Reckitt Benckiser

1 CLINICAL STUDY REPORT ERRATUM TITLE PAGE

EudraCT/IND 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
Erratum Report Date:	16 Oct 2014 (Date of Final CSR: 26 August 2009)
Principal Investigator:	Dr D McNally, Ormeau Health Centre, 120 Onneau Road, Belfast.BTl 2EB.
Study Conduct Statement:	This study was designed in accordance with ICH Good Clinical Practice and the ethical principles contained within the Declaration of Helsinki, as referenced in EU Directive 2001/20/EC and with US Good Clinical Practice Regulations (21 CFR 50, 21 CFR 54). Documents defined by ICH GCP as "essential documents" will be archived in the RB company archive in Hull, HU8 7DS, UK The purpose of this erratum is to document non-compliances.

Reviewed and Agreed by:

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Date

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

2 UPDATED STUDY SYNOPSIS

<table>
<tr><td>Name of Sponsor/ Company:
Reckitt Benckiser Healthcare International Ltd</td><td rowspan="3">Individual Trial Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority use only)</td></tr>
<tr><td>Name of Finished Product:
1) AMC throat lozenge
2) DCBA throat lozenge</td></tr>
<tr><td>Name of Active Ingredient(s):
1) 0.6 mg Amylmetacresol BP (AMC)
2) 1.2 mg 2,4- Dichlorobenzyl alcohol (DCBA)</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(s): Dr D McNally, Ormeau Health Centre, 120 Ormeau Road, Belfast, BT7 2EB.
Investigator(s): Dr D McNally (Ormeau Health Centre), Dr M McCaughey (Randalstown Medical Practice), Dr M Nagle (Abbots Cross Medical Practice), Dr J Durkan (Parkside Surgery), Dr N Doran (Crocus Street Surgery).</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. Eligible patients were randomised to one of the three treatment regimens (AMC only lozenge, DCBA only lozenge or non-medicated lozenge). If necessary patients underwent a washout period before randomisation. Each patient was provided with their allocated treatment by the site staff. Immediately following completion of the baseline eligibility assessments, the patient was asked to suck the lozenge slowly, moving it around the mouth, until it had dissolved and not to chew or crunch the lozenge. The site staff watched the patients put the lozenge in their mouths and checked compliance by conducting a mouth inspection.
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. Patients were required to complete a consumer questionnaire, the first</td></tr>
</table>

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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, and concomitant medications, occurring from discharge until 24 hours after dosing. The diary was returned at the follow-up visit, one to three days after dosing.

The non-medicated placebo used in this study was not matched to the active lozenges. There were distinct differences in appearance, odour and flavour of the active treatments and the non-medicated placebo. The purpose of this study was to investigate the analgesic in-vivo effects of the single actives AMC, and DCBA at their current OTC dosage with the non-medicated placebo controlling for demulcency.

Number of Subjects: **Planned:** 150

Analysed: 150 (safety); 150 (full analysis set); 145 (per protocol)

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.

Test Products:

Single oral doses of:

Test 1: AMC throat lozenge: unintagliated lozenges, opaque red in colour with an aniseed flavour and odour containing 0.6 mg AMC (FR 0172021)

Test 2: DCBA throat lozenge; unintagliated lozenges, opaque red in colour with an aniseed flavour and odour containing 1.2 mg DCBA (FR 0178114)

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

Reference Therapy: Single dose of a shaped matched non-medicated, unintagliated, sugar-based placebo throat lozenge, clear red in colour with a sweet bland flavour and with an odour predominantly of sugar (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;

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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.

SUMMARY & CONCLUSIONS

EFFICACY RESULTS:

The treatment groups were well balanced for the demographic variables. Patient ages ranged from 18 to 74 years with a mean age of 31.8 years. All patients were Caucasian, there were slightly more males than females (80:70 M:F). In the ANCOVA model for the full analysis set (n=150) for the primary endpoint 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). Results for the primary efficacy variable are summarised in Table 1.

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

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

	0.6 mg AMC throat lozenge	1.2 mg DCBA throat lozenge	Placebo throat lozenge
FULL ANALYSIS SET			
N	50	49	46
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 in the CSR

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 ($p < 0.03$).

Mean change from baseline in Throat Soreness from 1 to 120 minutes post first dose is pictorially represented in Figure 1.

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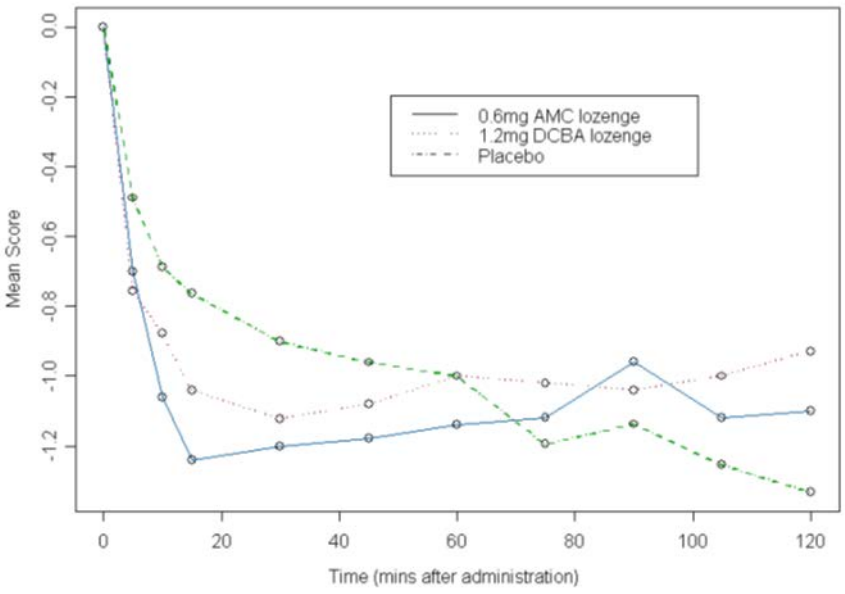
Figure 1: Mean Change from Baseline in Throat Soreness from 5 to 120 minutes post first dose – Full Analysis Set



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.

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

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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:

There is potential for the blinding of the study to have been compromised by the choice of placebo, as this did not match the active product for flavour and appearance and therefore had the potential to bias the study and compromise the double blind. However, with the parallel design, the patients would not have been able to detect, nor been aware of, the differences between the active and placebo product. There is no evidence to suggest that systematic unblinding occurred during the study.

Limited efficacy was observed with 0.6 mg AMC throat lozenge and the 1.2 mg DCBA throat lozenges compared with the placebo throat lozenge. There was a perceived faster action but a shorter duration of action for the active throat lozenges compared with the placebo throat lozenge. Further development of single active lozenges with 0.6mg AMC or 1.2mg DCBA may not be merited.

Date of the erratum: 16 Oct 2014

3 TABLE OF CONTENTS

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS FOR ERRATUM REPORT

Abbreviation	Abbreviation in Full
ABPI	Association of the British Pharmaceutical Industry
AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
AMC	Amylmetacresol BP
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AR	Adverse reaction
AUC	Area under the curve
BNF	British National Formulary
CFR	Code of Federal Regulations
CI	Confidence Interval
CLIN	Practitioners Clinical Assessment of the Study Medication
CPM	Clinical Project Manager
CRF	Case report form
CRO	Contract research organisation
CSR	Clinical Study Report
CTA	Clinical Trial Application
CV	Curriculum vitae
DCBA	2,4-Dichlorobenzyl alcohol
DSS	Difficulty Swallowing Scale
EC	Ethics Committee
eCRF	Electronic case report form
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLOBAL	Patient Global Evaluation of the Study Medication
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
HIV	Human immunodeficiency virus

Abbreviation	Abbreviation in Full
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IMSU	Investigational Material Supplies Unit
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
LS	Least Square
LSD	Least Significant Difference
MedDRA	Medical Dictionary for Regulatory Authorities
N	Number
NCR	No carbon required
NHS	National Health Service
NSAID	Non steroidal anti-inflammatory drug
p	Probability
PAIN	Practitioner's Assessment of Pharyngeal Inflammation
PIS	Patient Information Sheet
PK	Pharmacokinetic
QA	Quality assurance
QC	Quality control
R & D	Research and Development
RB	Reckitt Benckiser
SAE	Serious adverse event
SD	Standard Deviation
SDV	Source data verification
SMO	Site management organisation
SOP	Standard operating procedure
SwoTS	Swollen Throat Scale
TMF	Trial Master File
TOTPAR	Summed changes from baseline in sore throat pain relief
TPA	Tonsillopharyngitis Assessment
TS	Throat Soreness Scale

Abbreviation	Abbreviation in Full
UK	United Kingdom (of Great Britain and Northern Ireland)
URTI	Upper Respiratory Tract Infection
US	United States (of America)
VAS	Visual Analogue Scale
WCT	Worldwide Clinical Trials
WHO	World Health Organisation

5 INTRODUCTION TO STUDY REPORT ERRATUM

Following production of the original Clinical Study Report (CSR) for TH0809, potential issues relating to Good Clinical Practice (GCP) compliance of the study have been highlighted which were not adequately described in the original CSR. Specifically that the placebo throat lozenge was not matched to the active lozenges in terms of flavour or appearance. These findings prompted a review of the Trial Master File (TMF) including the previous CSR to identify where information was lacking or incomplete in the original CSR. This document is an erratum to the original CSR and provides additional information concerning the blinding of the study and other key operational details. In addition the opportunity has been taken to update certain sections of the report with more complete information than originally provided.

Information is presented as amended CSR sections using the same numbering system as appears in the CSR. This starts from section 5 below, hence two sections numbered 5 being present in this report erratum.

5 CSR SECTION - ETHICS

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

The name and full address of the IEC consulted is provided in Appendix 16.1.3 of the CSR. The study protocol together with patient information and consent documents were reviewed by the Office for Research Ethics Committees (IEC) in Northern Ireland (ORECNI) Independent Ethics Committee. The Participant Information Sheet and Participant Consent Form were revised following comments from the IEC and the final protocol together with the amended Participant Information Sheet and Participant Consent Form were reviewed and favourable opinion was provided by the Office for Research Ethics Committees (IEC) in Northern Ireland (ORECNI) on 04 November 2008.

5.2 Ethical Conduct of the Study

This study was designed in accordance with the Declaration of Helsinki, as referenced in EU Directive 2001/20/EC. It was carried our according to the principles

of International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

5.3 Patient Information and Consent

Copies of the representative Participant Information Sheet version 2.0 dated 01 October 2008 and a blank Participant Consent Form version 2.0 dated 01 October 2008 are provided in Appendix 16.1.3 of the CSR.

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

9 CSR SECTION – INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan – Description

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

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

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

Patients were screened at the primary care investigative sites in Northern Ireland. A washout period, if required, was permitted before the baseline assessment, in order to allow the patients who had taken prohibited therapies such as other throat pastilles, boiled sweets etc., to be considered for entry. The washout period was determined by the type of prohibited therapy taken by the patient.

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

Following completion of the two-hour assessment, patients left the investigative site with a patient diary to record adverse events and concomitant medication up to 24 hours post-dose. The patients were asked to return to the investigational site for a post-study follow-up visit between one and three days post-dose. The patients were asked about any adverse events that had occurred and any concomitant medication taken since discharge. The site staff reviewed the patient diary for completeness and questioned the patient about any missing or potentially erroneous data e.g., dates not in chronological order. Data regarding and adverse events/symptoms or concomitant medications recorded in the diary by the patient were transferred into the patient's case record form by the study nurse.

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

One hundred and fifty patients (50 per treatment group) were required to complete the first two-hour assessment period to provide data for the primary endpoint (the change from baseline in severity of throat soreness to two hours post-dose.

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

The methodology and 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[1-6].

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)[1]. 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.

The safety profiles of 0.6 mg AMC and 1.2 mg DCBA in combination have been well established over many years of use as non-prescription products and the potential risks to patients of these actives 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.

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[10].

The choice of control group was based on the previous studies conducted with Strespils Original (BH5013 and TH0705). The lozenge format itself provides soothing relief through demulcency, sucking a throat lozenge helps to increase saliva production[11, 12] and the mucosa remains lubricated[13, 14]. This can be enhanced by the excipients and flavourings added to throat lozenges which provide sensorial effects[13] and in some cases actually further provoke saliva production[15]. The placebo throat lozenge used in this study was the same as that used in BH5013 and TH0705; a shaped matched lozenge, clear red in colour and with a sweet but bland flavour. The intention of this placebo throat lozenge was to control for demulcency so any differences observed would be contributable to the new formulations as a whole, not just the active components i.e. AMC and DCBA. This choice was not the most appropriate approach given that the purpose of the study was to investigate the analgesic properties of the single active ingredients AMC, and DCBA. In addition the non-medicated placebo used in this study was not matched to the active lozenges. There were distinct differences in appearance, odour and flavour of the active treatments and the non-medicated placebo which had the potential to compromise the blinding of the study.

9.4.1 Treatments Administered

Patients were randomly allocated to one of three treatment groups:

- Unintagliated AMC throat lozenge, containing 0.6 mg AMC, opaque red in colour with an aniseed flavour and odour
- Unintagliated DCBA throat lozenge containing 1.2 mg DCBA, opaque red in colour with an aniseed flavour and odour
- Unintagliated non-medicated sugar-based placebo throat lozenge, clear red in colour with a sweet bland flavour and with an odour predominantly of sugar

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

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)

The identities of the medications supplied in the study were:

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 177913
Non-medicated sugar-based placebo throat lozenges	RB	FR 0125022 WO 0172727

Drug supplies were to be stored below 25°C.

9.4.6 Blinding

The study was described as double-blind however the active and placebo lozenges were unmatched in terms of their appearance; the two actives were opaque red un-intagliated and the placebo was clear red un-intagliated. In addition, the actives and placebo lozenges were unmatched for flavour and odour; the actives had a predominately aniseed flavour and odour, and the placebo had a predominately bland, sugar flavour and odour.

There was no provision for unblinded dispensing staff or blind folding of patients, therefore there is a potential for the study to have been unblinded if the dispensing staff or patients had access to trial documentation to identify the active and placebo and dispensing staff influenced the patients.

13 CSR SECTION - DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

Reckitt Benckiser Healthcare UK Limited (RB) had 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[3, 6, 16, 17.]

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)[17]. 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.

The placebo throat lozenge used in this study was the same as that used in previous studies with Strepsils lozenges; a shaped matched lozenge, red in colour and with a sweet but bland flavour. However, although the placebo throat lozenge was matched for size and shape, the placebo was unmatched for flavour and appearance (the active lozenges were aniseed flavour and opaque red; the placebo was unflavoured and clear red). This meant that the study staff may have been able to differentiate between the active and the placebo lozenges during administration of the study treatments which had the potential to introduce bias during this study. For this to impact the results would have required a deliberate step on behalf of the study team in order to influence the patients' subjective study assessments. There is no evidence that this was the case. In addition, the lack of flavour with the placebo throat lozenge may have also unblinded the patients. However, the study was a parallel group study and there was no opportunity for one trial patient to try more than one treatment

Apart from the potential unblinding issues with the lack of flavour in the placebo lozenges, the choice of a placebo with the flavouring and excipients omitted is problematic. The purpose of the study was to investigate the analgesic properties of

AMC alone and DCBA alone so, as flavouring systems and excipients can promote salivation enhancing the soothing and efficacious properties of lozenges, this may have led to inflated differences between the active lozenges and the placebo which were then attributed to the action of the single actives alone. However, given the results, no further development is planned.

Sore throat studies have typically used either AUC for sore throat pain relief or change from baseline throat soreness AUC as the primary endpoint[3, 4, 6, 16, 18].

Studies using flurbiprofen[3, 4, 6, 18] and a study using the combination of 0.6 mg AMC and 1.2 mg DCBA[17] (Strepsils®) have indicated that throat soreness and sore throat pain relief AUCs are similarly sensitive endpoints.

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.

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 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 ($p\leq0.008$). 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[17], 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

There is potential for the blinding of the study to have been compromised by the choice of placebo, as this did not match the active product for flavour and appearance and therefore had the potential to bias the study and compromise the double blind. However, with the parallel design, the patients would not have been able to detect, nor been aware of, the differences between the active and placebo product. There is no evidence to suggest that systematic unblinding occurred during the study.

Limited efficacy was observed with 0.6 mg AMC throat lozenge and the 1.2 mg DCBA throat lozenges compared with the placebo throat lozenge. There was a perceived faster action but a shorter duration of action for the active throat lozenges compared with the placebo throat lozenge. Further development of single active lozenges with 0.6mg AMC or 1.2mg DCBA may not be merited.

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Reckitt Benckiser

PRINCIPAL INVESTIGATOR'S SIGNATURE

Study Number: TH0809

Report 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

Phase: III

Principal Investigator:

By my signature below, I hereby state that I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study. I agree its conclusions and wish/do not wish to make an additional statement regarding the safety of the product under test.

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Date