indicated that effects are evident at 5 minutes. Early analgesic effects were further supported by the consumer questionnaire; at five minutes post-dose, 101/154 (66%) patients in the Strepsils Original group reported relief from the moment they swallowed compared to 23/147 (16%) in the placebo group, this difference was highly statistically significant (p<0.0001).

The single dose data all implied that peak effect was 75 minutes after initial dosing. This is reassuring as it indicates that relief provided by the Strepsils Original lozenges is not confined to the time the lozenge remains in the mouth and relief is felt long after the lozenge is gone. In addition the consumer questionnaire indicated that at two hours, 98/151 (65%) patients in the Strepsils Original group felt better than before they took the lozenge compared to 40/152 (26%) in the placebo group ($p<0.0001$).

Overall the majority of patients 228/308 (74%) rated soothing action as being very or extremely important with the two most popular terms for describing the type of relief obtained with the Strepsils Original Lozenges being soothing relief and soreness relief, selected by 97/155 (63%) and 63/155 (41%) respectively. There were differences highly in favour of Strepsils Original for the patients' opinion on pain relief, what the relief felt like (e.g. soothing, coating, site of action of the lozenge within the mouth, how fast acting the product was, duration of action, how satisfied the patient was with the pain relief attained).

The secondary objective of this study was to determine additional patient/consumer benefits associated with Strepsils Original throat lozenges. These benefits were assessed by measuring freedom from symptoms and also the responses to a consumer questionnaire. The number of patients achieving freedom of symptoms (defined as the patient reporting complete sore throat relief and no throat soreness) were low and fewer than expected. This may be due to the stringent definition of freedom from symptoms but it is also interesting to note that no patient was withdrawn from the study due to resolution of sore throat. This confirms that sore throats due to URTI are a source of considerable discomfort for the affected individuals and last for some time. Although small numbers reported freedom from symptoms, the difference between treatment groups was highly statistically significant with more patients in the Strepsils Original group (13%) being symptom free compared to placebo (2%) by the end of Day 3. The number of patients achieving this objective and the magnitude of the differences over placebo were both greater when the definition of freedom of symptoms was relaxed to include those with a throat soreness score of 1. A statistically significant difference was then also observed at the end of Day 2.

The multiple dose data for changes in sore throat severity, difficulty in swallowing and sore throat relief supported the freedom from symptoms data in that differences over placebo increased over the 3 day study period. At each time point, at the end of day 1, 24 hours post initial dose, at the end of day 2 and the end of day 3 there were highly statistically significant differences in favour of Strepsils Original ($p<0.0001$) with the greatest differences observed at the end of Day 3. This again is reassuring as it indicates that continued use of Strepsils lozenges over a 3 day period benefits patients with treatment differences getting greater and patients becoming symptom free quicker than those on placebo. Combined with the patients satisfaction ratings from the consumer questionnaire it can be concluded that Strepsils Original Lozenges offer effective management of the symptoms of sore throat.

Not unsurprisingly for patients with a sore throat the three functional areas which were considered to be most impaired at baseline were swallowing, eating a meal 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 Strepsils Original obtained for these three areas at the end of the 3 day study period (swallowing (p=0.0007), eating a meal (p=0.005), and talking (p=0.002)).

There were no safety issues highlighted by this study.

There was no difference between the treatment groups in relation to the proportion of patients reporting adverse events. There were no treatment emergent serious adverse events. The majority of adverse events were mild with only five treatment emergent events classified as severe. Most adverse events were events related to the patient's upper respiratory tract infection such as headache, cough, chills, and pyrexia. By far the most common adverse event reported was headache with 13 (8%) patients reporting 17 headaches in the Strepsils Original group and 9 (6%) reporting 9 events in the placebo group.

Five of the six events considered to be possibly or probably related to the lozenges were related to effects in the mouth; mouth ulceration and tongue disorders (wounds on tongue). Two patients in the Strepsils Original group and one patient in the placebo group reported mouth ulcers, possibly or probably related to the lozenges. The reports of tongue disorders (wounds on tongue) were reported in the placebo group. These events are due to the mechanical damage caused when sucking a sugar-based lozenge.

13.2 Conclusion

Strepsils Original Throat Lozenges provide fast, safe and effective relief for sore throats due to upper respiratory tract infections. Following a single dose, relief is evident at 5 minutes post dose and lasts for at least 2 hours with maximal effects at 75 minutes post dose. Patients can feel the lozenge working as soon as they swallow and feel better at 2 hours. Analgesic effects continue over the 3 day study period with additional functional benefits in swallowing, eating and talking evident at 3 days.

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 (4 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)
14.1.5	Screening assessments – Full analysis set (1 page)
14.1.6	Baseline efficacy assessments – Full analysis set (4 pages)
14.1.7	Concomitant medication ongoing at randomisation – Full analysis set (2 pages)
14.2.1.1	Primary efficacy endpoint – change from baseline in severity of throat soreness at two hours post first dose - Full analysis set (2 pages)
14.2.1.2	Primary efficacy endpoint – change from baseline in severity of throat soreness at two hours post first dose – Per-protocol set (2 pages)
14.2.2.1	AUC from baseline to two hours post first dose for the change from baseline in throat soreness - Full analysis set (1 page)
14.2.2.2	AUC from baseline to two hours post first dose for the change from baseline in throat soreness - Per-protocol set (1 page)
14.2.3.1	AUC from baseline to two hours post first dose for sore throat relief (TOTPAR) - Full analysis set (1 page)
14.2.3.2	AUC from baseline to two hours post first dose for sore throat relief (TOTPAR) – Per-protocol set (1 page)
14.2.4	Sore throat relief at 5, 10, 15, 30, 45, 60, 75, 90 and 105 minutes post dose - Full analysis set (9 pages)
14.2.5	Sore throat relief at two hours post first dose - Full analysis set (2 pages)
14.2.6	Sore throat relief at the end of Day 1 - Full analysis set (2 pages)
14.2.7	Sore throat relief at 24 hours post first dose - Full analysis set (2 pages)
14.2.8	Sore throat relief at the end of Day 2 - Full analysis set (2 pages)
14.2.9	Sore throat relief at the end of Day 3 - Full analysis set (2 pages)
14.2.10	Onset of analgesia – time to first reporting "moderate pain relief" - Full analysis set (2 pages)
14.2.11	Change from baseline in throat soreness at 5, 10, 15, 30, 45, 60, 75, 90 and 105 minutes post dose - Full analysis set (9 pages)
14.2.12	Change from baseline in the severity of throat soreness at the end of Day 1 - Full analysis set (2 pages)

Table number	Table Title
14.2.13	Change from baseline in the severity of throat soreness at 24 hours post first dose - Full analysis set (2 pages)
14.2.14	Change from baseline in the severity of throat soreness at the end of Day 2 - Full analysis set (2 pages)
14.2.15	Change from baseline in the severity of throat soreness at the end of Day 3 - Full analysis set (2 pages)
14.2.16	Change from baseline in difficulty in swallowing at 5, 10, 15, 30, 45, 60, 75, 90 and 105 minutes post dose - Full analysis set (9 pages)
14.2.17	Change from baseline in difficulty in swallowing at two hours post dose - Full analysis set (2 pages)
14.2.18	AUC from baseline to two hours for the change from baseline in difficulty in swallowing - Full analysis set (1 page)
14.2.19	Change from baseline in difficulty in swallowing at the end of Day 1 - Full analysis set (2 pages)
14.2.20	Change from baseline in difficulty in swallowing at 24 hours post first dose - Full analysis set (2 pages)
14.2.21	Change from baseline in the difficulty in swallowing at the end of Day 2 - Full analysis set (2 pages)
14.2.22	Change from baseline in difficulty in swallowing at the end of Day 3 - Full analysis set (2 pages)
14.2.23	Overall treatment rating at two hours and at the end of Day 3 - Full analysis set (4 pages)
14.2.24	Whether the patient was symptom free at the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3 - Full analysis set (4 pages)
14.2.25	The time taken for patients to be free from symptoms for the first time - Full analysis set (1 page)
14.2.26	Overall lozenge consumption as recorded in the patient diary up to the end of Day 3 - Full analysis set (1 page)
14.2.27	Overall rescue medication (paracetamol) consumption as recorded in the patient diary - Full analysis set (2 pages)
14.2.28	Whether patient discontinued trial medication due to resolution of sore throat - Full analysis set (1 page)
14.2.29	Consumer questionnaire - Full analysis set (33 pages)
14.2.30	Change from pre-dose to the end of Day 3 in the functional impairment scale (each component and overall total score) - Full analysis set (18 pages)

Table number	Table Title
14.2.31	Primary efficacy endpoint – change from baseline in severity of throat soreness at two hours post first dose by centre - Full analysis set (11 pages)
14.2.32	Primary efficacy endpoint – change from baseline in severity of throat soreness at two hours post first dose by baseline throat soreness severity - Full analysis set (3 pages)
14.2.33	Primary efficacy endpoint – change from baseline in severity of throat soreness at two hours post first dose by age at study entry - Full analysis set (3 pages)
14.2.34	Primary efficacy endpoint – change from baseline in severity of throat soreness at two hours post first dose by gender - Full analysis set (3 pages)
14.2.35	Primary efficacy endpoint – change from baseline in severity of throat soreness at two hours post first dose by total score from tonsillo-pharyngitis assessment at baseline - Full analysis set (3 pages)
14.2.36	Primary efficacy endpoint - Change from baseline in severity of throat soreness at two hours post first dose by Functional impairment score at baseline - Full analysis set (4 pages)
14.2.37	Primary efficacy endpoint - Change from baseline in severity of throat soreness at two hours post first dose by VAS for difficulty in swallowing at baseline - Full analysis set (4 pages)
14.2.38	Whether the patient was symptom free (alternative definition) at the end of Day 1, at 24 hours post first dose and at the ends of Day 2 and 3 - Full analysis set (4 pages)
14.2.39	Time taken for patients to be free from symptoms (alternative definition) for the first time - Full analysis set (2 pages)
14.2.40	Onset of analgesia (alternative definition) - time to first reporting "mild pain relief" - Full analysis set (2 pages)
14.3 Safety Data	
14.3.1	Extent of exposure to study medication - Safety set (3 pages)
14.3.2	Summary of treatment emergent adverse event reporting – Safety set (1 page)
14.3.3	MedDRA Summary of treatment emergent adverse events by primary system organ class – Safety set (1 page)
14.3.4	MedDRA Summary of treatment emergent adverse events by primary system organ class and preferred term – Safety set (2 pages)
14.3.5	MedDRA Summary of treatment emergent adverse events by primary system organ class, preferred term, severity and relationship to study medication – Safety set (9 pages)
14.3.6	Concomitant medication commencing during the study – Safety set (1 page)

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