1 STUDY REPORT TITLE PAGE

EudraCT Number:	2008-005059-67
Study Number:	TH0809
Protocol Title:	A multi-centre, randomised, double blind, placebo-controlled, parallel group, single dose, pilot study of the efficacy of 0.6 mg Amylmetacresol BP (AMC) and 1.2 mg 2,4-Dichlorobenzyl alcohol (DCBA) throat lozenges in the relief of sore throat due to upper respiratory tract infection.
Study Phase:	III
Date First Subject Enrolled:	10 December 2008
Date Last Subject Completed:	04 March 2009
Report Date:	26 August 2009
Co-ordinating Investigator:	Dr D McNally, Ormeau Health Centre, 120 Ormeau Road, Belfast, BT7 2EB.
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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2 SYNOPSIS

<table>
<tr><td>Name of Sponsor/ Company:</td><td>Individual Trial Table Referring to Part of the Dossier</td><td rowspan="3">(For National Authority use only)</td></tr>
<tr><td>Name of Finished Product:</td><td>Volume:</td></tr>
<tr><td>Name of Active Ingredient(s):</td><td>Page:</td></tr>
<tr><td colspan="3">Title of Trial: A multi-centre, randomised, double blind, placebo controlled, parallel group, single dose, pilot study of the efficacy of 0.6 mg Amylmetacresol BP (AMC) and 1.2 mg 2,4-Dichlorobenzyl alcohol (DCBA) throat lozenges in the relief of sore throat due to upper respiratory tract infection.</td></tr>
<tr><td colspan="3">Co-ordinating Investigator: Dr D McNally, Ormeau Health Centre, 120 Ormeau Road, Belfast, BT7 2EB.</td></tr>
<tr><td colspan="3">Trial Centre(s): 5 primary care investigation centres in Northern Ireland</td></tr>
<tr><td colspan="3">Publication (reference): None</td></tr>
<tr><td colspan="2">Studied Period: 12 weeks
Date first subject enrolled: 10 December 2008
Date last subject completed: 04 March 2009</td><td>Phase of Development: III</td></tr>
<tr><td colspan="3">Objectives: The primary objective was to determine the analgesic properties of 0.6 mg AMC only and 1.2 mg DCBA only throat lozenges in patients with sore throat due to upper respiratory tract infection. In addition to the analgesic endpoints, functional measures of difficulty in swallowing and throat numbness were assessed. The secondary objective was to determine additional patient/consumer benefits associated with 0.6 mg AMC only throat lozenges and 1.2 mg DCBA only throat lozenges.</td></tr>
<tr><td colspan="3">Methodology: Patients were recruited to the study centres via advertising, referral from community pharmacies and direct attendance of patients seeking sore throat remedies at the study centres. Patients deemed eligible according to a pre-screening checklist attended one of the five study centres for a screening visit, at which they gave written consent before any study-specific procedures were undertaken. Details of the patients' demographics, concomitant medication and medical history were documented. Patients were instructed to complete the Throat Soreness Scale and those with a sufficiently sore throat underwent the Tonsillo-Pharyngitis Assessment to confirm eligibility in terms of sore throat symptoms. Patients deemed eligible according to the "Diagnosis and main criteria for inclusion" section below were randomised to one of the three treatment regimens (two test and one reference) described below. If necessary, patients underwent a washout period before randomisation. Efficacy was assessed at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post-dose using subjective rating scales for throat soreness, sore throat pain relief, difficulty in swallowing and throat numbness as detailed in the "Criteria for evaluation" section below. Patients were required to complete a consumer questionnaire, the first question of which was completed five minutes after dosing and the remainder after the two-hour assessment period. Patients were then discharged with a diary in which they were to record symptoms occurring from discharge until 24 hours after dosing. The diary was returned at the follow-up visit, one to three days after dosing.</td></tr>
<tr><td colspan="3">Number of Subjects: Planned: 150
Analysed: 150 (safety); 150 (full analysis set); 145 (per protocol)</td></tr>
<tr><td colspan="3">Diagnosis and Main Criteria for Inclusion: Male and female patients aged ≥ 18 ≤ 75 years with a sore throat associated with an upper respiratory tract infection of ≤ four days duration. It was required that the sore throat be confirmed by a score ≥ 5 on the Tonsillo-Pharyngitis Assessment and a score ≥ 6 on the 0-10 Throat Soreness Scale. Patients were excluded from randomisation if they had taken sore throat remedies, medicated confectionary, analgesics, antipyretics or "cold" remedies for the times specified by the protocol before enrolment.</td></tr>
<tr><td colspan="3">Test Product: Test 1: One AMC throat lozenge containing 0.6 mg AMC (FR 0172021)</td></tr>
</table>

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Test 2: One DCBA throat lozenge containing 1.2 mg DCBA (FR 0178114)

Duration of Treatment: Single dose (one throat lozenge sucked until completely dissolved)

Reference Therapy: One non-medicated sugar-based placebo throat lozenge (FR 0125022)

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the area under the curve (AUC) for the change from baseline in throat soreness from baseline to two hours post-dose, assessed using the 11-point ordinal Throat Soreness Scale where '0= not sore' and '10= very sore'.

The secondary endpoints were: Change from baseline in throat soreness at each timepoint; AUC for pain relief from baseline to two hours post-dose, assessed using a 7-point scale: 'no relief', 'slight relief', 'mild relief', 'moderate relief', 'considerable relief', 'almost complete relief' and 'complete relief'; sore throat relief at each timepoint; AUC for difficulty in swallowing from baseline to two hours, assessed using a 100 mm Visual Analogue Scale (VAS) with endpoints of "Not difficult" and "Very difficult" at each end; change from baseline in difficulty in swallowing at each timepoint; AUC for throat numbness from five minutes to two hours, assessed using a 5-point scale: 'none', 'mild', 'moderate', 'considerable' and 'complete'; throat numbness at each timepoint; onset of analgesia defined as time to first reporting 'moderate pain relief'; overall treatment rating at two hours, assessed using an 11-point ordinal scale from 0 (indicating poor) to 10 (indicating excellent) and responses to a consumer questionnaire relating to acceptability of the product, perceived efficacy, characterization of the relief and patient satisfaction.

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

Statistical Methods: All statistical tests performed were 2-tailed with significance determined by reference to the 5% significance level, unless otherwise stated. The null hypothesis at all times was the equality of the treatments being compared. All comparisons between the treatments were reported with 95% confidence intervals for the difference. Normality assumptions were evaluated by an examination of the residual plots and the Shapiro-Wilk test of normality. All tabulations involving change from baseline data only included patients with cohort data i.e. with data at baseline and at follow-up.

The primary efficacy endpoint was analysed by analysis of covariance (ANCOVA) with baseline throat soreness as a covariate and factors for treatment group and centre. Treatment group differences were estimated using the mean square error from the ANCOVA and using Fisher's protected LSD method i.e. if the overall treatment effect in the ANCOVA model was significant at the 5% level, comparison of the 0.6 mg AMC only and 1.2 mg DCBA only groups versus the placebo group were performed without any requirement to adjust the significance level for the pairwise comparisons.

All calculations and figures were produced using SAS Version 9.1 or S-PLUS 6.2. For continuous variables, the mean, median, standard deviation, standard error of the mean, minimum, maximum and lower and upper 95% confidence limits for the mean for the population and for the individual treatment groups were computed. Categorical data were presented in contingency tables with cell frequencies and percentages for the patient population and for the individual treatment groups.

The comparability of treatment groups with respect to patient demographics and baseline characteristics was assessed in a descriptive manner, but no formal statistical testing was performed. Concomitant medications ongoing at randomisation were coded using the ATC level 2 categories from the WHO dictionary Enhanced 3.9 Version. All secondary endpoints and the supportive analyses were considered as descriptive evidence of efficacy and were analysed without any procedures to account for multiple comparisons.

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SUMMARY & CONCLUSIONS

EFFICACY RESULTS: In the ANCOVA model for the full analysis set (n=150) for the primary endpoint (area under the change from baseline curve (AUC) in severity of throat soreness, from baseline to two hours) none of the terms in the model (treatment, centre and baseline throat soreness) was statistically significant. The LS means reductions were -1.05 (0.6 mg AMC throat lozenge), -0.91 (1.2 mg DCBA throat lozenge) and -0.95 (placebo throat lozenge).

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

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

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
FULL ANALYSIS SET			
N	50	49	51
Mean±sd	-1.08±1.02	-0.99±1.18	-1.00±1.23
LS mean[a]	-1.05	-0.91	-0.95
Parameter estimates	LS mean[b]	95% CI	P
0.6mg AMC throat lozenge – Placebo	-0.10	-0.56,0.35	0.66
1.2mg DCBA throat lozenge – Placebo	0.04	-0.42,0.49	0.88
0.6mg AMC throat lozenge – 1.2mg DCBA throat lozenge	-0.14	-0.60,0.32	0.56
PER-PROTOCOL SET			
N	50	46	49
Mean±sd	-1.08±1.02	-0.97±1.21	-1.02±1.25
LS mean[a]	-1.04	-0.86	-0.95
Parameter estimates	LS mean[b]	95% CI	P
0.6mg AMC throat lozenge – Placebo	-0.09	-0.55,0.38	0.72
1.2mg DCBA throat lozenge – Placebo	0.09	-0.39,0.57	0.71
0.6mg AMC throat lozenge – 1.2mg DCBA throat lozenge	-0.17	-0.65,0.30	0.47

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A negative difference favours the first treatment against second treatment
Source: Tables 14.2.1.1 and 14.2.1.2

There was no statistically significant overall difference between treatments for the change from baseline in severity of throat soreness at any timepoint. The maximum decrease in throat soreness occurred at 15 minutes for the 0.6 mg AMC throat lozenge group, 30 minutes for the 1.2 mg DCBA throat lozenge group and two hours for the placebo throat lozenge group.

There was no statistically significant overall difference between treatments for the sore throat relief scores either in terms of AUC for sore throat pain relief over two hours or at each individual timepoint, with the exception of at 10 and 15 minutes post-dose, when significantly more relief was obtained with the 0.6 mg AMC throat lozenge than with the placebo throat lozenge ($p < 0.03$).

Analyses of change from baseline in difficulty in swallowing revealed statistically significant effects for baseline throat soreness and baseline difficulty in swallowing in some cases, but there was no statistically significant overall difference between treatments, either in terms of AUC to two hours or at any individual timepoint. The maximum improvement in swallowing occurred at 15 minutes for the 0.6 mg AMC throat lozenge group, 30 minutes for the 1.2 mg DCBA throat lozenge group and two hours for the placebo throat lozenge group.

For the AUC for throat numbness from five minutes to two hours, there was no statistically significant overall difference between treatments, although this factor was statistically significant and higher throat numbness scores were reported for both active throat lozenges compared with placebo throat lozenge at 5, 10 and 15 minutes post-dose. Maximum numbness was obtained at 15 minutes for the 0.6 mg AMC throat lozenge group, 10 and 30 minutes for the 1.2 mg DCBA throat lozenge group and 30 and 60 minutes for the placebo throat lozenge group.

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There were no statistically significant treatment differences in terms of overall treatment rating.

The overall comparison between treatment groups of time to reporting moderate sore throat pain relief failed to achieve statistical significance (p=0.054), however the pairwise comparison between the 0.6 mg AMC throat lozenge group and the 1.2 mg DCBA throat lozenge group was statistically significant (p=0.02) in favour of the 0.6 mg AMC throat lozenge.

Significantly more patients in the active throat lozenge groups claimed to have felt relief from the moment the throat lozenges were swallowed than in the placebo throat lozenge group (p≤0.003 in each case). The comparison between the two active throat lozenges was not statistically significant.

Patients in the 1.2 mg DCBA throat lozenge group reported that the throat lozenges had acted significantly faster compared with those in the placebo throat lozenge group (p=0.03) when graded on a 5-point scale where 1 = “Very fast acting” and 5 = “Very slow acting”. Both active throat lozenges were thought to have lasted a statistically significantly shorter time in the throat than placebo (p≤0.008). The comparison between the two active throat lozenges was not statistically significant. The numbers of patients who reported duration of action of less than half an hour were as follows: 19 (39%) for the 0.6 mg AMC throat lozenge, 15 (31%) for the 1.2 mg DCBA throat lozenge and nine (18%) for the placebo throat lozenge.

SAFETY RESULTS: Four (8%) patients reported at least one treatment emergent event in the 0.6 mg AMC throat lozenge group compared to two (4%) patients in the 1.2 mg DCBA throat lozenge group and one (2%) patient in the placebo throat lozenge group. A total of five treatment emergent events were reported in each of the two active throat lozenge groups compared to one event in the placebo throat lozenge group. No adverse event was considered serious or graded “definitely”, “probably” or “possibly” related to the study medication, and all were mild in severity. The most common treatment emergent adverse event reported was headache with four reports during the study involving four patients (three in the 0.6 mg AMC throat lozenge group and one in the 1.2 mg DCBA throat lozenge group).

CONCLUSION: In terms of the efficacy assessment subjective rating scales, statistically significant treatment group differences in favour of the 0.6 mg AMC throat lozenge and/or the 1.2 mg DCBA throat lozenge compared with the placebo throat lozenge were observed only at isolated individual timepoints up to 15 minutes post-dose and not in terms of AUC to two hours. Responses to the various consumer questions relating to onset and duration of action indicated a perceived faster action for either one or both active throat lozenges compared with the placebo throat lozenge and a shorter duration of action than the placebo throat lozenge. Failure of both the 0.6 mg AMC and 1.2 mg DCBA throat lozenges to demonstrate a consistent advantage over the placebo throat lozenge suggests their combination is required to achieve the well-established efficacy of Strepsils® throat lozenges.

Date of the report: 26 August 2009

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

3.2 List of Appendices

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16.1 STUDY INFORMATION

16.1.1 Protocol and protocol amendments

16.1.2 Sample case report form (unique pages only)

16.1.3 List of IECs or IRBs

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

16.1.5 Signature of principal or co-ordinating investigator(s)

16.1.6 Listing of subjects receiving test drug(s) from specific batches, where more than one batch was used. All subjects in this study received study medication from one batch, so this appendix is not present.

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

16.1.8 Audit certificates

16.1.9 Documentation of statistical methods

16.1.10 Documentation of inter-laboratory standardisation methods and Quality
assurance procedures if used. Laboratory samples were not collected 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 is appended.

16.2 SUBJECT DATA LISTINGS

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

16.2.2 Protocol Deviations

16.2.3 Subjects Excluded from the Efficacy Analysis

16.2.4 Demographic data

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

16.2.6 Individual efficacy response data.

16.2.7 Adverse event listings (each subject)

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

16.3 CASE REPORT FORMS

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

16.3.2 Other CRFs submitted – no other CRFs are appended

16.4 INDIVIDUAL SUBJECT DATA LISTINGS (US ARCHIVAL LISTINGS). The information required for this Appendix is not applicable for this study. It will be provided as a report addendum if required by a regulatory authority.

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Abbreviation in Full
ABPI	Association of the British Pharmaceutical Industry
AE	Adverse event
AMC	Amylmetacresol BP
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
AR	Adverse reaction
CPM	Clinical Project Manager
CRF	Case report form
CRO	Contract research organisation
CV	Curriculum vitae
DCBA	2,4-Dichlorobenzyl alcohol
EC	Ethics Committee
eCRF	Electronic case report form
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IMSU	Investigational Material Supplies Unit
IRB	Institutional Review Board
ITT	Intent-to-treat
LSD	Least Significant Difference
NHS	National Health Service
NSAID	Non steroidal anti-inflammatory drug
QA	Quality assurance
RB	Reckitt Benckiser Healthcare UK Ltd
SAE	Serious adverse event
SDV	Source data verification
SMO	Site management organisation
SOP	Standard operating procedure

TPA	Tonsillo-Pharyngitis Assessment
UAR	Unexpected adverse reaction
UK	United Kingdom (of Great Britain and Northern Ireland)

5 ETHICS

5.1 Independent Ethics Committee (IEC)

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

The study protocol together with patient information and consent documents were reviewed and approved by the Office for Research Ethics Committees in Northern Ireland (ORECNI) Independent Ethics Committee.

5.2 Ethical Conduct of the Study

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

5.3 Patient Information and Consent

Copies of a representative patient information sheet and a blank consent form are provided in Appendix 16.1.3.

Patients who were considered by the investigator to be suitable for entry into the study were given the opportunity to read the patient 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 before the patient signed 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 principal investigator at each centre is also included in the Appendix.

As study sponsor, Reckitt Benckiser Healthcare UK Ltd (RB) took overall responsibility for the items listed in ICH E6 Section 5. RB delegated various activities to the parties listed below:

- Medevol Ltd (Belfast, Northern Ireland) was the Clinical Research Organisation responsible for centre selection, project management and centre monitoring.

- The Coordinating Investigator also served as Principal Investigator for one of the five centres.
- Worldwide Clinical Trials Ltd (Nottingham, UK) performed data management activities, conducted the statistical analyses and wrote the statistical sections of the study report.
- Clearcut Clinical Consulting (Nottingham, UK) wrote the clinical sections of the study report.

7 INTRODUCTION

The independent blocking effects of Amylmetacresol (AMC) and 2, 4-Dichlorobenzyl alcohol (DCBA) on heterologously expressed voltage-gated neuronal sodium channels have recently been investigated *in-vitro*[1]. Both compounds were found to reversibly block depolarization-induced sodium inward currents and therefore to constitute a novel class of sodium channel blocking drugs with an *in-vitro* pharmacological profile comparable with the local anaesthetic Lidocaine. AMC was found to be approximately 10-fold more potent than Lidocaine, while DCBA was similar to Lidocaine with respect to blocking of resting channels.

Reckitt Benckiser Healthcare UK Limited (RB) has developed two new throat lozenges containing 0.6 mg AMC and 1.2 mg DCBA, respectively. The purpose of this study was to determine whether the *in-vitro* action of blocking depolarization-induced sodium inward currents by AMC alone and DCBA alone would translate to an *in vivo* analgesic effect. It was planned that the efficacy data provided would be used to determine the future development of these single active agent throat lozenges.

Efficacy of antiseptic throat lozenges has been established in many sore throat studies[2-5] and more recently in a study by McNally (2008)[6], which compared a known antiseptic throat lozenge with a non-medicated, sugar-based, placebo throat lozenge. The placebo throat lozenge matched the active throat lozenge in shape and colour, thus controlling for demulcency. The study demonstrated a statistically significant difference in favour of the antiseptic throat lozenge for change from baseline throat soreness at two hours ($p<0.0001$ for the per protocol population) and was used as the basis of the sample size calculation for the current study, which examined the effects of 0.6 mg AMC only and 1.2 mg DCBA only throat lozenges versus a non-medicated, sugar-based, placebo throat lozenge in patients with sore throat over a period of two hours.

In the current study, efficacy was assessed via patient assessment of throat soreness, sore throat pain relief, difficulty in swallowing and throat numbness up to two hours after dosing. Additional data regarding consumer acceptability of the product including perceived efficacy, characterization of the relief and patient satisfaction was also evaluated using a consumer questionnaire.

8 STUDY OBJECTIVES

The primary objective of this study was to determine the analgesic properties of 0.6 mg AMC only and 1.2 mg DCBA only throat lozenges in patients with sore throat due to upper respiratory tract infection (URTI). The secondary objective was to determine additional patient/consumer benefits associated with 0.6 mg AMC only throat lozenges and 1.2 mg DCBA only throat lozenges.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan – Description

The study protocol is included as Appendix 16.1.1. Unique pages from the case report form (CRF) are included as Appendix 16.1.2.

This study was a multi-centre, randomised, double blind, placebo-controlled, parallel group, single dose, pilot efficacy and safety study.

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

In order to discriminate between active and placebo treatment, it was necessary to include patients with sufficiently sore throat at baseline. This was achieved using the Throat Soreness Scale, an ordinal 11-point scale on which patients assessed their throat soreness by circling a number on the scale after swallowing. Patients with a score of 6 or more then underwent a Tonsillo-Pharyngitis Assessment (TPA), performed by the investigator. The TPA has been used in sore throat studies by Schachtel[7, 8] and in the antiseptic throat lozenge study conducted by McNally (2008)[6] and is detailed in Table 9.2.1 below. This assessment ensured that only patients with acute tonsillopharyngitis, the condition causing sore throat (as opposed to chronic, recurrent tonsillitis or laryngitis), were recruited to the study. The TPA consisted of assessments of seven pertinent features of tonsillopharyngitis: oral temperature, size of tonsils, oropharyngeal colour, number of oropharyngeal exanthems, size, number and tenderness of anterior cervical lymph nodes. Each of the parameters was rated 0-3 (whereby 0 represented a normal state of health and 1, 2 and 3 represented a sequentially greater degree of pathology relating to sore throat). A minimum score of 5 (of a maximum 21) was required to confirm the presence of tonsillopharyngitis and eligibility regarding sore throat.

Table 9.2.1 Tonsillo- Pharyngitis Assessment

Item	0 Points	1 Point	2 Points	3 Points
Oral Temperature	≤ 98.6°F	98.7 – 98.9°F	99.0 – 99.9°F	≥ 100.0°F
Oropharyngeal color	Normal / Pink	Slightly Red	Red	Beefy red
Size of Tonsils	Normal / absent	Slightly enlarged	Moderately enlarged	Much enlarged
Number of oropharyngeal exanthems (vesicles, petechiae, or exudates)	None	Few	Several	Many
Largest size of anterior cervical lymph nodes	Normal	Slightly enlarged	Moderately enlarged	Much enlarged
Number of anterior cervical lymph nodes	Normal	Slightly increased	Moderately increased	Greatly Increased
Maximum tenderness of some anterior cervical lymph nodes	Not tender	Slightly tender	Moderately tender	Very tender

A non-medicated, sugar-based, placebo throat lozenge was used in this study to control for the demulcent effect seen with sucking any sugar based sweet. The placebo throat lozenge was matched to the active throat lozenges for colour, size and shape and was therefore an adequate control.

The safety profiles of 0.6 mg AMC and 1.2 mg DCBA have been well established over many years of use as non-prescription products and the potential risks to patients are considered to be low. Patients who are known to be pregnant or lactating were excluded from the study. However formal pregnancy testing was not performed to eliminate those patients that did not know at time of study entry whether or not they were pregnant. This approach was justified, as a study performed by Berkovitch *et al*[9] showed that the use of a known antiseptic throat lozenge containing 0.6 mg AMC and 1.2 mg DCBA during the first trimester of pregnancy was not associated with an increased risk of malformations, spontaneous abortions or decreased birth weight.

The assessment ratings relating to analgesia i.e. throat soreness, sore throat pain relief and difficulty in swallowing are well accepted, validated analgesic assessments and have been used in previous clinical studies[6, 10-14].

Further areas of interest in the 0.6 mg AMC only throat lozenges and 1.2 mg DCBA only throat lozenges are the numbing properties within the throat. To quantify anaesthesia/numbness patients were instructed to circle the phrase that best described the numbness of their throat on a five point categorical scale. This method is a validated method used in a previous clinical study[15].

9.3 Selection of Study Population

Patients were recruited to the study centres via advertising, referral from community pharmacies and direct attendance of patients seeking sore throat remedies at the study centres.

9.3.1 Inclusion Criteria

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

1. Age: ≥ 18 to ≤ 75
2. Male and female patients
3. Primary diagnosis: Patients with a sore throat of onset within the past 4 days (i.e. ≤ 4 days)
4. Patients who had a sore throat (≥ 6) on the Throat Soreness Scale at baseline. They were instructed by the study nurse to swallow and circle the number on the scale that showed how sore their throat was when they swallowed. Ratings on this 0-10 ordinal scale were marked with 0 = Not sore (besides '0' rating) and 10 = Very Sore (beside '10').
5. Objective findings that confirmed the presence of tonsillopharyngitis (≥ 5 points on the expanded 21-point Tonsillo-Pharyngitis 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:

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 and glucose
2. Those whose sore throat had been present for more than four days
3. Those who had evidence of mouth breathing
4. Those who had evidence of severe coughing
5. Those who had any disease that could compromise breathing e.g. bronchopneumonia
6. Those who had taken any medicated confectionary, throat pastille, spray, or any product with demulcent properties such as boiled sweets in the previous two hours
7. Those who had used any sore throat medication containing a local anaesthetic within the previous four hours
8. Those who had used any analgesic, antipyretic or cold medication (e.g. decongestant, antihistamine, antitussive or throat lozenge) within the previous eight hours

9. Those who had used a longer acting or slow release analgesic during the previous 24 hours e.g. Piroxicam and Naproxen
10. Those who had taken antibiotics during the previous 14 days
11. Those with any painful condition that might have distracted attention from sore throat pain e.g. mouth ulcers etc.
12. Those with a history of severe renal impairment
13. Those with a history of severe hepatic impairment
14. Those taking warfarin and other coumarins
15. Those taking carbamezepine, phenobarbitone, phenytoin, primidone, rifampicin, St Johns Wort or other drugs that induce liver enzymes in the 14 days before enrolment into the study (i.e. before first dosing day)
16. 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)
17. Those who were glutathione-deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia
18. Those with any painful condition that required analgesic usage
19. Those unable to refrain from smoking during their stay in the study centre
20. 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 or an intrauterine device. A women of child bearing potential was defined as any female who was less than two years post-menopausal or had not undergone a hysterectomy or surgical sterilisation, e.g. bilateral tubal ligation, bilateral ovariectomy (oophorectomy)
21. Those previously randomised into the study
22. Those who had participated in a clinical study in the previous 30 days. Thirty days were calculated from time of last dosing in the previous study to time of anticipated dosing in this study.
23. Those unable in the opinion of the investigator to comply fully with the study requirements, e.g. such as those who could not comprehend or correctly use the pain rating scales.

9.3.3 Removal of Patients from Therapy or Assessment

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

- AEs that in the judgement of the Investigator might have caused severe or permanent harm (significant clinical deterioration is an AE)

- Violation of the study protocol
- In the Investigators judgement, it was in the patient's best interest
- The patient declined further study participation

The primary reason for withdrawal was to be documented as one of the following: AE; lack of efficacy; lost to follow-up; withdrawal of conset; protocol violation; Investigator decision; death or other. The Investigator was to make reasonable attempts to contact patients who were lost to follow-up to return their adverse event diary. A minimum of two documented telephone calls or a letter was considered reasonable.

If a patient was to be withdrawn prematurely from the study, the following assessments were to be carried out.

- Documentation of any AEs
- The clinical assessments detailed in section 11.2.3.1 of the study protocol (follow-up visit) and any others that were deemed appropriate for the clinical care of the patient
- Review of the patient diary and check for completeness

Withdrawn patients withdrawing less than two hours after dosing were to be replaced by a patient randomised to the next sequential number on the randomisation list.

9.4 Treatments

9.4.1 Treatments Administered

Patients were randomly allocated to one of three treatment groups:

- One throat lozenge containing 0.6 mg AMC
- One throat lozenge containing 1.2 mg DCBA
- One non-medicated, sugar-based, placebo throat lozenge

All treatments were administered as a single dose to be sucked until dissolution.

All study drug supplies were manufactured, primary packed, secondary packed into patient packs and labelled to Good Manufacturing Practice (GMP) standards by the Investigational Material Supplies Unit (IMSU), Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS. Supplies were shipped directly from the IMSU to the Investigational sites(s).

9.4.2 Identity of Investigational Product(s)

Study Medication	Manufacturer	Formulation Reference (FR) number and Works Order (WO) number
AMC throat lozenge	RB	FR 0172021, WO 0172678
DCBA throat lozenge	RB	FR 0178114, WO 0177913
Placebo throat lozenge	RB	FR 0125022, WO 0172727

Drug supplies were to be stored below 25°C.

9.4.3 Method of Assigning Subjects to Treatment Groups

A detailed description of the randomisation method, including how it was executed, is presented in Appendix 16.1.7. The block size was six.

Drug supplies were packed and labelled by RB IMSU according to a computer produced randomisation schedule provided by the RB statistician who was not involved with the analysis of the study. Blocks of study medication packs were supplied to each site. Sites were required to allocate sequential treatment numbers, starting with the lowest number.

The RB statistician and RB IMSU held the master randomisation list. The investigator at each site was provided with the randomisation code-break envelopes corresponding to the patient packs received at that site. The code was only to be broken for an individual subject in an emergency such as a serious adverse event that required knowledge of which study drug had been taken in order that the patient could be treated appropriately. If the code for a patient was to be broken, the Investigator was to withdraw the subject from the study, document the details of the event in the patient's case report form and promptly inform the RB Clinical Project Manager.

The study monitor checked the randomisation code break envelopes on a regular basis at monitoring visits to ensure the above procedures were being followed. All codes, whether sealed or opened, were to be returned to RB at the end of the study. No code-break envelopes had been opened.

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

It was planned that patients withdrawing less than two hours after dosing would be replaced by patients randomised to the next sequential number. Sufficient patients were enrolled to ensure that 150 evaluable patients completed the two-hour assessment period.

9.4.4 Selection of Doses in the Study

Each treatment (one throat lozenge, see section 9.4.1) was administered as a single oral dose to be sucked until dissolution. The doses of the two test treatments (one throat lozenge containing 0.6 mg AMC and one throat lozenge containing 1.2 mg DCBA) were used because they are the recommended non-prescription doses of these actives.

9.4.5 Selection of Timing of Dose for Each Patient

Patients were randomly assigned to treatment groups as described in Section 9.4.3.

Patients were instructed to take the medication by study staff after they had rated their throat soreness as at least 6 on the Throat Soreness Scale and had scored at least 5 on the Tonsillo-Pharyngitis Assessment, performed by the investigator. The patients were instructed to suck the throat lozenge until it had completely dissolved.

9.4.6 Blinding

Each treatment consisted of one throat lozenge. All throat lozenges were of a similar size and appearance.

No person had access to unblinded data during the study and no interim analysis was performed.

The blind was only to be broken in exceptional circumstances (see section 9.4.3).

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 that the patients received during the course of the study.

The centre staff recorded any medications given in treatment of AEs on the concomitant medication page of the patient's case report form. Any medication taken by the patient during the course of the study was also to be recorded on this form. Any changes in concomitant therapy during the study were to be documented, including cessation of therapy, initiation of therapy and dose changes.

The use of the following treatments was not permitted:

- Use of sore throat medication containing a local anaesthetic in the four hours before enrolment into the study (i.e. before the first dosing day)
- Use of medicated confectionary, throat pastilles, spray or any product with demulcent properties such as boiled sweets in the two hours before enrolment into the study
- Use of analgesic, antipyretic or "cold" medication (e.g. decongestant, antihistamine, antitussive, or throat lozenge) in the eight hours before enrolment into the study

- Use of longer acting or slow release analgesic e.g. piroxicam and naproxen, in the 24 hours before enrolment into the study
- Use of 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
- Use of antibiotic in the 14 days before enrolment into the study
- No food or drink was permitted during the two-hour assessment period.
- No smoking was permitted during the two-hour assessment period.

9.4.8 Treatment Compliance

Study staff observed the patients take the study medication.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flowchart

The efficacy and safety measurements assessed during the study are presented in the table below. A full version of the study procedure flowchart is provided in the study protocol (Appendix 16.1.1).

Table 9.5.1 Flowchart of study procedures

Study Period	Screening Pre-dose	Treatment Period Time (minutes) after dosing (Day 1)		Follow-up (1-3 days after doing)
Study Day	N/A	0		
Questioning regarding adverse events		X (pre-dose)[1]	X (120 minutes)	X[2]
Throat Soreness	X	X	X 5,10,15,30,45,60, 75,90,105,120	
Difficulty in Swallowing Assessment	X	X	X 5,10,15,30,45,60, 75,90,105,120	
Numbness Rating Assessment			X 5,10,15,30,45,60, 75,90,105,120	
Sore Throat Pain Relief Assessment			X 5,10,15,30,45,60, 75,90,105,120	
Overall Treatment Rating			X (120 minutes)	
Consumer Questionnaire.			X (5, 120 minutes)	

[1] Signs and symptoms occurring before dosing were documented on the medical history page and were not classed as adverse events; [2] All adverse events recorded on the patient's diary up to 24 hours after dosing were recorded on the CRF

All efficacy assessments recorded by patients were conducted under supervision of centre staff. The recording of efficacy assessments was standardised between sites by ensuring that site staff were trained to use the same wording when instructing subjects to complete the assessment scales and that they all dealt with observed discrepancies regarding patient responses in the same way. The sequence of questions and procedures was standardised across centres.

9.5.1.1 Efficacy Assessments

The assessments of throat soreness, difficulty in swallowing, throat numbness and sore throat relief were completed at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes after dosing. Throat soreness and difficulty in swallowing were also assessed at baseline.

Patients were instructed "We will ask you to complete four ratings scales at various times. These times will be every five minutes for the first 15 minutes and then every

15 minutes up to two hours. On each occasion you must complete all four rating scales within a period of 30 seconds".

The four rating scales were as follows:

Throat soreness using the 11-point ordinal scale

The patient was instructed: "Swallow and circle the number on the scale that shows how sore your throat is when you swallow". Ratings on this 0 to 10 ordinal scale were marked with "0= not sore" (beside the 0 rating) and "10= very sore" (beside the 10 rating). The patient was instructed: "We will ask you to tell us how sore your throat is using this scale [the study nurse showed the patient the scale on the CRF]. If you choose 0 it means that your throat is not sore at all. The higher the number you select, the more sore your throat is, so if you choose 10 it means your throat is very sore. You will be asked to put a circle around only one number. Do you understand this scale?"

Difficulty in swallowing using the VAS

The patient was instructed: "Swallow and place a line through the scale to indicate the degree of difficulty you are currently experiencing with swallowing". Scores on this horizontal 100 mm visual analogue scale (with endpoints of "not difficult" on the left hand side and "very difficult" on the right hand side) were measured by WCT during data entry to the nearest millimetre from the left.

Throat numbness using a 5-point categorical scale

The patient was instructed: "Circle the phrase which best describes the numbness of your throat now" on a scale of "none", "mild", "moderate", "considerable" and "complete".

Sore throat relief assessed on a 7-point rating scale

Before dosing, the patient was instructed: "We will ask you how much relief you get from the sore throat pain you report to be having just before you take the medication [the study nurse then showed the patient the categories]. You will have to select one answer only. Do you understand the use of this scale?" The patient was instructed by the study nurse to tick the phrase that best described the relief of their sore throat on a scale of "no relief", "slight relief", "mild relief", "moderate relief", "considerable relief", "almost complete relief" and "complete relief". At the scheduled timepoints after dosing, the patient was instructed: "Please tell us how much relief from your sore throat pain you have now compared with just before you took the medication".

Consumer Questionnaire

At five minutes after dosing the patient completed a question asking whether he/she had felt any relief from the moment of swallowing. Two hours after dosing the patient completed questions relating to acceptability of the product, perceived efficacy, characterization of the relief (how it felt, site of action, onset and duration) and patient satisfaction (Appendix IV of protocol).

Overall Treatment Rating

Two hours after dosing the patient was asked by the study nurse to provide an overall rating of the throat lozenge: “How would you rate this throat lozenge as a treatment for sore throat?” The patient selected a number from 0 (indicating poor) to 10 (indicating excellent) on an 11-point ordinal scale.

9.5.1.2 Safety Assessments

Adverse Events (AEs)

Patients were asked whether they had any untoward signs or symptoms immediately before dosing, after randomisation and at the end of the two-hour assessment. Patients were asked to record untoward signs and symptoms occurring from the time of discharge up to 24 hours after dosing.

Definitions

An AE was defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which did not necessarily have a causal relationship with this treatment.

An adverse reaction to an investigational medicinal product (AR) was defined as any untoward and unintended responses to an investigational medicinal product related to any dose administered. All AEs judged by either the reporting Investigator or the sponsor as having a reasonable causal relationship to a medicinal product were to be classed as ARs. The expression “reasonable causal relationship” was meant to convey in general that there was evidence or argument to suggest causal relationship.

A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose:

- resulted in death
- was life-threatening
- required hospitalisation or prolongation of existing hospitalisation
- resulted in persistent or significant disability/incapacity
- was a congenital anomaly/birth defect

Life-threatening in the definition of a SAE or serious AR referred to an event in which the subject was at risk of death at the time of the event; rather than to an event which hypothetically might have caused death had it been more severe.

Medical judgement was exercised in deciding whether an AE or AR was serious in other situations. Important AEs and ARs that were not immediately life-threatening or did not result in death or hospitalisation but may have jeopardised the subject or may have required intervention to prevent one of the other outcomes listed in the definition above, were also to be considered serious.

An unexpected AR (UAR) was defined as an AR, the nature or severity of which was not consistent with the applicable product information (e.g. Investigator’s Brochure for

an unauthorised investigational product or summary of product characteristics for an authorised product). When the outcome of the AR was not consistent with the applicable product information the AR was to be considered as unexpected.

The term “severe” described the intensity (severity) of a specific event. This was not the same as “serious,” which was based on patient/event outcome or action criteria.

Information collected on AEs

Each AE was recorded according to the criteria given in the table below. “Relationship to study medication” had to be determined by the Investigator (if medically qualified) or by a medically qualified Co-investigator.

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.

Procedure for reporting AEs

All AEs reported spontaneously by a randomised patient or in response to questioning or observation by the investigator, which were not directly related to the patient's sore throat, were recorded in the patient's CRF. If, following randomisation, the patient had reported a worsening of their sore throat or any other condition or infection relating to their sore throat, it was to be recorded as an AE.

Signs and symptoms occurring during the screening phase were to be recorded in the patient's source data file regardless of whether or not the patient subsequently entered the study and was randomised to treatment. They were however, only to be entered into the CRF if the patient entered the study. Those resulting in screen failure were to be listed on the screening log as the reason for screen failure.

In the event of an SAE, the Investigator was to telephone the RB Clinical Project Manager within 24 hours of knowledge of the event.

It was the responsibility of the RB Pharmaceutical Physician, together with the European Qualified Person for Pharmacovigilance, to decide whether an event was serious for the purpose of reporting to authorities. However if an event had been recorded as serious in the CRF, the investigator would not have been required to change it.

The investigator was not to break the randomisation code except when it would have been necessary to do so in order to ensure the patient received appropriate medical care (section 9.4.3).

The Investigator was required to inform his/her local ethics committee of all SAEs occurring in the study.

Reporting to regulatory authorities

Serious and non-serious AEs were to be reported to the appropriate regulatory authorities by RB, in accordance with the authorities' requirements.

Follow-up of patients experiencing AEs upon completion of / withdrawal from the study

All SAEs, and those that caused premature withdrawal of the subject from the study, that had not resolved by the end of the study, were to be followed up by the Investigator until resolution or until the Investigator believed there would be no further change.

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

The minimum data required are the final outcome and date, which may be obtained by the Investigator in a documented telephone conversation with the patient or patient's GP.

Procedures for patient experiencing AEs after completion of the study

If a patient experienced the onset of an AE within a period following study completion that did not exceed five half-lives of one of the active study drugs and, in the opinion of the Investigator, it was associated with the study, it was to be followed up and reported. For the purpose of this study, the half-life of AMC and DCBA was taken to be two hours. Therefore if the patient experienced the onset of an AE within 10 hours after dosing, the AE was to be reported and followed-up as described above.

9.5.2 Appropriateness of Measurements

All assessments of efficacy and safety parameters were made using standard, widely used, published and reliable methodologies.

9.5.3 Primary Efficacy Variable(s)

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

9.5.4 Drug Concentration Measurements

Drug concentrations were not measured in this study.

9.6 Data Quality Assurance

All data were entered onto the WCT NODES computer database by a member of the Data Management Section and then verified by repeat data entry by a further Section member. SAS Version 9.1[16] edit checks were used for consistency checks.

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

Audit component 1: Consistency checking and query generation

Eight cases were randomly selected to undergo full consistency checking whereby an error would be 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.

Audit component 2: Transcription and annotation procedures

The eight subjects selected for component 1 were also selected for full audit whereby errors could be either transcription or other failures with respect to standard procedures for annotating working copies etc. The total error rate for component 2 was 0.086%. The error rate for "significant data errors" (any error in a data field which had the potential to affect the statistical analysis or any summary table) was 0%. The acceptance level for the significant data error rate in the interim audit was the default error rate of 0.1%.

Audit component 3: Critical data fields

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

- Randomisation number
- Date and time of throat lozenge administration
- 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 adverse event data

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

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

- Study database
- Statistical analyses
- Clinical Study Report

An audit certificate is included in Appendix 16.1.8.

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

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

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

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

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

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

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

All calculations and figures were produced using SAS Version 9.1[16] or S-PLUS 6.2[17].

For continuous variables, the mean, median, standard deviation, standard error of the mean, minimum, maximum and lower and upper 95% confidence limits for the mean were computed, both overall (where appropriate) and for the individual treatment groups.

Categorical data were presented in contingency tables with cell frequencies and percentages both overall and for individual treatment groups.

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

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

9.7.1 Statistical and Analytical Plans

A copy of the final statistical analysis plan is presented as Appendix 16.1.9.

9.7.1.1 Efficacy

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

Primary Endpoint

The primary efficacy endpoint was 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 and using Fisher's protected LSD method i.e. if the overall treatment effect in the ANCOVA model was significant at the 5% level, comparison of the 0.6 mg AMC only and 1.2 mg DCBA only groups versus the placebo group were performed without any requirement to adjust the significance level for the pairwise comparisons.

Secondary Endpoints

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

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

- The change from baseline in severity of throat soreness (using the 11-point throat soreness scale) at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post-dose
- AUC from baseline to two hours post-dose for sore throat relief
- Sore throat relief at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post-dose

- AUC for throat numbness measurements from 5 to 120 minutes
- Throat numbness at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post-dose
- Overall treatment rating at two hours post-dose

The AUC for change from baseline in difficulty in swallowing and the change from baseline in difficulty in swallowing at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post-dose were analysed by ANCOVA with factors for treatment group and centre and covariates for the baseline value for difficulty in swallowing and baseline throat soreness severity.

The time taken for patients to first report at least moderate sore throat relief (i.e. onset of analgesia) was compared between treatment groups using a Cox proportional hazards model with factors for treatment group and centre and a covariate for baseline throat soreness severity. Patients not reporting at least moderate sore throat relief were censored at the time of their last recorded follow-up assessment.

For the consumer questionnaire, responses to 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 response to the question “How long does the action of the throat lozenge last in your throat?” recorded on a non-numeric ordinal scale was analysed using a proportional odds model[18] using PROC LOGISTIC in SAS with factors for treatment group and centre and a covariate for baseline throat soreness severity. Responses recorded under category “Not known” were not included in the formal analysis. Responses to questions on numeric ordinal scales were analysed using the same ANCOVA model as the primary efficacy endpoint.

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

Exploratory analysis

Analyses of the primary efficacy endpoint were performed by key baseline characteristics. For each subgroup, the main effect and treatment-by-subgroup interaction terms were added to the standard model used in the primary endpoint analysis. Key variables of interest were centre, baseline throat soreness severity (≤median, >median), age at study entry (≤median, >median), gender, total score from tonsillo-pharyngitis assessment at baseline (≤median, >median) and baseline VAS for difficulty in swallowing (≤median, >median). Any interactions that seemed noteworthy had their nature described. These models were used to estimate treatment comparisons within the subgroups that correspond with the sub-grouping factor. For the investigation of baseline throat soreness severity subgroup effect, the model fitted was analysis of variance (ANOVA) rather than ANCOVA as baseline

throat soreness severity was considered a two-level factor rather than as a continuous covariate.

9.7.1.2 Safety

All treatment emergent adverse events were listed and tabulated by treatment, severity, relationship to therapy and primary system organ class according to MedDRA Version 12.0. In counting the number of events reported, a continuous event, i.e. an event reported more than once and which did not cease, was counted only once; non-continuous adverse events reported several times by the same patient were counted as multiple events. Events present immediately prior to the dose of study medication that did not worsen in severity, were not included.

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

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

9.7.2 Determination of Sample Size

In a previous study conducted with a well known antiseptic throat lozenge[6] the difference in the mean AUC for the change from baseline in the severity of throat soreness (using the 11-point Throat Soreness Scale) from 0 to two hours between active throat lozenge and placebo was 1.26 with a standard deviation of 1.27. Assuming that the variability for the same variable for 0.6 mg AMC only and 1.2 mg DCBA only throat lozenges was of a similar magnitude as for the known antiseptic throat lozenge in the previous study, 50 patients per group would be required to provide 90% power to detect a difference of 0.84 in the mean AUC (two thirds of the effect seen in the previous study) between either of the throat lozenges and placebo using a 2-sample t-test at the 5% significance level.

9.8 Changes in the Conduct of the Study or Planned Analysis

9.8.1 Changes in the Conduct of the Study

No changes were made in the conduct of the study.

9.8.2 Changes in the Planned Statistical Analysis of the Study

No changes were made in the planned statistical analyses.

10 STUDY SUBJECTS

10.1 Disposition of Patients

A total of 150 subjects were screened and randomised into the study (50 subjects received 0.6 mg AMC throat lozenge, 49 subjects received 1.2 mg DCBA throat lozenge and 51 subjects received placebo throat lozenge) between 10th December 2008 and 2nd March 2009. There were no screen failures and all subjects completed the study. The number of patients randomised at each site is given in Table 10.1.1 below.

Table 10.1.1 Number of patients randomised per treatment per site

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge	Total
01 Ormeau Health Centre	28 (56.0%)	25 (51.0%)	28 (54.9%)	81 (54.0%)
02 Abbots Cross Medical Practice	8 (16.0%)	10 (20.4%)	8 (15.7%)	26 (17.3%)
03 Randalstown Medical Practice	8 (16.0%)	7 (14.3%)	8 (15.7%)	23 (15.3%)
04 Crocus Street Surgery	4 (8.0%)	4 (8.2%)	5 (9.8%)	13 (8.7%)
05 Parkside Surgery	2 (4.0%)	3 (6.1%)	2 (3.9%)	7 (4.7%)
Total	50 (100.0%)	49 (100.0%)	51 (100.0%)	150 (100.0%)

10.2 Protocol Deviations

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

There were five patients excluded from the per-protocol dataset. Two patients (one in the 1.2 mg DCBA throat lozenge group one in the placebo throat lozenge group) had inadmissible timings of assessment. One patient in the placebo throat lozenge group was taking Primidone, an inadmissible concomitant medication during the study. One patient in the 1.2 mg DCBA throat lozenge group took an analgesic (paracetamol) within eight hours prior to dosing. One patient in the 1.2 mg DCBA throat lozenge group had a TPA score of less than five at screening.

There were no treatment administration errors.

11 EFFICACY EVALUATION

11.1 Data Sets Analysed

Appendix 16.2.3 contains a tabular listing of all patients, visits and observations excluded from the efficacy analysis. The reasons for exclusion are presented for the whole treatment group over time.

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

The **safety set** included all patients who took the study medication. The safety set was analysed as treated. The safety set consisted of all 150 subjects randomised into the study.

The analysis of efficacy data used two datasets.

The full analysis set. This analysis set consisted of all patients who were randomised to the study and took the study medication. Any patients with treatment administration errors were to be analysed according to the treatment to which they were randomised. This was the primary efficacy analysis population. For this study the full analysis and safety sets were identical and consisted of all 150 subjects randomised into the study.

The per-protocol set. This analysis set was a subset of the full analysis set and consisted of all patients who satisfied all of the inclusion/exclusion criteria, who

correctly received the treatment to which they were randomised, and who successfully completed the treatment period up to the two-hour assessment. All protocol deviations were assessed and documented on a case-by-case basis prior to the database lock, and any incidence of deviations considered having a serious impact on the efficacy results led to the relevant patient being excluded from the analysis set. It was planned that major protocol deviations would include:

- Treatment administration errors.
- Taking inadmissible concomitant medication (within the first two hours post-dose or inadequate washout prior to randomisation).
- Inadmissible timing of the follow-up assessments within the first two hours post-dose.
    - 5, 10 and 15 minute assessment not performed within +/- 1 minute of the scheduled times.
    - 30, 45, 60, 75, 90, 105 and 120 minute assessments not performed within +/- 5 minutes of the scheduled times.

Five patients (three in the 1.2mg DCBA throat lozenge group and two in the placebo throat lozenge group) were excluded from the per-protocol analysis set, which therefore consisted of 145 subjects.

The only variables which were assessed using the per-protocol analysis set were the primary efficacy endpoint (the area under the change from baseline curve (AUC) in severity of throat soreness, from baseline to two hours) and the AUC for sore throat pain relief.

11.2 Demographic and Other Baseline Characteristics

Patient demographics are presented in Tables 14.1.2 to 14.1.7 and summarised below in Table 11.2.1. 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 and baseline characteristics.

Patients were recruited by five centres. The largest number of patients randomised at any one centre was 81 (54%) patients, the next largest was 26 (17%) patients and the smallest was seven (5%) patients.

Overall, patient age ranged from 18 to 74 years, with a mean of 31.8 years. Eighty (53%) patients were male and all patients were Caucasian. There were marginally more males in the active groups (56% in the 0.6 mg AMC throat lozenge group and 55% in the 1.2 mg DCBA throat lozenge group), than the placebo throat lozenge group (49%). Height ranged from 146 cm to 190 cm, with a mean of 169.6 cm. Mean weight was 73.2 kg with a range of 44.0 kg to 112.0 kg. BMI ranged from 16.5 kg/m^2 to 49.5 kg/m^2, with a mean of 25.5 kg/m^2. A total of 110 (73%) patients drank alcohol, 64 (43%) were current smokers and 20 (13%) were former smokers. There was a minor imbalance between treatments with respect to the number of current smokers,

namely 51% in the 1.2 mg DCBA throat lozenge group, 44% in the 0.6 mg AMC throat lozenge group and 33% in the placebo throat lozenge group.

Table 14.1.2 presents full summary statistics of demographic variables.

Table 11.2.1 Demographics – full analysis set

Variable	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge	Overall
Number of subjects	50	49	51	150
Age (yr) (Mean ± sd)	31.6±12.1	32.8±14.7	31.0±13.5	31.8±13.4
Gender (% male)	56.0%	55.1%	49.0%	53.3%
Race (% Caucasian)	100.0%	100.0%	100.0%	100.0%
Height (cm) (Mean ± sd)	169.4±10.5	170.7±10.0	168.9±10.3	169.6±10.2
Weight (kg) (Mean ± sd)	74.9±15.2	72.5±14.8	72.1±15.5	73.2±15.1
BMI (kg/m^2) (Mean ± sd)	26.3±6.1	24.9±4.8	25.3±5.3	25.5±5.4
Alcohol drinker (%)	74.0%	69.4%	76.5%	73.3%
Current smoker (%)	44.0%	51.0%	33.3%	42.7%
Former smoker (%)	14.0%	10.2%	15.7%	13.3%

Source: Table 14.1.2, yr = years, sd = standard deviation

A total of 21 (14%) patients reported a previous medical condition (Table 14.1.3) and 64 (43%) patients reported an ongoing medical condition of which 26 (17%) had psychiatric disorders and 14 (9%) had conditions of the musculoskeletal system (Table 14.1.4).

The mean total score from the Tonsillo-Pharyngitis Assessment (TPA) at screening was 8.1 with a range of 4 to 17, one patient entering the study with a TPA score less than 5, violating the protocol inclusion criteria. Throat soreness was measured on an 11-point scale at screening where 0 = “not sore” and 10 = “very sore” and the subject was required to score at least 6 to be eligible for entry. The mean score was 7.12 with a range of 6 to 10 (Table 14.1.5).

Mean baseline values for the assessment of throat soreness and VAS for difficulty swallowing are presented in Table 14.1.6 and summarised in Table 11.2.2 below. The mean score for throat soreness was 7.09 (range 6 to 10). For the pre-dose VAS for difficulty in swallowing the mean score was 63.5 mm (range 2, 98 mm).

Table 11.2.2 Mean ± sd for baseline efficacy assessments – full analysis set

Variable	0.6mg AMC throat lozenge	1.2mg DCBA throat lozenge	Placebo throat lozenge	Overall
Number of subjects	50	49	51	150
Assessment of throat soreness on a 11-point scale (0 = Not Sore and 10 = Very Sore)	7.22±0.93	6.96±0.82	7.08±1.06	7.09±0.94
VAS of difficulty swallowing (0mm = Not difficult, 100mm = Very difficult)	63.9±17.4	64.0±12.5	62.7±18.1	63.5±16.2

Source: Table 14.1.6, sd = standard deviation

Details of concomitant medication ongoing at time of randomisation are presented in Table 14.1.7. Seventy (47%) patients reported the use of at least one concomitant medication. In terms of WHO ATC level 2 categories, the most commonly reported categories were sex hormones and modulators of the genital system with 37 (25%) subjects reporting and psychoanaleptics with 19 (13%) subjects reporting. One patient was reported taking an analgesic (Temgesic for osteoarthritis). However this patient was not excluded from the per-protocol population as the medication was taken on an "as required basis" and not during or immediately prior to the study. This patient was also taking an anti-inflammatory and anti-rheumatic product, glucosamine for their condition, which was permitted by the protocol. One patient in the placebo throat lozenge group was taking Primidone, an inadmissible concomitant medication during the study for hallucinations and was excluded from the per-protocol analysis.

11.3 Measurements of Treatment Compliance

All patients took their study medication dose.

11.4 Efficacy Results

11.4.1 Analysis of Efficacy

14.4.1.1 Primary measure of efficacy

The primary endpoint was the area under the change from baseline curve (AUC) in severity of throat soreness, from baseline to two hours. All patients provided data for this measure. In the ANCOVA model for the full analysis set (n=150), none of the effects in the model (treatment, centre and baseline throat soreness) achieved statistical significance (p-values 0.83, 0.83 and 0.12 respectively). The LS mean reductions were -1.05 (0.6 mg AMC throat lozenge), -0.91 (1.2 mg DCBA throat lozenge) and -0.95 (placebo throat lozenge: Table 14.2.1.1).

Five (3%) subjects were not included in the equivalent per-protocol analysis. The statistical conclusions were qualitatively identical to those obtained with the full analysis set as described above. The LS mean reductions were -1.04 (0.6 mg AMC throat lozenge), -0.86 (1.2 mg DCBA throat lozenge) and -0.95 (placebo throat lozenge: Table 14.2.1.2).

Table 11.4.1 below summarises these results.

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

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

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
FULL ANALYSIS SET			
N	50	49	51
Mean±sd	-1.08±1.02	-0.99±1.18	-1.00±1.23
LS mean[a]	-1.05	-0.91	-0.95
Parameter estimates	LS mean[b]	95% CI	p
0.6mg AMC throat lozenge – Placebo	-0.10	-0.56,0.35	0.66
1.2mg DCBA throat lozenge – Placebo	0.04	-0.42,0.49	0.88
0.6mg AMC throat lozenge – 1.2mg DCBA throat lozenge	-0.14	-0.60,0.32	0.56
PER-PROTOCOL SET			
N	50	46	49
Mean±sd	-1.08±1.02	-0.97±1.21	-1.02±1.25
LS mean[a]	-1.04	-0.86	-0.95
Parameter estimates	LS mean[b]	95% CI	p
0.6mg AMC throat lozenge – Placebo	-0.09	-0.55,0.38	0.72
1.2mg DCBA throat lozenge – Placebo	0.09	-0.39,0.57	0.71
0.6mg AMC throat lozenge – 1.2mg DCBA throat lozenge	-0.17	-0.65,0.30	0.47

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A negative difference favours the first treatment against second treatment
Source: Tables 14.2.1.1 and 14.2.1.2

11.4.1.2 Secondary efficacy endpoints

Change from baseline in severity of throat soreness (using the 11-point throat soreness scale) at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post-dose

The individual changes from baseline in throat soreness at each follow-up are summarised in Table 11.4.2 below and presented in more detail in Tables 14.2.2 to 14.2.11. There was no statistically significant overall difference between treatments for the change from baseline in severity of throat soreness at any timepoint ($p>0.05$ in each case). The centre effect was statistically significant in the ANCOVA model at five minutes post-dose ($p<0.03$) but not at any other timepoint; the covariate baseline throat soreness was never statistically significant.

Table 11.4.2 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

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

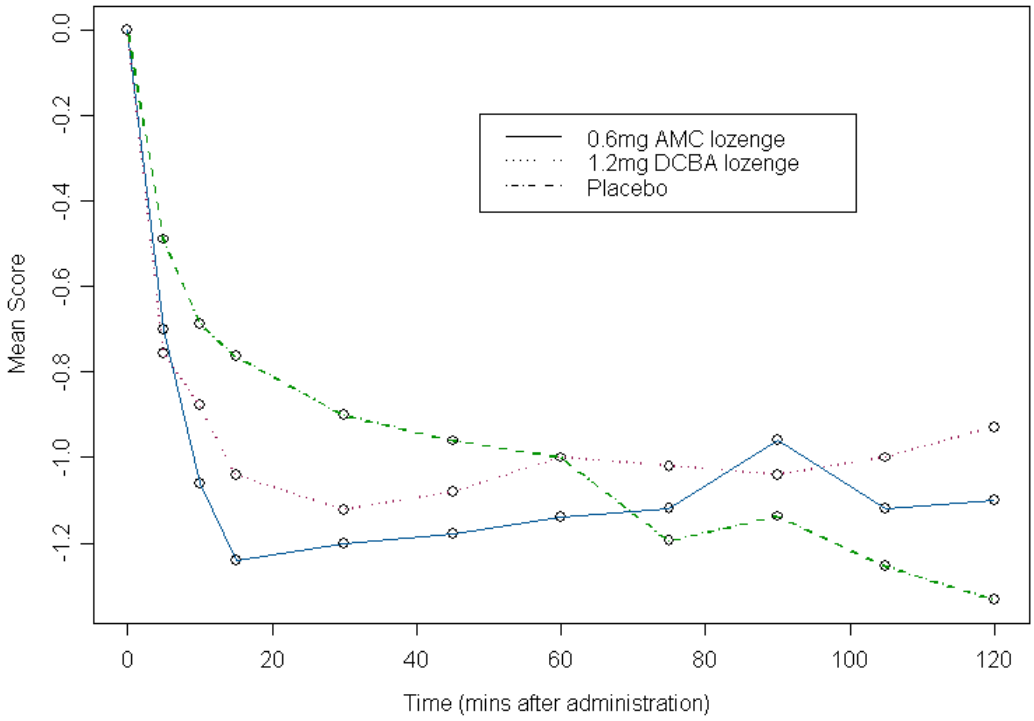
Minutes post-dose	0.6 mg AMC throat lozenge (n)	1.2 mg DCBA throat lozenge (n)	Placebo throat lozenge (n)	Overall p-value	0.6 mg AMC throat lozenge versus Placebo throat lozenge	1.2 mg DCBA throat lozenge versus Placebo throat lozenge	0.6 mg AMC throat lozenge versus 1.2 mg DCBA throat lozenge
0	7.22±0.93 (50)	6.96±0.82 (49)	7.08±1.06 (51)				
5	-0.70±1.23 (50)	-0.76±1.35 (49)	-0.49±1.17 (51)	0.56	ns	ns	ns
10	-1.06±1.32 (50)	-0.88±1.33 (49)	-0.69±1.19 (51)	0.32	ns	ns	ns
15	-1.24±1.60 (50)	-1.04±1.38 (49)	-0.76±1.14 (51)	0.19	ns	ns	ns
30	-1.20±1.48 (50)	-1.12±1.33 (49)	-0.90±1.12 (51)	0.48	ns	ns	ns
45	-1.18±1.21 (50)	-1.08±1.38 (49)	-0.96±1.20 (51)	0.63	ns	ns	ns
60	-1.14±1.20 (50)	-1.00±1.27 (49)	-1.00±1.34 (51)	0.72	ns	ns	ns
75	-1.12±1.19 (50)	-1.02±1.36 (49)	-1.20±1.47 (51)	0.73	ns	ns	ns
90	-0.96±1.14 (50)	-1.04±1.38 (49)	-1.14±1.59 (51)	0.84	ns	ns	ns
105	-1.12±1.52 (50)	-1.00±1.37 (49)	-1.25±1.73 (51)	0.69	ns	ns	ns
120	-1.10±1.50 (50)	-0.93±1.35 (49)	-1.33±1.85 (51)	0.42	ns	ns	ns

ns Comparison not statistically significant
Source: Tables 14.2.2 to 14.2.11

The maximum reductions in throat soreness were recorded at 15 minutes post-dose for the 0.6 mg AMC throat lozenge, 30 minutes post-dose for the 1.2 mg DCBA throat lozenge and two hours post-dose for the placebo throat lozenge group. This is clearly seen in Figure 11.4.1 below.

Figure 11.4.1 Mean change from baseline in throat soreness from 5 to 120 minutes post-dose – full analysis set

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



AUC for sore throat pain relief: Defined as the AUC from baseline to two hours post first dose for sore throat pain relief

The results of the analyses related to the AUC from baseline to two hours post-dose for sore throat pain relief are given in Table 11.4.3 below. In the ANCOVA model for the full analysis set (n=150), none of the effects in the model (treatment, centre or baseline throat soreness) achieved statistical significance (p-values 0.87, 0.44 and 0.08 respectively). The LS means were 1.06 (0.6 mg AMC throat lozenge), 1.15 (1.2 mg DCBA throat lozenge) and 1.05 (placebo throat lozenge: Table 14.2.12.1).

Five (3%) subjects were not included in the equivalent per-protocol analysis. The statistical conclusions were qualitatively identical to those obtained with the full analysis set as described above. The LS mean reductions were 1.06 (0.6 mg AMC throat lozenge), 1.12 (1.2 mg DCBA throat lozenge) and 1.08 (placebo throat lozenge). Further details are provided in Table 14.2.12.2.

Table 11.4.3 AUC from baseline to two hours post-dose for sore throat pain relief

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

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
FULL ANALYSIS SET			
N	50	49	51
Mean±sd	1.13±0.96	1.27±1.16	1.13±1.16
LS mean[a]	1.06	1.15	1.05
Parameter estimates	LS mean[b]	95% CI	p
0.6mg AMC throat lozenge – Placebo	0.02	-0.41,0.45	0.94
1.2mg DCBA throat lozenge – Placebo	0.11	-0.33,0.54	0.63
0.6mg AMC throat lozenge – 1.2mg DCBA throat lozenge	-0.09	-0.53,0.35	0.69
PER-PROTOCOL SET			
N	50	46	49
Mean±sd	1.13±0.96	1.26±1.18	1.16±1.17
LS mean[a]	1.06	1.12	1.08
Parameter estimates	LS mean[b]	95% CI	p
0.6mg AMC throat lozenge – Placebo	-0.02	-0.46,0.42	0.93
1.2mg DCBA throat lozenge – Placebo	0.04	-0.41,0.49	0.85
0.6mg AMC throat lozenge – 1.2mg DCBA throat lozenge	-0.06	-0.51,0.39	0.79

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
Source: Tables 14.2.12.1 and 14.2.12.2

Sore throat pain relief at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post-dose

The individual sore throat pain relief scores at each follow-up assessment are summarised in Table 11.4.4 below and presented in more detail in Tables 14.2.13 to 14.2.22. There was no statistically significant overall difference between treatments in sore throat relief at any timepoint ($p>0.05$ in each case). However, the pairwise comparison between the 0.6 mg DCBA throat lozenge and the placebo throat lozenge was statistically significant at 10 and 15 minutes post-dose ($p<0.03$ in both cases). None of the other pairwise comparisons was statistically significant. Neither the centre effect nor the covariate baseline throat soreness achieved statistical significance in any of the ANCOVA models.

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

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

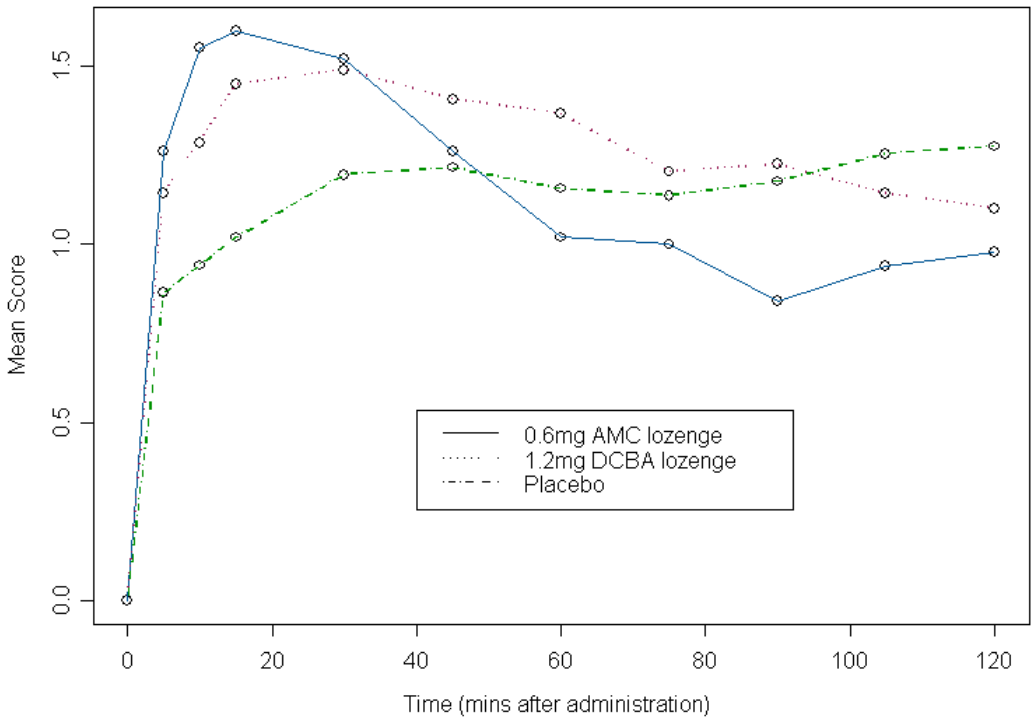
Minutes post-dose	0.6 mg AMC throat lozenge (n)	1.2 mg DCBA throat lozenge (n)	Placebo throat lozenge (n)	Overall p-value	0.6 mg AMC throat lozenge versus Placebo throat lozenge	1.2 mg DCBA throat lozenge versus Placebo throat lozenge	0.6 mg AMC throat lozenge versus 1.2 mg DCBA throat lozenge
5	1.26±1.50 (50)	1.14±1.37 (49)	0.86±1.25 (51)	0.34	ns	ns	ns
10	1.55±1.40 (49)	1.29±1.37 (49)	0.94±1.14 (51)	0.06	*	ns	ns
15	1.60±1.50 (50)	1.45±1.39 (49)	1.02±1.17 (51)	0.09	*	ns	ns
30	1.52±1.34 (50)	1.49±1.39 (49)	1.20±1.18 (51)	0.40	ns	ns	ns
45	1.26±1.24 (50)	1.41±1.35 (49)	1.22±1.30 (51)	0.85	ns	ns	ns
60	1.02±1.06 (50)	1.37±1.32 (49)	1.16±1.27 (51)	0.47	ns	ns	ns
75	1.00±1.05 (50)	1.20±1.22 (49)	1.14±1.34 (51)	0.77	ns	ns	ns
90	0.84±1.06 (50)	1.22±1.25 (49)	1.18±1.40 (51)	0.30	ns	ns	ns
105	0.94±1.24 (50)	1.14±1.22 (49)	1.25±1.51 (51)	0.53	ns	ns	ns
120	0.98±1.20 (50)	1.10±1.19 (49)	1.27±1.59 (51)	0.57	ns	ns	ns

ns Comparison not statistically significant
* Comparison statistically significant at 5% level
Source: Tables 14.2.13 to 14.2.22

Maximum mean pain relief was reported at 15 minutes post-dose for the 0.6 mg AMC throat lozenge, 30 minutes post-dose for the 1.2 mg DCBA throat lozenge and two hours post-dose for the placebo throat lozenge, see Figure 11.4.2 below.

Figure 11.4.2 Mean sore throat relief from 5 to 120 minutes post-dose – full analysis set

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



AUC for change from baseline in difficulty swallowing from baseline to two hours post-dose

Details of the analysis of the AUC for difficulty in swallowing from baseline to two hours post-dose are presented in Table 11.4.5 below. In the ANCOVA model for the full analysis set (n=150) the covariates baseline score for difficulty in swallowing (p=0.0005) and baseline throat soreness severity (p=0.0009) were statistically significant whereas the effects for centre (p=0.76) and treatment group (p=0.87) failed to achieve statistical significance. The LS mean reductions were -9.9 mm (0.6 mg AMC throat lozenge), -9.9 mm (1.2 mg DCBA throat lozenge) and -11.0 mm (placebo throat lozenge: Table 14.2.23).

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

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

	0.6mg AMC throat lozenge	1.2mg DCBA throat lozenge	Placebo throat lozenge
N	50	49	51
Mean±sd	-8.8±12.3	-10.2±10.7	-10.2±13.9
LS mean[a]	-9.9	-9.9	-11.0
Parameter estimates	LS mean[b]	95% CI	p
0.6mg AMC throat lozenge – Placebo	1.1	-3.6,5.8	0.64
1.2mg DCBA throat lozenge – Placebo	1.0	-3.7,5.8	0.67
0.6mg AMC throat lozenge – 1.2mg DCBA throat lozenge	0.1	-4.7,4.9	0.98

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

b A negative difference favours the first treatment against second treatment

Source: Tables 14.2.23

Change from baseline in difficulty in swallowing at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post-dose

The change from baseline in difficulty in swallowing at each follow-up assessment is summarised in Table 11.4.6 below and presented in more detail in Tables 14.2.24 to 14.2.33. There was no statistically significant overall difference between treatments for the change from baseline in difficulty in swallowing at any timepoint (p>0.05 in each case). The centre effect was statistically significant at five minutes post-dose (p<0.03); the covariate baseline score for difficulty in swallowing was statistically significant (p<0.05) at all timepoints from 10 minutes post-dose onwards and the covariate baseline throat soreness severity was statistically significant (p<0.05) at all timepoints from 15 minutes post-dose onwards.

Table 11.4.6 Mean ± sd (n) 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

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

Minutes post-dose	0.6 mg AMC throat lozenge (n)	1.2 mg DCBA throat lozenge (n)	Placebo throat lozenge (n)	Overall p-value	0.6 mg AMC throat lozenge versus Placebo throat lozenge	1.2 mg DCBA throat lozenge versus Placebo throat lozenge	0.6 mg AMC throat lozenge versus 1.2mg DCBA throat lozenge
0	63.9±17.4 (50)	64.0±12.5 (49)	62.7±18.1 (51)				
5	-4.1±13.2 (50)	-5.0±10.8 (49)	-4.9±12.1 (51)	0.95	ns	ns	ns
10	-8.7±16.3 (50)	-9.7±12.5 (49)	-7.1±12.9 (51)	0.78	ns	ns	ns
15	-11.9±18.1 (50)	-11.6±12.1 (49)	-8.6±13.3 (51)	0.47	ns	ns	ns
30	-10.3±15.8 (50)	-11.7±12.7 (49)	-10.2±13.9 (51)	0.99	ns	ns	ns
45	-9.8±13.7 (50)	-10.8±12.9 (49)	-9.0±13.6 (51)	0.92	ns	ns	ns
60	-8.2±13.8 (49)	-10.3±13.4 (49)	-9.9±15.3 (51)	0.87	ns	ns	ns
75	-7.8±12.6 (50)	-9.8±12.4 (49)	-12.0±16.5 (51)	0.31	ns	ns	ns
90	-8.3±13.8 (50)	-10.9±13.6 (49)	-11.2±17.1 (51)	0.68	ns	ns	ns
105	-10.0±16.2 (50)	-10.4±15.0 (49)	-12.9±18.3 (51)	0.53	ns	ns	ns
120	-8.6±15.9 (50)	-10.8±15.1 (49)	-13.7±19.0 (51)	0.30	ns	ns	ns

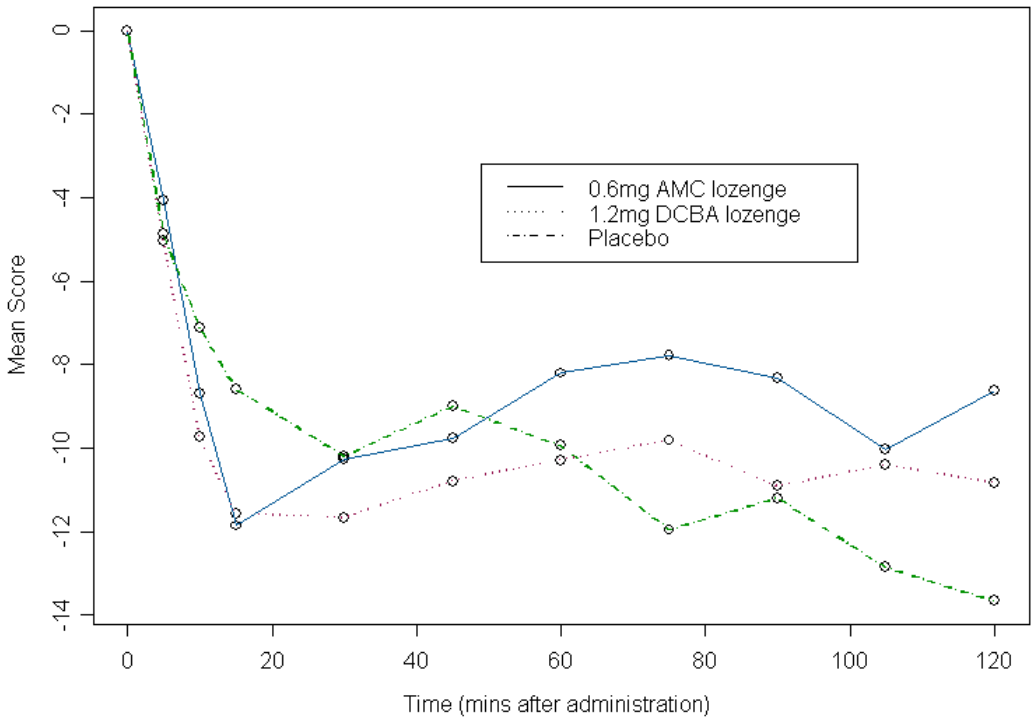
ns Comparison not statistically significant
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level

Source: Tables 14.2.24 to 14.2.33

Maximum mean reductions in difficulty in swallowing were reported at 15 minutes post-dose for the 0.6 mg AMC throat lozenge, 30 minutes post-dose for the 1.2 mg DCBA throat lozenge and two hours post-dose for the placebo throat lozenge, see Figure 11.4.3 below.

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

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



AUC for throat numbness measurements from 5 to 120 minutes

Details of the analysis of the AUC for throat numbness from five minutes to two hours post-dose are presented in Table 11.4.7 below. In the ANCOVA model for the full analysis set (n=150) none of the effects (treatment, centre or baseline throat soreness) achieved statistical significance (p-values 0.35, 0.19 and 0.90 respectively). The LS mean scores for throat numbness were 1.67 (0.6 mg AMC throat lozenge), 1.80 (1.2 mg DCBA throat lozenge) and 1.56 (placebo throat lozenge: Table 14.2.34).

Table 11.4.7 AUC for throat numbness measurements from 5 to 120 minutes post-dose – full analysis set

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

	0.6mg AMC throat lozenge	1.2mg DCBA throat lozenge	Placebo throat lozenge
N	50	49	51
Mean±sd	1.78±0.71	1.90±0.88	1.67±0.86
LS mean[a]	1.67	1.80	1.56
Parameter estimates	LS mean[b]	95% CI	p
0.6mg AMC throat lozenge – Placebo	0.10	-0.22,0.43	0.53
1.2mg DCBA throat lozenge – Placebo	0.24	-0.09,0.56	0.15
0.6mg AMC throat lozenge – 1.2mg DCBA throat lozenge	-0.14	-0.46,0.19	0.42

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment

Source: Tables 14.2.34

Throat numbness at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post-dose

Throat numbness at each follow-up assessment is summarised in Table 11.4.8 below and presented in more detail in Tables 14.2.35 to 14.2.44. There was a statistically significant overall difference between treatments in throat numbness at 5, 10 and 15 minutes post-dose ($p<0.01$ in each case). For each of these time points throat numbness scores were statistically significantly higher for the 0.6 mg AMC throat lozenge compared with the placebo throat lozenge ($p<0.01$) and also for the 1.2 mg DCBA throat lozenge compared with the placebo throat lozenge ($p<0.05$). There was no statistically significant overall difference between treatments in throat numbness at any of the other time points ($p>0.05$ in each case). Neither the centre effect nor the covariate baseline throat soreness achieved statistical significance in any of the ANCOVA models.

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

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

Minutes post-dose	0.6mg AMC throat lozenge (n)	1.2 mg DCBA throat lozenge (n)	Placebo throat lozenge (n)	Overall p-value	0.6 mg AMC throat lozenge versus Placebo throat lozenge	1.2 mg DCBA throat lozenge versus Placebo throat lozenge	0.6 mg AMC throat lozenge versus 1.2mg DCBA throat lozenge
5	2.10±0.93 (50)	1.96±1.08 (49)	1.53±0.83 (51)	0.009 **	**	*	ns
10	2.16±0.89 (50)	2.08±0.98 (49)	1.57±0.85 (51)	0.003 **	**	**	ns
15	2.22±1.02 (50)	2.06±0.99 (49)	1.57±0.85 (51)	0.002 **	***	*	ns
30	2.06±0.91 (50)	2.08±0.98 (49)	1.73±0.96 (51)	0.12	ns	ns	ns
45	1.80±0.78 (50)	1.96±0.98 (49)	1.71±0.90 (51)	0.34	ns	ns	ns
60	1.70±0.79 (50)	1.90±0.92 (49)	1.73±0.98 (51)	0.43	ns	ns	ns
75	1.66±0.80 (50)	1.80±0.98 (49)	1.71±0.94 (51)	0.67	ns	ns	ns
90	1.54±0.76 (50)	1.82±1.01 (49)	1.65±0.96 (51)	0.27	ns	ns	ns
105	1.56±0.84 (50)	1.76±0.97 (49)	1.63±0.96 (51)	0.46	ns	ns	ns
120	1.54±0.84 (50)	1.71±0.91 (49)	1.65±1.02 (51)	0.58	ns	ns	ns

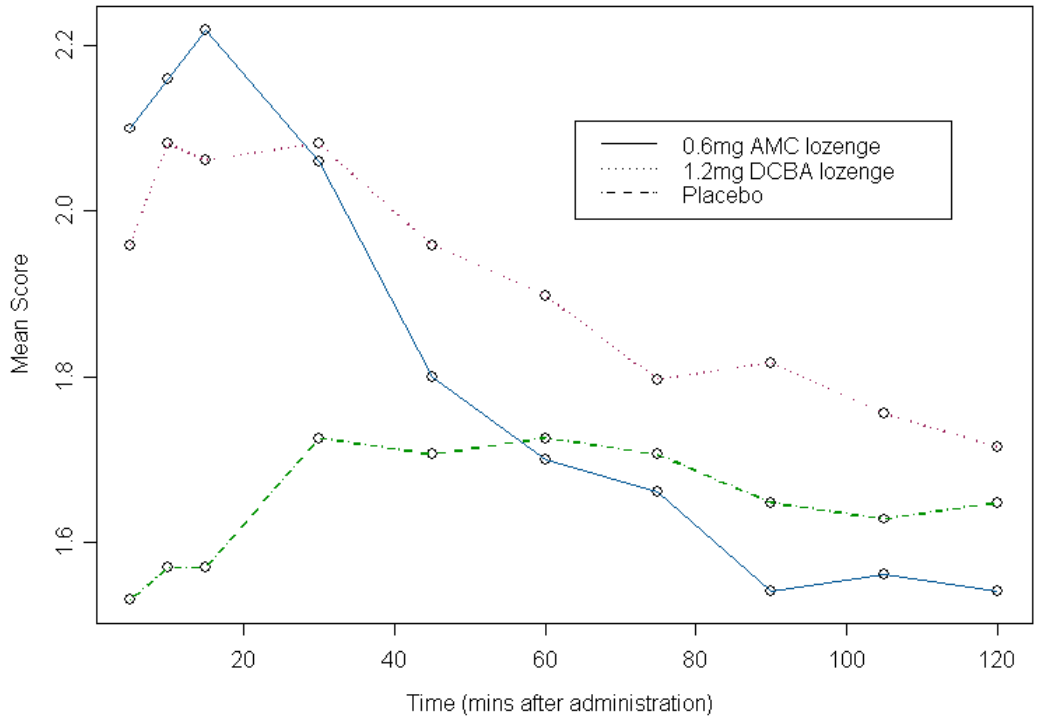
ns Comparison not statistically significant
* Comparison statistically significant at 5% level
** Comparison statistically significant at 1% level
*** Comparison statistically significant at 0.1% level

Source: Tables 14.2.35 to 14.2.44

Maximum mean throat numbness was recorded at 15 minutes post-dose for the 0.6 mg AMC throat lozenge, 10 and 30 minutes post-dose for the 1.2 mg DCBA throat lozenge and 30 and 60 minutes post-dose for the placebo throat lozenge. The rapid decline in mean numbness after 15 minutes post-dose for the 0.6 mg AMC throat lozenge group can clearly be seen in Figure 11.4.4 below. There was also a less marked decline in the in the 1.2 mg DCBA throat lozenge group after 30 minutes post-dose.

Figure 11.4.4 Mean throat numbness from 5 to 120 minutes post-dose – full analysis set

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



Overall treatment rating at two hours

There was no statistically significant overall difference between treatment groups with respect to the question asked at two hours “How you would rate this throat lozenge as a treatment for sore throat” recorded on an 11-point scale where 0 = “Poor” and 10 = “Excellent” (p=0.76). The centre effect was statistically significant (p=0.04) in the model, but the covariate baseline throat soreness failed to achieve statistical significance (p=0.15). The LS mean scores estimated from the ANCOVA model were 3.77, 3.49 and 3.36 for the 0.6 mg AMC throat lozenge, 1.2 mg DCBA throat lozenge and placebo throat lozenge groups respectively. Table 11.4.9 summarises these data, more detailed information is presented in Table 14.2.45.

Table 11.4.9 Overall treatment rating at two hours post dose – full analysis set

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

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	50	49	51
Mean±sd	4.10±2.75	3.88±2.91	3.71±3.15
LS mean[a]	3.77	3.49	3.36
Parameter estimates	LS mean[b]	95% CI	p
0.6mg AMC throat lozenge – Placebo	0.41	-0.72,1.54	0.47
1.2mg DCBA throat lozenge – Placebo	0.13	-1.01,1.27	0.82
0.6mg AMC throat lozenge – 1.2mg DCBA throat lozenge	0.28	-0.87,1.43	0.63

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment

Source: Tables 14.2.45

Onset of analgesia defined as time to first reporting "moderate sore throat pain relief" (which is the mid point on the 7-point sore throat relief scale)

Table 14.2.46 gives the results of the analysis relating to the time taken for subjects to report moderate sore throat pain relief. In total, 25/50 (50%) reported moderate pain relief in the 0.6 mg AMC throat lozenge group, 13/49 (27%) in the 1.2 mg DCBA throat lozenge group and 20/51 (39%) in the placebo throat lozenge group. The overall comparison between treatment groups of time to reporting moderate pain relief failed to achieve statistical significance (p=0.054). However the pairwise comparison between the 0.6 mg AMC throat lozenge group and the 1.2 mg DCBA throat lozenge group was statistically significant (p=0.02) in favour of the 0.6 mg AMC throat lozenge. The centre effect and the covariate baseline throat soreness failed to achieve statistical significance. It was not possible to estimate median times to reporting since moderate pain relief had not been achieved by more than 50% of patients in any treatment group.

Consumer questionnaire (question completed five minutes after dosing)

"After taking the product, did you feel any relief from the moment you swallowed?"

There was a statistically significant overall difference between treatments in consumer perception of immediate relief reported five minutes after dosing (p=0.004). More patients reported feeling relief from the moment the throat lozenges were swallowed for both active throat lozenges compared with the placebo throat lozenge (p=0.003). The comparison between the two active throat lozenges was not statistically significant (p=0.95). The number of subjects who felt relief was as follows: 22 (45%) for the 1.2 mg DCBA throat lozenge, 22 (45%) for the 0.6 mg AMC throat lozenge and eight (16%) for the placebo throat lozenge. Table 11.4.10 summarises these data. The centre effect and the covariate baseline throat soreness failed to achieve statistical significance.

Table 11.4.10 Consumer questionnaire at 5 minutes post-dose: "After taking the product, did you feel any relief from the moment you swallowed?" – full analysis set

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	49	49	50
Number (%) reporting	22 (44.9%)	22 (44.9%)	8 (16.0%)
Parameter estimates	Odds ratio[b]	95% CI	p
0.6mg AMC throat lozenge vs. Placebo	4.44	1.68,11.70	0.003 **
1.2mg DCBA throat lozenge vs. Placebo	4.32	1.63,11.41	0.003 **
0.6mg AMC throat lozenge vs. 1.2mg DCBA throat lozenge	1.03	0.45,2.34	0.95

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

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

Source: Table 14.2.47

Consumer questionnaire (questions completed two hours after dosing)

"Do you feel any better than before you took the throat lozenge?"

There was no statistically significant overall difference between the treatment groups regarding whether the patients felt better than before they took the throat lozenge (p=0.50). The centre effect was statistically significant (p=0.047) in the model but the covariate baseline throat soreness failed to achieve statistical significance. The numbers of patients who reported feeling better than before dosing were as follows: 21 (42%) for the placebo throat lozenge, 16 (33%) for the 0.6 mg AMC throat lozenge and 15 (31%) for the 1.2 mg DCBA throat lozenge. Table 11.4.11 summarises these data.

Table 11.4.11 Consumer questionnaire at two hours post-dose: "Do you feel any better than before you took the throat lozenge?" – full analysis set

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	49	48	50
Number (%) reporting	16 (32.7%)	15 (31.3%)	21 (42.0%)
Parameter estimates	Odds ratio[b]	95% CI	p
0.6 mg AMC throat lozenge vs. Placebo	0.65	0.28,1.54	0.33
1.2 mg DCBA throat lozenge vs. Placebo	0.63	0.27,1.51	0.30
0.6 mg AMC throat lozenge vs. 1.2 mg DCBA throat lozenge	1.03	0.42,2.51	0.95

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

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

Source: Table 14.2.48

"How can you describe the type of relief this throat lozenge gave you?"

Table 11.4.12 presents details of number of subjects reporting each type of relief the throat lozenge provided. There was no statistically significant overall difference between the treatment groups for any of the seven types of relief (p>0.10 in all cases). The centre effect was statistically significant in the model for "no relief" (p<0.02) and the covariate baseline throat soreness was statistically significant for "soothing relief" (p=0.02). The number of subjects reporting "no relief" in each treatment group were 22 (43%) for the placebo throat lozenge, 17 (35%) for the 1.2 mg DCBA throat lozenge and 16 (32%) for the 0.6 mg AMC throat lozenge. Further details are given in Tables 14.2.49 to 14.2.55.

Table 11.4.12 Number (%) patients reporting each type of relief the throat lozenge provided at two hours post-dose – full analysis set

Type	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge	Overall p-value	0.6 mg AMC throat lozenge versus Placebo throat lozenge	1.2 mg DCBA throat lozenge versus Placebo throat lozenge	0.6 mg AMC throat lozenge versus 1.2mg DCBA throat lozenge
N	50	49	51				
Pain	10 (20.0%)	4 (8.2%)	7 (13.7%)	0.19	ns	ns	ns
Soreness	11 (22.0%)	9 (18.4%)	11 (21.6%)	0.76	ns	ns	ns
Relief from burning	10 (20.0%)	7 (14.3%)	7 (13.7%)	0.59	ns	ns	ns
Soothing	22 (44.0%)	24 (49.0%)	20 (39.2%)	0.61	ns	ns	ns
Coating	4 (8.0%)	4 (8.2%)	3 (5.9%)	0.79	ns	ns	ns
Relief from swelling	2 (4.0%)	2 (4.1%)	2 (3.9%)	1.00	ns	ns	ns
No relief	16 (32.0%)	17 (34.7%)	22 (43.1%)	0.44	ns	ns	ns

ns Comparison not statistically significant

Source: Tables 14.2.49 to 14.2.55

"Overall, how satisfied are you with the speed with which the throat lozenge began to give you any relief?"

There was no statistically significant overall difference between treatment groups in the responses to this question, recorded on a 5-point scale where 1 = "Very satisfied" and 5 = "Not at all satisfied" (p=0.47). Neither the centre effect nor the covariate baseline throat soreness achieved statistical significance. The LS mean scores estimated from the ANCOVA model were 3.23, 3.10 and 3.43 for the 0.6 mg AMC throat lozenge, 1.2 mg DCBA throat lozenge and placebo throat lozenge groups respectively. Table 11.4.13 summarises these data, more detailed information is presented in Table 14.2.56.

Table 11.4.13 Consumer questionnaire at two hours post-dose: "Overall, how satisfied are you with the speed with which the throat lozenge began to give you any relief?" – full analysis set

Measured on a 5-point scale where 1 = Very satisfied, 2 = Quite satisfied, 3 = Average, 4 = Not very satisfied, 5 = Not at all satisfied

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	50	49	51
Mean±sd	3.20±1.31	3.02±1.31	3.37±1.36
LS mean[a]	3.23	3.10	3.43
Parameter estimates	LS mean[b]	95% CI	p
0.6mg AMC throat lozenge – Placebo	-0.20	-0.72,0.33	0.46
1.2mg DCBA throat lozenge – Placebo	-0.32	-0.85,0.20	0.22
0.6mg AMC throat lozenge – 1.2mg DCBA throat lozenge	0.13	-0.40,0.66	0.63

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A negative difference favours the first treatment against second treatment
Source: Table 14.2.56

"Overall, how satisfied are you with any soothing relief that the throat lozenge gave you?"

There was no statistically significant overall difference between treatment groups in the responses to this question, recorded on a 5-point scale where 1 = "Very satisfied" and 5 = "Not at all satisfied" (p=0.53). Neither the centre effect nor the covariate baseline throat soreness achieved statistical significance in the ANCOVA model. The LS mean scores estimated from the ANCOVA model were 3.25, 3.16 and 3.46 for the 0.6 mg AMC throat lozenge, 1.2 mg DCBA throat lozenge and placebo throat lozenge groups respectively. Table 11.4.14 summarises these data and more detailed information is presented in Table 14.2.57.

Table 11.4.14 Consumer questionnaire at two hours post-dose: "Overall, how satisfied are you with any soothing relief that the throat lozenge gave you?" – full analysis set

Measured on a 5-point scale where 1 = Very satisfied, 2 = Quite satisfied, 3 = Average, 4 = Not very satisfied, 5 = Not at all satisfied

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	50	49	51
Mean±sd	3.20±1.37	3.06±1.34	3.39±1.36
LS mean[a]	3.25	3.16	3.46
Parameter estimates	LS mean[b]	95% CI	p
0.6 mg AMC throat lozenge – Placebo	-0.21	-0.74,0.32	0.44
1.2 mg DCBA throat lozenge – Placebo	-0.30	-0.83,0.24	0.28
0.6 mg AMC throat lozenge – 1.2mg DCBA throat lozenge	0.09	-0.46,0.63	0.75

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A negative difference favours the first treatment against second treatment
Source: Table 14.2.57

"Overall, how satisfied are you with the length of time of pain relief that the throat lozenge gave you?"

There was no statistically significant overall difference between treatment groups in the responses to this question, recorded on a 5-point scale where 1 = "Very satisfied" and 5 = "Not at all satisfied" (p=0.86). Neither the centre effect nor the covariate baseline throat soreness achieved statistical significance. The LS mean scores estimated from the ANCOVA model were 3.76, 3.88 and 3.79 for the 0.6 mg AMC throat lozenge, 1.2 mg DCBA throat lozenge and placebo throat lozenge groups respectively. Table 11.4.15 summarises these data and more detailed information is presented in Table 14.2.58.

Table 11.4.15 Consumer questionnaire at two hours post-dose: "Overall, how satisfied are you with the length of time of pain relief that the throat lozenge gave you?" – full analysis set

Measured on a 5-point scale where 1 = Very satisfied, 2 = Quite satisfied, 3 = Average, 4 = Not very satisfied, 5 = Not at all satisfied

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	50	49	51
Mean±sd	3.60±1.26	3.69±1.00	3.63±1.20
LS mean[a]	3.76	3.88	3.79
Parameter estimates	LS mean[b]	95% CI	p
0.6 mg AMC throat lozenge – Placebo	-0.04	-0.49,0.41	0.86
1.2 mg DCBA throat lozenge – Placebo	0.09	-0.37,0.54	0.71
0.6 mg AMC throat lozenge – 1.2mg DCBA throat lozenge	-0.12	-0.58,0.33	0.59

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A negative difference favours the first treatment against second treatment
Source: Table 14.2.58

"Overall, how satisfied are you with the strength of pain relief with which the throat lozenge began to give you relief?"

There was no statistically significant overall difference between treatment groups in the responses to this question, recorded on a 5-point scale where 1 = "Very satisfied" and 5 = "Not at all satisfied" (p=0.73). Neither the centre effect nor the covariate baseline throat soreness achieved statistical significance. The LS mean scores estimated from the ANCOVA model were 3.60, 3.64 and 3.78 for the 0.6 mg AMC throat lozenge, 1.2 mg DCBA throat lozenge and placebo throat lozenge groups respectively. Table 11.4.16 summarises these data and more detailed information is presented in Table 14.2.59.

Table 11.4.16 Consumer questionnaire at two hours post-dose: "Overall, how satisfied are you with the strength of pain relief with which the throat lozenge began to give you relief?" – full analysis set

Measured on a 5-point scale where 1 = Very satisfied, 2 = Quite satisfied, 3 = Average, 4 = Not very satisfied, 5 = Not at all satisfied

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	50	49	51
Mean±sd	3.54±1.16	3.53±1.16	3.71±1.22
LS mean[a]	3.60	3.64	3.78
Parameter estimates	LS mean[b]	95% CI	p
0.6 mg AMC throat lozenge – Placebo	-0.18	-0.64,0.29	0.45
1.2 mg DCBA throat lozenge – Placebo	-0.14	-0.61,0.33	0.56
0.6 mg AMC throat lozenge – 1.2mg DCBA throat lozenge	-0.04	-0.51,0.43	0.88

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A negative difference favours the first treatment against second treatment
Source: Table 14.2.59

"Where in the mouth/throat did you feel the throat lozenge working?"

Table 11.4.17 gives details of where in the mouth the patients felt the throat lozenge working. The most commonly-reported area was the back of the throat, with 25 (50%) reporting within the 0.6 mg AMC throat lozenge group, 23 (48%) reporting within the 1.2 mg DCBA throat lozenge group and 22 (43%) reporting within the placebo throat lozenge group.

Table 11.4.17 Consumer questionnaire at two hours post-dose: "Where in the mouth/throat did you feel the throat lozenge working?" – full analysis set

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	50	48	51
Tonsils	6 (12.0%)	5 (10.4%)	4 (7.8%)
Back of mouth	13 (26.0%)	10 (20.8%)	9 (17.6%)
Back of throat	25 (50.0%)	23 (47.9%)	22 (43.1%)
Whole of throat	7 (14.0%)	5 (10.4%)	3 (5.9%)
Deep down in the throat	8 (16.0%)	1 (2.1%)	6 (11.8%)
Throughout the throat	2 (4.0%)	7 (14.6%)	2 (3.9%)
Where it hurts	5 (10.0%)	9 (18.8%)	9 (17.6%)
In the right place	2 (4.0%)	3 (6.3%)	3 (5.9%)
Other	10 (20.0%)	13 (27.1%)	18 (35.3%)

Source: Table 14.2.60

"How deep down within the throat was the relief felt?

There was no statistically significant overall difference between treatment groups in the responses to this question, recorded on a 10-point scale where 1 = "Not at all deep in throat" and 10 = "Very deep in throat" (p=0.35). The centre effect was statistically significant (p=0.03) in the ANCOVA model, but the covariate baseline throat soreness failed to achieve statistical significance. The LS mean scores estimated from the ANCOVA model were 3.87, 3.59 and 3.19 for the 0.6 mg AMC throat lozenge, 1.2 mg DCBA throat lozenge and placebo throat lozenge groups

respectively. Table 11.4.18 summarises these data and more detailed information is presented in Table 14.2.61.

Table 11.4.18 Consumer questionnaire at two hours post-dose: "How deep down within the throat was the relief felt?" – full analysis set

Measured on a 10-point scale where 1 = Not at all deep in the throat, 10 = Very deep in the throat

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	50	49	51
Mean±sd	4.28±2.50	4.00±2.38	3.59±2.33
LS mean[a]	3.87	3.59	3.19
Parameter estimates	LS mean[b]	95% CI	p
0.6mg AMC throat lozenge – Placebo	0.68	-0.25,1.61	0.15
1.2mg DCBA throat lozenge – Placebo	0.40	-0.53,1.34	0.40
0.6mg AMC throat lozenge – 1.2mg DCBA throat lozenge	0.27	-0.67,1.22	0.57

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment

Source: Tables 14.2.61

"How deep down within the throat do you think the throat lozenge coats the throat?"

There was no statistically significant overall difference between treatment groups in the responses to this question recorded on a 10-point scale where 1 = "Not at all deep in throat" and 10 = "Very deep in throat" (p=0.86). The centre effect was statistically significant (p=0.03) in the ANCOVA model, but the covariate baseline throat soreness failed to achieve statistical significance. The LS mean scores estimated from the ANCOVA model were 3.52, 3.57 and 3.33 for the 0.6 mg AMC throat lozenge, 1.2 mg DCBA throat lozenge and placebo throat lozenge groups respectively. Table 11.4.19 summarises these data, more detailed information is presented in Table 14.2.62.

Table 11.4.19 Consumer questionnaire at two hours post-dose: "How deep down within the throat do you think the throat lozenge coats the throat?" – full analysis set

Measured on a 10-point scale where 1 = Not at all deep in the throat, 10 = Very deep in the throat

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	50	49	51
Mean±sd	3.98±2.27	4.00±2.26	3.78±2.47
LS mean[a]	3.52	3.57	3.33
Parameter estimates	LS mean[b]	95% CI	p
0.6 mg AMC throat lozenge – Placebo	0.19	-0.72,1.09	0.68
1.2 mg DCBA throat lozenge – Placebo	0.23	-0.68,1.14	0.61
0.6 mg AMC throat lozenge – 1.2mg DCBA throat lozenge	-0.05	-0.96,0.87	0.92

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment

Source: Tables 14.2.62

"How moisturising/lubricating is the throat lozenge?"

There was no statistically significant overall difference between treatment groups in the responses to this question recorded on a 10-point scale where 1 = "Not moisturising/lubricating at all" and 10 = "Very moisturising/lubricating" (p=0.70). Neither the centre effect nor the covariate baseline throat soreness achieved statistical significance. The LS mean scores estimated from the ANCOVA model were 4.35, 3.94 and 4.24 for the 0.6 mg AMC throat lozenge, 1.2 mg DCBA throat lozenge and placebo throat lozenge groups respectively. Table 11.4.20 summarises these data and more detailed information is presented in Table 14.2.63.

Table 11.4.20 Consumer questionnaire at two hours post-dose: "How moisturising/lubricating is the throat lozenge?" – full analysis set

Measured on a 10-point scale where 1 = Not moisturising/lubricating at all, 10 = Very moisturising/lubricating

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	50	49	51
Mean±sd	4.58±2.46	4.20±2.29	4.49±2.63
LS mean[a]	4.35	3.94	4.24
Parameter estimates	LS mean[b]	95% CI	p
0.6 mg AMC throat lozenge – Placebo	0.11	-0.85,1.07	0.82
1.2 mg DCBA throat lozenge – Placebo	-0.30	-1.26,0.67	0.54
0.6 mg AMC throat lozenge – 1.2mg DCBA throat lozenge	0.41	-0.57,1.38	0.41

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment

Source: Tables 14.2.63

"How soothing do you think this throat lozenge is?"

There was no statistically significant overall difference between treatment groups in the responses to this question, recorded on a 10-point scale where 1 = "Not at all soothing" and 10 = "Very soothing" (p=0.41). The centre effect was statistically significant (p=0.03) in the ANCOVA model, but the covariate baseline throat soreness did not achieve statistical significance. The LS mean scores estimated from the ANCOVA model were 4.43, 4.29 and 3.77 for the 0.6 mg AMC throat lozenge, 1.2 mg DCBA throat lozenge and placebo throat lozenge groups respectively. Table 11.4.21 summarises these data, more detailed information is presented in Table 14.2.64.

Table 11.4.21 Consumer questionnaire at two hours post-dose: "How soothing do you think this throat lozenge is?" – full analysis set

Measured on a 10-point scale where 1 = Not at all soothing, 10 = Very soothing

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	50	49	50
Mean±sd	4.72±2.76	4.63±2.64	4.08±2.65
LS mean[a]	4.43	4.29	3.77
Parameter estimates	LS mean[b]	95% CI	p
0.6 mg AMC throat lozenge – Placebo	0.66	-0.37,1.70	0.21
1.2 mg DCBA throat lozenge – Placebo	0.52	-0.52,1.57	0.32
0.6 mg AMC throat lozenge – 1.2mg DCBA throat lozenge	0.14	-0.91,1.19	0.79

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
Source: Tables 14.2.64

"How important is the soothing action to you?"

There was no statistically significant overall difference between treatment groups in the responses to this question recorded on a 5-point scale where 1 = "Not at all important" and 5 = "Extremely important" (p=0.97). Neither the centre effect nor the covariate baseline throat soreness achieved statistical significance. The LS mean scores estimated from the ANCOVA model were 3.53, 3.55 and 3.58 for the 0.6 mg AMC throat lozenge, 1.2 mg DCBA throat lozenge and placebo throat lozenge groups respectively. Table 11.4.22 summarises these data and more detailed information is presented in Table 14.2.65.

Table 11.4.22: Consumer questionnaire at two hours post-dose: "How important is the soothing action to you?" – full analysis set

Measured on a 5-point scale where 1 = Not at all important, 2 = A little important, 3 = Moderately important, 4 = Very important, 5 = Extremely important

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	50	49	51
Mean±sd	3.58±1.03	3.59±1.15	3.63±0.94
LS mean[a]	3.53	3.55	3.58
Parameter estimates	LS mean[b]	95% CI	p
0.6 mg AMC throat lozenge – Placebo	-0.05	-0.46,0.37	0.82
1.2 mg DCBA throat lozenge – Placebo	-0.03	-0.45,0.39	0.89
0.6 mg AMC throat lozenge – 1.2mg DCBA throat lozenge	-0.02	-0.44,0.40	0.93

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
Source: Table 14.2.65

"How long does the action of the throat lozenge last in your throat?"

There was a statistically significant overall difference between treatment groups in the consumer perception of the duration of action of the lozenges in the throat (p<0.01). Both active throat lozenges were thought to last for a statistically significantly shorter time in the throat than the placebo throat lozenge (p≤0.008). The comparison between the two active throat lozenges was not statistically significant (p=0.74). The covariate baseline throat soreness was also statistically significant

(p=0.0098) in the ANCOVA model, but the centre effect failed to achieve statistical significance. The number of subjects who reported duration of action less than half an hour were as follows: 19 (39%) for the 0.6 mg AMC throat lozenge, 15 (31%) for the 1.2 mg DCBA throat lozenge and nine (18%) for the placebo throat lozenge. Table 11.4.23 summarises these data, further details are given in Table 14.2.66.

Table 11.4.23 Consumer questionnaire at two hours post-dose: "How long does the action of the throat lozenge last in your throat?" – full analysis set

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	49	49	51
1 1/2 to 2 hours	2 (4.1%)	2 (4.1%)	10 (19.6%)
1 to 1 1/2 hours	7 (14.3%)	6 (12.2%)	8 (15.7%)
1/2 hour to 1 hour	13 (26.5%)	18 (36.7%)	10 (19.6%)
Less than 1/2 hour	19 (38.8%)	15 (30.6%)	9 (17.6%)
Not known	8 (16.3%)	8 (16.3%)	14 (27.5%)
Parameter estimates	Odds ratio[b]	95% CI	p
0.6 mg AMC throat lozenge vs. Placebo	0.28	0.12,0.65	0.003 **
1.2 mg DCBA throat lozenge vs. Placebo	0.32	0.14,0.74	0.008 **
0.6 mg AMC throat lozenge vs. 1.2mg DCBA throat lozenge	0.87	0.38,1.98	0.74

a Estimated from proportional odds model with factors for treatment and centre and a covariate for baseline throat soreness. A value > 1 indicates the first treatment has a longer duration of action. Responses recorded as "not known" are excluded from the analysis

** Comparison statistically significant at 1% level

Source: Table 14.2.66

"How much do you think this throat lozenge coats the throat?"

There was no statistically significant overall difference between treatment groups in the responses to this question recorded on a 10-point scale where 1 = "Not at all coating" and 10 = "Very coating" (p=0.68). Neither the centre effect nor the covariate baseline throat soreness achieved statistical significance. The LS mean scores estimated from the ANCOVA model were 3.53, 3.71 and 3.31 for the 0.6 mg AMC throat lozenge, 1.2 mg DCBA throat lozenge and placebo throat lozenge groups respectively. Table 11.4.24 summarises these data and more detailed information is presented in Table 14.2.67.

Table 11.4.24 Consumer questionnaire at two hours post-dose: "How much do you think this throat lozenge coats the throat?" – full analysis set

Measured on a 10-point scale where 1 = Not at all coating, 10 = Very coating

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	50	49	51
Mean±sd	4.00±2.28	4.14±2.23	3.78±2.44
LS mean[a]	3.53	3.71	3.31
Parameter estimates	LS mean[b]	95% CI	p
0.6 mg AMC throat lozenge – Placebo	0.22	-0.68,1.12	0.63
1.2 mg DCBA throat lozenge – Placebo	0.40	-0.50,1.31	0.38
0.6 mg AMC throat lozenge – 1.2mg DCBA throat lozenge	-0.18	-1.10,0.73	0.69

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
Source: Table 14.2.67

Opinion of the throat lozenge in terms of speed of action

There was no statistically significant overall difference between treatment groups in the consumer perception of the speed of action recorded on a 5-point scale where 1 = "Very fast acting" and 5 = "Very slow acting" (p=0.08). However, in pairwise comparison, the 1.2 mg DCBA throat lozenge was considered to act statistically significantly faster than the placebo throat lozenge (p=0.03). The two other pairwise comparisons failed to achieve statistical significance. The covariate baseline throat soreness was statistically significant (p=0.03) in the ANCOVA model, but the centre effect failed to achieve statistical significance. The LS mean scores estimated from the ANCOVA model were 2.79, 2.57 and 3.23 for the 0.6 mg AMC throat lozenge, 1.2 mg DCBA throat lozenge and placebo throat lozenge groups respectively. Table 11.4.25 summarises these data and more detailed information is presented in Table 14.2.68.

Table 11.4.25 Consumer questionnaire at two hours post-dose: Opinion of the throat lozenge in terms of speed of action – full analysis set

Measured on a 5-point scale where 1 = Very fast acting, 5 = Very slow acting

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	50	47	50
Mean±sd	2.78±1.53	2.47±1.43	3.18±1.49
LS mean[a]	2.79	2.57	3.23
Parameter estimates	LS mean[b]	95% CI	p
0.6 mg AMC throat lozenge – Placebo	-0.44	-1.02,0.14	0.14
1.2 mg DCBA throat lozenge – Placebo	-0.67	-1.26,-0.07	0.03 *
0.6 mg AMC throat lozenge – 1.2mg DCBA throat lozenge	0.23	-0.37,0.82	0.46

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A negative difference favours the first treatment against second treatment
* Comparison statistically significant at 5% level
Source: Table 14.2.68

Opinion of the throat lozenge in terms of how soothing it was

There was no statistically significant overall difference between treatment groups in the responses to this question recorded on a 5-point scale where 1 = "Not very soothing" and 5 = "Very soothing" (p=0.93). Neither the centre effect nor the covariate baseline throat soreness achieved statistical significance. The LS mean scores estimated from the ANCOVA model were 2.64, 2.74 and 2.67 for the 0.6 mg AMC throat lozenge, 1.2 mg DCBA throat lozenge and placebo throat lozenge groups respectively. Table 11.4.26 summarises these data and more detailed information is presented in Table 14.2.69.

Table 11.4.26 Consumer questionnaire at two hours post-dose: Opinion of the throat lozenge in terms of how soothing it was – full analysis set

Measured on a 5-point scale where 1 = Not very soothing, 5 = Very soothing

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo
N	50	47	50
Mean±sd	2.76±1.33	2.87±1.28	2.78±1.45
LS mean[a]	2.64	2.74	2.67
Parameter estimates	LS mean[b]	95% CI	p
0.6 mg AMC throat lozenge – Placebo	-0.03	-0.57,0.50	0.91
1.2 mg DCBA throat lozenge – Placebo	0.07	-0.47,0.62	0.79
0.6 mg AMC throat lozenge – 1.2mg DCBA throat lozenge	-0.11	-0.65,0.44	0.70

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
Source: Table 14.2.69

Opinion of the throat lozenge in term of how long it lasted

There was no statistically significant overall difference between treatment groups in the responses to this question recorded on a 5-point scale where 1 = "Not very long lasting" and 5 = "Very long lasting" (p=0.77). Neither the centre effect nor the covariate baseline throat soreness achieved statistical significance. The LS mean scores estimated from the ANCOVA model were 2.02, 2.10 and 2.21 for the 0.6 mg AMC throat lozenge, 1.2 mg DCBA throat lozenge and placebo throat lozenge groups respectively. Table 11.4.27 summarises these data and more detailed information is presented in Table 14.2.70.

Table 11.4.27 Consumer questionnaire at two hours post-dose: Opinion of the throat lozenge in term of how long it lasted – full analysis set

Measured on a 5-point scale where 1 = Not very long lasting, 5 = Very long lasting

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	50	47	50
Mean±sd	2.22±1.25	2.30±1.21	2.40±1.36
LS mean[a]	2.02	2.10	2.21
Parameter estimates	LS mean[b]	95% CI	p
0.6 mg AMC throat lozenge – Placebo	-0.18	-0.69,0.32	0.47
1.2 mg DCBA throat lozenge – Placebo	-0.10	-0.62,0.41	0.69
0.6 mg AMC throat lozenge – 1.2mg DCBA throat lozenge	-0.08	-0.60,0.44	0.76

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
Source: Table 14.2.70

Opinion of the throat lozenge in terms of how strong it was

There was no statistically significant overall difference between treatment groups in the responses to this question recorded on a 5-point scale where 1 = “Not very strong” and 5 = “Very strong” (p=0.55). Neither the centre effect nor the covariate baseline throat soreness achieved statistical significance. The LS mean scores estimated from the ANCOVA model were 2.50, 2.35 and 2.23 for the 0.6 mg AMC throat lozenge, 1.2 mg DCBA throat lozenge and placebo throat lozenge groups respectively. Table 11.4.28 summarises these data and more detailed information is presented in Table 14.2.71.

Table 11.4.28 Consumer questionnaire at two hours post-dose: Opinion of the throat lozenge in terms of how strong it was – full analysis set

Measured on a 5-point scale where 1 = Not very strong, 5 = Very strong

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
N	50	49	51
Mean±sd	2.52±1.33	2.37±1.13	2.25±1.13
LS mean[a]	2.50	2.35	2.23
Parameter estimates	LS mean[b]	95% CI	p
0.6 mg AMC throat lozenge – Placebo	0.27	-0.21,0.74	0.27
1.2 mg DCBA throat lozenge – Placebo	0.12	-0.36,0.60	0.63
0.6 mg AMC throat lozenge – 1.2mg DCBA throat lozenge	0.15	-0.34,0.63	0.55

a Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b A positive difference favours the first treatment against second treatment
Source: Table 14.2.71

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 one minor outlier for the analyses involving the primary endpoint for the full analysis set. Subject number 058 in the placebo throat lozenge group had a baseline sore throat severity of 8 with all the post-baseline scores being 10. As a

consequence, the value for the AUC for the change from baseline in throat soreness was 1.96 yet the next highest value overall was 0.98 and the next highest value in the placebo throat lozenge group was 0.44. Given that the data for the other two treatment groups were clearly normally distributed, it was decided to appeal to the robustness of the F-test rather than perform additional non-parametric analyses to accommodate this single outlier.

There was also evidence of non-normality for a number 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

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

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

Although, the terms for baseline scores and centre were statistically significant for some variables, there was no obvious trend among the efficacy variables to suggest that either had a major influence on the study results.

11.4.2.2 Handling of Dropouts or Missing Data

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

Because there were no missing data for the primary efficacy parameter (the area under the change from baseline curve in severity of throat soreness from baseline to two hours), no additional sensitivity analyses were performed for this endpoint. 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 statistical models included centre as a factor. There was no evidence to suggest that the results differed significantly between centres. Patients were recruited from

five centres. The largest number of patients randomised at any one centre was 81 (54%) patients, followed by 26 (17%) subjects, with the smallest number randomised being seven (5%) patients.

11.4.2.5 Multiple Comparison/Multiplicity

For the primary efficacy endpoint, treatment group differences were assessed using Fisher's protected LSD method i.e. if the overall treatment effect in the ANCOVA model was significant at the 5% level, pairwise comparison of the treatment groups was performed without any requirement to adjust the significance level for the pairwise comparisons.

11.4.2.6 Use of an "Efficacy Subset" of Subjects

The use of the Per Protocol (PP) population (defined in Section 11.1) was restricted to the primary efficacy endpoint (the area under the change from baseline curve (AUC) in severity of throat soreness, from baseline to two hours) and the AUC for sore throat pain relief. Five patients were excluded from the PP set but the statistical conclusions drawn from this subset were qualitatively identical to those drawn using the full analysis set.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

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

11.4.2.8 Examination of Subgroups

Exploratory subgroup analyses of the primary efficacy endpoint were performed for several key baseline characteristics. For each characteristic, the main effect and treatment-by-subgroup interaction terms were added to the model used in the primary endpoint analysis. Key variables of interest were centre (Table 14.2.72), baseline throat soreness severity (≤ median, > median: Table 14.2.73), age at study entry (≤ median, > median: Table 14.2.74), gender (Table 14.2.75), baseline Tonsillo-Pharyngitis Assessment score (≤ median, > median: Table 14.2.76) and baseline VAS for difficulty in swallowing (≤ median, > median: Table 14.2.77).

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

11.4.3 Tabulation of Individual Response Data

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

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

11.4.4 Drug Dose, Drug Concentration and Relationships to Response

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

11.4.5 Drug-Drug and Drug-Disease Interactions

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

11.4.6 By-subject Displays

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

11.4.7 Efficacy Conclusions

In the ANCOVA model for the full analysis set (n=150) for the primary endpoint (area under the change from baseline curve (AUC) in severity of throat soreness, from baseline to two hours) none of the effects in the model (treatment, centre and baseline throat soreness) achieved statistical significance (p-values 0.83, 0.83 and 0.12 respectively). The LS means reductions were -1.05 (0.6 mg AMC throat lozenge), -0.91 (1.2 mg DCBA throat lozenge) and -0.95 (placebo throat lozenge).

There was no statistically significant overall difference between treatment groups for the change from baseline in severity of throat soreness at any timepoint ($p>0.05$ in each case). The maximum decrease in throat soreness occurred at 15 minutes for the 0.6 mg AMC throat lozenge group, 30 minutes for the 1.2 mg DCBA throat lozenge group and two hours for the placebo throat lozenge group.

There was no statistically significant overall difference between treatment groups for the sore throat pain relief scores either in terms of AUC for sore throat pain relief over two hours or at each individual timepoint, with the exception of at 10 and 15 minutes post-dose, when significantly more relief was obtained with the 0.6 mg AMC throat lozenge than with the placebo throat lozenge ($p < 0.03$).

In the analysis of the AUC for change from baseline in difficulty in swallowing from baseline to two hours, the covariates baseline throat soreness and difficulty in swallowing were statistically significant, but there was no statistically significant overall difference between treatments. There was also no statistically significant overall difference between treatments at any individual timepoint. The maximum improvement in swallowing occurred at 15 minutes for the 0.6 mg AMC throat lozenge group, 30 minutes for the 1.2 mg DCBA throat lozenge group and two hours for the placebo throat lozenge group.

For the AUC for throat numbness from five minutes to two hours, the overall treatment effect was not statistically significant, although statistically significantly higher throat numbness scores were reported for both active throat lozenges compared with the placebo throat lozenge at 5, 10 and 15 minutes post-dose. Maximum numbness was obtained at 15 minutes for the 0.6 mg AMC throat lozenge group, 10 and 30 minutes for the 1.2 mg DCBA throat lozenge group and 30 and 60 minutes for the placebo throat lozenge group.

There was no statistically significant overall difference between treatments in terms of overall treatment rating.

The overall comparison between treatment groups of time to reporting moderate sore throat pain relief failed to achieve statistical significance (p=0.054), however the pairwise comparison between the 0.6 mg AMC throat lozenge group and the 1.2 mg DCBA throat lozenge group was statistically significant (p=0.02) in favour of the 0.6 mg AMC throat lozenge.

Statistically significantly more patients in the active throat lozenge groups claimed to have felt relief from the moment the throat lozenges were swallowed than in the placebo throat lozenge group (p = 0.003). The comparison between the two active throat lozenges was not statistically significant.

Patients in the 1.2 mg DCBA throat lozenge group reported that the throat lozenges had acted significantly faster compared with those in the placebo throat lozenge group (p=0.03) when graded on a 5-point scale where 1 = “Very fast acting” and 5 = “Very slow acting”. Both active throat lozenges were thought to have lasted a statistically significantly shorter time in the throat than the placebo throat lozenge (p≤0.008). The comparison between the two active throat lozenges was not statistically significant. The number of patients who reported duration of action less than half an hour were as follows: 19 (39%) for the 0.6 mg AMC throat lozenge, 15 (31%) for the 1.2 mg DCBA throat lozenge and nine (18%) for the placebo throat lozenge.

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

One hundred and fifty patients each took one throat lozenge, 50 patients receiving the 0.6 mg AMC throat lozenge, 49 receiving the 1.2 mg DCBA throat lozenge and 51 receiving the placebo throat lozenge.

12.2 Adverse Events (AEs)

12.2.1 Brief Summary of Events

Four (8%) patients reported a total of 5 treatment emergent adverse event in the 0.6 mg AMC lozenge group compared with two (4%) patients (5 events) in the 1.2 mg DCBA lozenge group and one (2%) patient (1 event) in the placebo group.

12.2.2 Display of Adverse Events

Table 14.3.3 presents a summary of treatment emergent adverse events by primary system organ class. The most common class for events reported was nervous system disorders with four reports (three in the 0.6 mg AMC throat lozenge and one in the 1.2 mg DCBA throat lozenge group).

Table 14.3.4 reports the number of patients reporting each preferred term. The most common treatment emergent adverse event reported was headache, with four

reports by four patients (three in the 0.6 mg AMC throat lozenge and one in the 1.2 mg DCBA throat lozenge group). Ear pain was reported once by one patient in the 0.6 mg AMC throat lozenge group and twice by one patient in the 1.2 mg DCBA throat lozenge group. The other event reported in the 0.6 mg AMC throat lozenge group was throat irritation (one event, one patient) while the other events reported in the 1.2 mg DCBA throat lozenge group were pain (one event, one patient) and nasal congestion (one event, one patient). One patient reported one event of cough in the placebo throat lozenge group.

Table 14.3.5 presents a summary of treatment emergent adverse events by primary system organ class, preferred term, severity and relationship to study medication. No adverse events were graded definitely, probably and possibly related to the study medication or as severe. All events were classed as mild.

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

Table 12.2.2 Severity and relationship of treatment-emergent adverse events to therapy – safety set

Total	0.6 mg AMC throat lozenge (n=50)		1.2 mg DCBA throat lozenge (n=49)		Placebo throat lozenge (n=51)	
	Number of subjects reporting	Number of reports (% of total)	Number of subjects reporting	Number of reports (% of total)	Number of subjects reporting	Number of reports (% of total)
Total	4 (8%)	5	2 (4%)	5	1 (2%)	1
Severity:						
Mild	4 (8%)	5 (100%)	2 (4%)	5 (100%)	1 (2%)	1 (100%)
Moderate	-	-	-	-	-	-
Severe	-	-	-	-	-	-
Relationship:						
Definite	-	-	-	-	-	-
Probable	-	-	-	-	-	-
Possible	-	-	-	-	-	-
Unlikely	3 (6%)	3 (60%)	1 (2%)	2 (40%)	1 (2%)	1 (100%)
None	1 (2%)	2 (40%)	1 (2%)	3 (60%)	-	-

Source: Appendix 16.2. Listings 16.2.7.1 and 16.2.7.2

12.2.3 Analysis of Adverse Events

There were no statistically significant pairwise treatment differences between the treatment groups in the number of patients reporting treatment emergent adverse events. For the 0.6 mg AMC throat lozenge group, four (8%) patients reported five adverse events. For the 1.2 mg DCBA throat lozenge group, two (4%) patients reported five adverse events. Within the placebo throat lozenge group, one (2%) patient reported one event.

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

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

12.4 Clinical Laboratory Evaluation

No clinical laboratory evaluations were performed in this study.

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

No other safety evaluations were performed in this study.

12.6 Safety Conclusions

Four (8%) patients reported at least one treatment emergent event in the 0.6 mg AMC throat lozenge group compared to two (4%) patients in the 1.2 mg DCBA throat lozenge group and one (2%) patient in the placebo throat lozenge group. A total of five treatment emergent events were reported in each of the two active throat lozenge groups compared to one event in the placebo throat lozenge group. No adverse event was graded “definitely”, “probably” or “possibly” related to the study medication and all were mild in severity. The most common treatment emergent adverse event reported was headache with four reports during the study involving four patients (three in the 0.6 mg AMC throat lozenge group and one in the 1.2 mg DCBA throat lozenge group).

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

Reckitt Benckiser Healthcare UK Limited (RB) has developed two new throat lozenges containing 0.6 mg AMC and 1.2 mg DCBA, respectively. The purpose of this study was to determine whether the known *in-vitro* action of blocking depolarization-induced sodium inward currents by AMC alone and DCBA alone would translate to an *in vivo* analgesic effect. It was planned that the efficacy data provided would be used to determine the future development of these single active throat lozenges.

A total of 150 patients with sore throat were randomised into the study (50 patients received the 0.6 mg AMC throat lozenge, 49 patients received the 1.2 mg DCBA throat lozenge and 51 patients received the placebo throat lozenge). The treatment groups were similar in terms of baseline sore throat severity, as assessed using the 11-point throat soreness scale, the 100 mm VAS for difficulty in swallowing and the 21-point Tonsillo-Pharyngitis Assessment scale. Treatment groups were similar in terms of demographic characteristics, with the exception that there were marginally more males in the active throat lozenge groups than the placebo throat lozenge group. The baseline severity of throat soreness in this study population was similar to that observed in other sore throat studies involving larger numbers of patients[11, 14, 19, 21].

The variability of the primary efficacy parameter (the area under the change from baseline curve (AUC) in severity of throat soreness, from baseline to two hours) observed during the study was 1.15 (root mean square error from the ANCOVA model of the full analysis set), which was slightly lower than the level of variability

observed in the study on which the power assessment was based (1.27). The level of variability observed in another recent study was also of the same magnitude (1.09)[21]. The current study was therefore adequately powered to meets its objectives.

There was no statistically significant overall difference between treatment groups in terms of the primary endpoint (the area under the change from baseline curve (AUC) in severity of throat soreness, from baseline to two hours). There was also no statistically significant overall difference between treatments in terms of the secondary endpoint AUC for sore throat pain relief over two hours.

Sore throat studies have typically used either AUC for sore throat pain relief or change from baseline throat soreness AUC as the primary endpoint[11, 12, 14, 19, 20]. Studies using flurbiprofen[11, 14, 20, 12] and a study using the combination of 0.6 mg AMC and 1.2 mg DCBA[21] (Strepsils®) have indicated that throat soreness and sore throat pain relief AUCs are similarly sensitive endpoints in that a statistically significant difference between active and placebo is often seen for both endpoints[11, 214, 12] or for none[20]. The current study conforms to this observed pattern.

There was no statistically significant overall difference between treatments in terms of change from baseline in severity of throat soreness at any individual timepoint. In terms of sore throat relief scores, however, significantly more relief was obtained with the 0.6 mg AMC throat lozenge than with the placebo throat lozenge ($p < 0.03$) at 10 and 15 minutes post-dose. This is consistent with the fact that the maximum decrease in throat soreness occurred at 15 minutes for the 0.6 mg AMC throat lozenge, whereas it did not occur until 30 minutes for the 1.2 mg DCBA throat lozenge group and two hours for the placebo throat lozenge group.

In terms of AUC from baseline to two hours for difficulty in swallowing, the covariates baseline throat soreness and difficulty in swallowing were statistically significant, with greater improvement in swallowing occurring in patients who had less difficulty in swallowing and a higher throat soreness score at baseline. However, there was no statistically significant overall difference between treatments either in terms of AUC from baseline to two hours or at any individual timepoint. The maximum improvement in ability to swallow occurred at 15 minutes for the 0.6 mg AMC throat lozenge group, 30 minutes for the 1.2 mg DCBA throat lozenge group and at two hours for the placebo throat lozenge group, again possibly indicating a trend towards greater effect at early timepoints of the 0.6 mg AMC throat lozenge compared with the placebo throat lozenge.

For the AUC for throat numbness from five minutes to two hours, the treatment effect was not statistically significant, although statistically significantly higher throat numbness scores were reported for the active throat lozenges compared with placebo at 5, 10 and 15 minutes post-dose. This further suggests that any difference between the active and placebo throat lozenges was short-lived. None of the other pairwise comparisons was statistically significant. Maximum numbness was obtained at 15 minutes for the 0.6 mg AMC throat lozenge group, 10 and 30 minutes for the 1.2 mg DCBA throat lozenge group and 30 and 60 minutes for the placebo throat lozenge group.

Although the overall comparison between treatment groups of time to reporting moderate sore throat pain relief failed to achieve statistical significance, the pairwise comparison between 0.6 mg AMC throat lozenge group and the 1.2 mg DCBA throat lozenge group was statistically significant (p=0.02) in favour of the 0.6 mg AMC throat lozenge. However, it was not possible to estimate median times to reporting since moderate pain relief was not achieved by more than 50% of patients in any of the treatment groups.

When asked at five minutes post-dose whether they had felt any relief from the moment the throat lozenge had been swallowed, significantly more patients answered “yes” in the active throat lozenge groups than in the placebo throat lozenge group (p = 0.003 in both cases). The comparison between the two active throat lozenges was not statistically significant.

Of the consumer questions asked at two hours post-dose relating to whether the patients felt better than before taking the throat lozenge; the type of relief provided; satisfaction with the speed, duration and strength of relief; location of action; depth of relief and coating action in throat; degree of moisturizing/lubricating and soothing action; duration of action; degree of throat coating and the patients overall opinion of the throat lozenge in terms of onset of action, ability to sooth, duration and strength, only two yielded statistically significant treatment differences. When asked at two hours post-dose how fast-acting the throat lozenges had been, the 1.2 mg DCBA throat lozenge was thought to have acted significantly faster than the placebo throat lozenge (p=0.03) when graded on a 5-point scale where 1 = “Very fast acting and 5 = “Very slow acting”. This is not consistent with the sore throat pain relief scores, which indicated a possible trend towards a greater effect of the 0.6 mg AMC throat lozenge at earlier timepoints.

Both active throat lozenges were thought to have lasted a statistically significantly shorter time in the throat than the placebo throat lozenge (p≤0.008). The comparison between the two active throat lozenges was not statistically significant. The numbers of patients who reported duration of action less than half an hour were as follows: 19 (39%) for the 0.6 mg AMC throat lozenge, 15 (31%) for the 1.2 mg DCBA throat lozenge and nine (18%) for the placebo throat lozenge. While 20% of patients in the placebo throat lozenge group reported duration of action between 1.5 and two hours, only 4% of patients in each of the active throat lozenge groups did likewise. This is consistent with the fact that maximum reduction in throat soreness and throat numbness occurred earlier in the active throat lozenge groups than in the placebo throat lozenge group.

Levels of satisfaction were relatively consistent for the questions relating to satisfaction with speed of action, soothing relief, duration and strength of relief, with more patients reporting either “not very satisfied” or “not at all satisfied” than those reporting either “very satisfied” or “quite satisfied”.

The fact that there were no significant treatment differences in terms of the overall treatment rating reflects the overall inability of the consumer questionnaire to discriminate between treatments.

In a study comparing the combination of 0.6 mg AMC and 1.2 mg DCBA (Strepsils®) throat lozenges with placebo throat lozenges[21], which used a very similar methodology with approximately 75 patients per treatment group, the superiority of Strepsils throat lozenges over the placebo throat lozenges was clearly apparent with highly statistically significant differences for all the analgesic variables related to sore throat relief, throat soreness, throat numbness and difficulty in swallowing, in addition to overall treatment rating. The fact that the single actives alone failed to show consistent advantage over placebo suggests that the efficacy of Strepsils® throat lozenges is due to the combination of the actives and would not support further development of either single active at the existing doses.

13.2 Conclusion

In terms of the efficacy assessment subjective rating scales, statistically significant treatment group differences in favour of the 0.6 mg AMC throat lozenge and/or the 1.2 mg DCBA throat lozenge compared with the placebo throat lozenge were observed only at isolated individual timepoints up to 15 minutes post-dose and not in terms of AUC to two hours. Responses to the various consumer questions relating to onset and duration of action indicated a perceived faster action for either one or both active throat lozenges compared with the placebo throat lozenge and a shorter duration of action than the placebo throat lozenge. Failure of both the 0.6 mg AMC and 1.2 mg DCBA throat lozenges to demonstrate a consistent advantage over the placebo throat lozenge suggests their combination is required to achieve the well-established efficacy of Strepsils® throat lozenges.

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

14.1 Demographic Data

14.1.1 Details of withdrawal – Safety set

14.1.2 Demographics – Full analysis set

14.1.3 Relevant previous medical history – Full analysis set

14.1.4 Relevant ongoing medical history – Full analysis set

14.1.5 Screening assessments – Full analysis set

14.1.6 Baseline efficacy assessments – Full analysis set

14.1.7 Concomitant medication ongoing at randomisation – Full analysis set

14.2 Efficacy Data

14.2.1.1 Primary efficacy endpoint - AUC from baseline to two hours post-dose for the change from baseline in throat soreness - Full analysis set

14.2.1.2 Primary efficacy endpoint - AUC from baseline to two hours post-dose for the change from baseline in throat soreness – Per-protocol set

14.2.2 Change from baseline in throat soreness at 5 minutes post-dose - Full

analysis set

14.2.3 Change from baseline in throat soreness at 10 minutes post-dose - Full analysis set

14.2.4 Change from baseline in throat soreness at 15 minutes post-dose - Full analysis set

14.2.5 Change from baseline in throat soreness at 30 minutes post-dose - Full analysis set

14.2.6 Change from baseline in throat soreness at 45 minutes post-dose - Full analysis set

14.2.7 Change from baseline in throat soreness at 60 minutes post-dose - Full analysis set

14.2.8 Change from baseline in throat soreness at 75 minutes post-dose - Full analysis set

14.2.9 Change from baseline in throat soreness at 90 minutes post-dose - Full analysis set

14.2.10 Change from baseline in throat soreness at 105 minutes post-dose - Full analysis set

14.2.11 Change from baseline in throat soreness at two hours post-dose - Full analysis set

14.2.12.1 AUC from baseline to two hours post-dose for sore throat relief - Full analysis set

14.2.12.2 AUC from baseline to two hours post-dose for sore throat relief - Per-protocol set

14.2.13 Sore throat relief at 5 minutes post-dose - Full analysis set

14.2.14 Sore throat relief at 10 minutes post-dose - Full analysis set

14.2.15 Sore throat relief at 15 minutes post-dose - Full analysis set

14.2.16 Sore throat relief at 30 minutes post-dose - Full analysis set

14.2.17 Sore throat relief at 45 minutes post-dose - Full analysis set

14.2.18 Sore throat relief at 60 minutes post-dose - Full analysis set

14.2.19 Sore throat relief at 75 minutes post-dose - Full analysis set

14.2.20 Sore throat relief at 90 minutes post-dose - Full analysis set

14.2.21 Sore throat relief at 105 minutes post-dose - Full analysis set

14.2.22 Sore throat relief at two hours post-dose - Full analysis set

14.2.23 AUC from baseline to two hours for the change from baseline in difficulty in swallowing - Full analysis set

14.2.24 Change from baseline in difficulty in swallowing at 5 minutes post-dose - Full analysis set

14.2.25 Change from baseline in difficulty in swallowing at 10 minutes post-dose - Full analysis set

14.2.26 Change from baseline in difficulty in swallowing at 15 minutes post-dose - Full analysis set

14.2.27 Change from baseline in difficulty in swallowing at 30 minutes post-

dose - Full analysis set

14.2.28 Change from baseline in difficulty in swallowing at 45 minutes post-dose - Full analysis set

14.2.29 Change from baseline in difficulty in swallowing at 60 minutes post-dose - Full analysis set

14.2.30 Change from baseline in difficulty in swallowing at 75 minutes post-dose - Full analysis set

14.2.31 Change from baseline in difficulty in swallowing at 90 minutes post-dose - Full analysis set

14.2.32 Change from baseline in difficulty in swallowing at 105 minutes post-dose - Full analysis set

14.2.33 Change from baseline in difficulty in swallowing at two hours post-dose - Full analysis set

14.2.34 AUC for throat numbness measurements from 5 to 120 minutes - Full analysis set

14.2.35 Throat numbness at 5 minutes post-dose - Full analysis set

14.2.36 Throat numbness at 10 minutes post-dose - Full analysis set

14.2.37 Throat numbness at 15 minutes post-dose - Full analysis set

14.2.38 Throat numbness at 30 minutes post-dose - Full analysis set

14.2.39 Throat numbness at 45 minutes post-dose - Full analysis set

14.2.40 Throat numbness at 60 minutes post-dose - Full analysis set

14.2.41 Throat numbness at 75 minutes post-dose - Full analysis set

14.2.42 Throat numbness at 90 minutes post-dose - Full analysis set

14.2.43 Throat numbness at 105 minutes post-dose - Full analysis set

14.2.44 Throat numbness at two hours post-dose - Full analysis set

14.2.45 Overall treatment rating at two hours post-dose - Full analysis set

14.2.46 Onset of analgesia - time to first reporting "moderate sore throat pain relief" - Full analysis set

14.2.47 Consumer questionnaire: After taking the product, did you feel any relief from the moment you swallowed at 5 minutes post-dose?- Full analysis set

14.2.48 Consumer questionnaire: Do you feel any better than before you took the throat lozenge at two hours post-dose?- Full analysis set

14.2.49 Consumer questionnaire: At two hours post-dose, did this throat lozenge give you pain relief? - Full analysis set

14.2.50 Consumer questionnaire: At two hours post-dose, did this throat lozenge give you soreness relief? - Full analysis set

14.2.51 Consumer questionnaire: At two hours post-dose, did this throat lozenge give you relief from burning? - Full analysis set

14.2.52 Consumer questionnaire: At two hours post-dose, did this throat lozenge give you soothing relief? - Full analysis set

14.2.53 Consumer questionnaire: At two hours post-dose, did this throat

lozenge give you coating relief? - Full analysis set

14.2.54 Consumer questionnaire: At two hours post-dose, did this throat lozenge give you relief from swelling? - Full analysis set

14.2.55 Consumer questionnaire: At two hours post-dose, did this throat lozenge give you no relief? - Full analysis set

14.2.56 Consumer questionnaire: At two hours post-dose, how satisfied are you with the speed with which the throat lozenge gave you any relief? - Full analysis set

14.2.57 Consumer questionnaire: Overall, how satisfied are you with any soothing relief that the throat lozenge gave you? - Full analysis set

14.2.58 Consumer questionnaire: Overall, how satisfied are you with the length of time of pain relief that the throat lozenge gave you? - Full analysis set

14.2.59 Consumer questionnaire: Overall, how satisfied are you with the strength of pain relief with which the throat lozenge began to give you relief? - Full analysis set

14.2.60 Consumer questionnaire: At two hours post-dose, where in the mouth/throat did you feel the throat lozenge working? - Full analysis set

14.2.61 Consumer questionnaire: How deep down within the throat was the relief felt? - Full analysis set

14.2.62 Consumer questionnaire: How deep down within the throat do you think this throat lozenge coats the throat? - Full analysis set

14.2.63 Consumer questionnaire: Please tell us your overall opinion of how moisturising/lubricating this throat lozenge is - Full analysis set

14.2.64 Consumer questionnaire: How soothing do you think this throat lozenge is? - Full analysis set

14.2.65 Consumer questionnaire: How important is the soothing action to you? - Full analysis set

14.2.66 Consumer questionnaire: How long does the action of the throat lozenge last in your throat? - Full analysis set

14.2.67 Consumer questionnaire: How much do you think this throat lozenge coats the throat? - Full analysis set

14.2.68 Consumer questionnaire: Please tell us your overall opinion of the throat lozenge in terms of speed of action - Full analysis set

14.2.69 Consumer questionnaire: Please tell us your overall opinion of the throat lozenge in terms of soothing action - Full analysis set

14.2.70 Consumer questionnaire: Please tell us your overall opinion of the throat lozenge in terms of duration of action - Full analysis set

14.2.71 Consumer questionnaire: Please tell us your overall opinion of the throat lozenge in terms of strength - Full analysis set

14.2.72 Primary efficacy endpoint – AUC from baseline to two hours post-dose for the change from baseline in throat soreness by centre - Full analysis set

14.2.73 Primary efficacy endpoint – AUC from baseline to two hours post-

dose for the change from baseline in throat soreness by baseline throat soreness severity - Full analysis set

14.2.74 Primary efficacy endpoint – AUC from baseline to two hours post-dose for the change from baseline in throat soreness by age at study entry - Full analysis set

14.2.75 Primary efficacy endpoint – AUC from baseline to two hours post-dose for the change from baseline in throat soreness by gender - Full analysis set

14.2.76 Primary efficacy endpoint – AUC from baseline to two hours post-dose for the change from baseline in throat soreness by total score from tonsillo-pharyngitis assessment at baseline - Full analysis set

14.2.77 Primary efficacy endpoint - AUC from baseline to two hours post-dose for the change from baseline in throat soreness by VAS for difficulty in swallowing at baseline - Full analysis set

14.3 Safety Data

14.3.1 Extent of exposure to study medication - Safety set

14.3.2 Summary of treatment emergent adverse event reporting – Safety set

14.3.3 MedDRA Summary of treatment emergent adverse events by primary system organ class – Safety set

14.3.4 MedDRA Summary of treatment emergent adverse events by primary system organ class and preferred term – Safety set

14.3.5 MedDRA Summary of treatment emergent adverse events by primary system organ class, preferred term, severity and relationship to study medication – Safety set

14.3.6 Concomitant medication commencing during the study – Safety set

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