Reckitt Benckiser

1 CLINICAL STUDY REPORT ERRATUM TITLE PAGE

EudraCT/IND Number:	2008-00-5596-10
Study Number:	TH0817
Protocol Title:	A multi-centre, randomised, double blind, placebo-controlled, parallel group, single dose study of the efficacy of two flavour variants of Strepsils throat lozenges in the relief of sore throat due to upper respiratory tract infection.
Study Phase:	III
Date First Subject Enrolled:	12th January 2009
Date Last Subject Completed:	20th February 2009
Original Report Date:	06th July 2009
Erratum Report Date:	26th June 2014
Principal Investigator:	Dr Alan Wade MB ChB FRCA, CPS Research, West of Scotland Science Park, Glasgow, G20 0XQ, United Kingdom
Study Conduct Statement:	This study was designed in accordance with the principles of ICH Good Clinical Practice and the ethical principles contained within the Declaration of Helsinki, 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 The purpose of this erratum is to document non-compliances.

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2 UPDATED STUDY SYNOPSIS

Name of Sponsor/ Company: Reckitt Benckiser Healthcare International Ltd	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority use only)**
Name of Finished Product: Strepsils Cool and Strepsils Warm Throat lozenges	**Volume:**	
Name of Active Ingredient(s): 0.6mg 2,4-dichlorobenzylalcohol, 1.2mg amylmetacresol,	**Page:**	
Title of Trial: A multi-centre, randomised, double blind, placebo-controlled, parallel group, single dose study of the efficacy of two flavour variants of Strepsils throat lozenges in the relief of sore throat due to upper respiratory tract infection.		
Investigator(s): Dr Alan Wade MB ChB FRCA, Dr Gordon Crawford BSc MB ChB MRCGP		
Trial Site(s): Community Pharmacology Services Ltd (CPS Research) recruited all patients by direct advertising or referrals from their GP network. In addition some patients were seen at the following medical practices in the Glasgow area; Waverley GP Practice, Chapelhall GP Practice and Rutherglen GP Practice.		
Publication (reference): Wade AG, Morris C, Shephard A, Crawford GM, Goulder MA. A multicentre, randomised, double-blind, single-dose study assessing the efficacy of AMC/DCBA Warm lozenge or AMC/DCBA Cool lozenge in the relief of acute sore throat. BMC Family Practice 2011, 12:6 doi 10.1186/1471-2297-12-6		
Studied Period: 6 weeks **Date first subject enrolled:** 12th January 2009 **Date last subject completed:** 23rd February 2009		**Phase of Development:** III
Objectives: The primary objective of this study was to determine the analgesic properties of two new Strepsils flavour variant throat lozenges (Strepsils Cool and Strepsils Warm) in patients with sore throat due to upper respiratory tract infection (URTI). The analgesic properties were assessed by comparing throat soreness and sore throat relief in patients treated with one of the two Strepsils flavour variant throat lozenges with patients treated with a placebo throat lozenge. In addition to the analgesic endpoints, functional measures of difficulty in swallowing and throat numbness were also assessed. The secondary objective of this study was to determine consumer acceptability of the product via responses to a consumer questionnaire.		
Methodology: Patients with a sore throat due to URTI, either presented opportunistically following response to advertisements for patients in local media or were referred directly to CPS Research from a number of GP referral practices in the Glasgow area. Patients were screened either at CPS Research or within the referral GP practice. Eligible patients (those who met the study inclusion criteria and not the exclusion criteria) were randomised to receive one of the three test products. Within 1 minute of the completion of baseline assessments of throat soreness (11 – point ordinal scale), difficulty in swallowing (100mm VAS) and a two-part consumer questionnaire, patients were blindfolded and dosed with the assigned trial medication according to their randomisation number (single active or placebo throat lozenge). At 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120 minutes post first dose, patients completed the throat soreness and difficulty in swallowing scales along with a 7–point categorical sore throat relief scale and a 5–point categorical throat numbness scale. Three questions on the consumer questionnaire concerning cooling sensation and relief were completed at 1 minute, two questions concerning the warming sensation were answered at 5 minutes, and other pain relief and sensation questions were completed at 20, 60 and 120		

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minutes post dose.

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

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

Each subject was to be blindfolded and provided with one throat lozenge by a research staff member not subsequently involved with the assessment/oversight of that subject within either CPS Research or the GP Practice. Patients were instructed to suck it slowly, moving the throat lozenge around the mouth until dissolved and not to chew or crunch the throat lozenge. Although blindfolding was a requirement of the protocol, the TMF documentation cannot verify that this requirement was adhered to.

Review of the individual CRFs indicated that investigational staff who had been involved with dosing of some patients were not involved in the study assessments for those patients however were involved with the assessments of patients dosed by other investigational staff. Blinding of the research staff was therefore not maintained throughout the study period but were maintained on a patient-by-patient basis.

The placebo throat lozenge used in this study was the same as that used in BH5013 and TH0705; a shaped matched lozenge, 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 AMC/DCBA. As the placebo throat lozenge was not the same colour as the Strepsils Cool and Strepsils Warm lozenge, which also differed from each other in appearance, the lozenges were packed into opaque blister packs. Numbers of patients in each treatment (warm, cool and placebo) all reported warming and cooling sensations. These data coupled with an examination of outliers data suggests that there was no systematic unblinding of the study.

Number of Subjects: **Planned:** 225
Randomised: 225
Analysed: 225

Diagnosis and Main Criteria for Inclusion: Male and female patients aged between 16 and 75 years of age with a sore throat due to URTI of onset within 4 days of presenting were eligible for study entry. Patients had to have confirmed objective findings of a sore throat as assessed by the expanded Tonsillopharyngitis Assessment (TPA) scoring at least 3 points on the TPA and had to score at least 6 on the 11 point ordinal Throat Soreness Scale at baseline, to be dosed.

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

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medication.

Test Products:

Strepsils Cool Throat lozenges white to pale yellow in colour with a mentholated flavour containing 1.2 mg, 2, 4 – dichlororbenzyl alcohol and 0.6 mg amylmetacresol. Un-intagliated. Batch No. 8M024.

Strepsils Warm Throat lozenges red to purple in colour with a spicy warming fruit flavour containing 1.2 mg, 2, 4 – dichlororbenzyl alcohol and 0.6 mg amylmetacresol. Un-intagliated. Batch No. 8M025.

Assessment Period: 2 hours

Reference Therapy: Shape matched non-medicated sugar-based throat lozenge red in colour with a bland sweet flavour. Batch No. 0172727

Criteria for Evaluation:

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

There were a number of secondary endpoints including the change from baseline in severity of throat soreness, difficulty swallowing and sore throat relief. Overall treatment rating and throat numbness were also included as secondary efficacy measures.

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

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

Normality assumptions were assessed by examination of the residual plots and by the Shapiro-Wilk test of normality. Depending on the degree of departure from these assumptions, an alternate nonparametric approach could have been used instead.

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

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

Concomitant medications on-going at randomisation were coded using the ATC level 2 categories from the WHO dictionary Enhanced March 2007 Version. All adverse events were

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listed and tabulated by treatment, severity, relationship to therapy and primary system organ class according to Version 12.0 of MedDRA.

SUMMARY & CONCLUSIONS

EFFICACY RESULTS:

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

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

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

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

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

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

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

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

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

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

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TABLE 3 **Mean ± sd (n) for sore throat relief at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post first dose – Full analysis set**
Measured on a 7-point scale where 0 = No relief, 1 = Slight relief, 2 = Mild relief, 3 = Moderate relief, 4 = Considerable relief, 5 = Almost complete relief, 6 = Complete Relief

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

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

TABLE 4 **Mean ± sd (n) for change from baseline in difficulty in swallowing at 1, 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes post first dose – Full analysis set**
Difficulty in swallowing measured on 100mm VAS where 0mm=Not difficult, 100mm=Very difficult

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

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

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

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

a	Estimated from ANCOVA model with factors for treatment and centre and a covariate for baseline throat soreness
b	A positive difference favours the first treatment against second treatment
c	Estimated from ANCOVA model with factors for treatment and centre and covariates baseline throat soreness and baseline score for difficulty in swallowing
d	A negative difference favours the first treatment against second treatment
***	Comparison statistically significant at 0.1% level

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

Throat numbness was evident by 1 minute for both Strepsils throat lozenges with peak effect seen at 10 minutes for the Strepsils Cool throat lozenge and 15 minutes for the Strepsils Warm throat lozenge. The throat numbness lasted 2 hours for the Strepsils Cool throat lozenge and 45 minutes for the Strepsils Warm throat lozenge.

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

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

SAFETY RESULTS:

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

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

CONCLUSION:

There is no evidence to suggest that systematic unblinding occurred during the study but choice of placebo did have the potential to affect the differences seen between placebo and active treatments. Despite this it can be concluded that Strepsils Cool throat lozenges and Strepsils Warm throat lozenges provide safe and fast relief for sore throats due to upper respiratory tract infections. Following a single dose, relief is evident from 1 minute post dose and lasts for at least 2 hours with maximal effects from 15 minutes post dose. Patients can feel relief as soon as they swallow and feel better at 2 hours.

Date of the report: 26 June 2014

3 TABLE OF CONTENTS

3.2 List of Appendices

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS FOR ERRATUM REPORT

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

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

5 INTRODUCTION TO STUDY REPORT ERRATUM

Following production of the original Clinical Study Report (CSR) for TH0817 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 and that the delegation of duties with respect to blinded vs. unblinded personnel was not clear. These findings have resulted in the full review of the 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.

5 CSR SECTION - ETHICS

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

The name and full address and approval letter of the IEC consulted is provided in Appendix 16.1.3. The study documentation was initially reviewed on 04th November 2008 with favourable ethical opinion received on 18th November 2008 dependent upon changes to the Participant Information Sheet and Consent documentation being implemented. The final protocol (04th September 2008) together with the amended participant information sheet (v2, 20th November 2008) and consent document (v2, 20th November 2008) were reviewed and approved by Fife, Forth Valley & Tayside Research Ethics Service on 15th December 2008. Amendments to the participant invitation letter (v2, 02nd November 2008) and advertisements (v2, 03rd December 2008) were approved by the Ethics Committee on 23rd December 2008.

Ethical approval was subject to management permission or approval being obtained from each host organisation prior to the start of the study. Local NHS R & D approvals for Lanarkshire sites and Greater Glasgow and Clyde were received on 17th December 2008 and 08th January 2009 respectively.

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 out according to the principles of International Conference on Harmonisation (ICH) GCP and according to applicable regulatory requirements.

6 CSR SECTION - INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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

The study was carried out at CPS Research in Glasgow under the guidance of the Chief and Principal Investigators. Some study related activities were delegated to suitably qualified site personnel. The majority of participants were seen at CPS Research premises in Glasgow but if participants could not attend CPS they were seen at one of the following medical practices in the Glasgow area by Research Team members from CPS Research: Waverley GP Practice, Chapelhall GP Practice and Rutherglen GP Practice. Medication was stored at CPS and taken to the satellite centres as required.

The study was managed and monitored by personnel from the Global Clinical Affairs department at Reckitt Benckiser Healthcare International (RBHI). Data management and the statistical analyses were performed by Worldwide Clinical Trials (WCT).

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

9 CSR SECTION – INVESTIGATIONAL PLAN

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

The methodology used in this study is accepted and validated analgesic methodology based on the Sore Throat Pain Model described in the literature by Schachtel[1,2,3]. The methodology has been previously used in studies BH5013 and TH0705 with Strepsils Original throat lozenges and in sore throat studies investigating the analgesic properties of a sore throat lozenge containing the non-steroidal anti-inflammatory (NSAID) drug flurbiprofen[4,5,6]. Differences exist in the studies on selection of primary endpoint and statistical analyses; namely use of TOTPAR (summed change in sore throat pain relief ratings from baseline (BH5013)), differences in throat soreness at the 2 hour timepoint (TH0705) or area under the curve for the change in sore throat ratings from baseline (this study). Additional analyses of the latter endpoint which were not presented in the BH5013 CSR were provided by WCT in order to provide the sample size for this study and allow across study comparisons to be made (see Section 13). This analysis only included patients with a baseline Tonsillopharyngitis Assessment score (TPA) >3 in order to give a more comparable analysis.

Sore throat due to Upper Respiratory Tract Infection (URTI) is a common illness for which most patients seek symptomatic relief; it is a minor, non-serious condition. The extent of possible improvement in symptoms is quite small, making comparisons between active treatments difficult. In this study to investigate the analgesic, numbing and consumer acceptability of the two new Strepsils variants – Strepsils Cool and Strepsils Warm the study required participants to have sufficient throat soreness at baseline and used a placebo throat lozenge without flavour or other excipients in order to discriminate between treatments.

Therefore to be eligible for study entry, patients had to have a throat soreness score of 6 or more as scored on the Throat Soreness Scale. In addition to this subjective measure of throat soreness, patients had to undergo an objective Tonsillopharyngitis

Assessment (TPA). The TPA ensured that patients had some objective sign of a sore throat and that only patients with acute tonsillopharyngitis were recruited into the study. The TPA consisted of assessments of 7 pertinent features of tonsillopharyngitis, oral temperature, size of tonsils, oropharyngeal colour, number of oropharyngeal enanthems, and size, number and tenderness of the anterior cervical lymph nodes. The TPA provided a score ranging from 0 to 21 points. A minimum score of 3 points was required to confirm the presence of tonsillopharyngitis and permit entry into the study. This score was less than that used in the previous studies BH5013 and TH0705 which required a TPA score of 5. The rationale for reducing the TPA from 5 to 3 was not provided in the protocol.

The choice of control group was based on the previous studies conducted with Strepsils Original (BH5013 and TH0705). The lozenge format itself provides soothing relief through demulcency; sucking a throat lozenge helps to increase saliva production[7, 8] and the mucosa remains lubricated[9, 10]. This can be enhanced by the excipients and flavourings added to throat lozenges which provide sensorial effects[9] and in some cases actually further provoke saliva production[11]. The placebo throat lozenge used in this study was the same as that used in BH5013 and TH0705; a shaped matched lozenge, 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 AMC/DCBA. As the placebo throat lozenge was not the same colour as the Strepsils Cool and Strepsils Warm lozenge, which also differed from each other in appearance, the lozenges were packed into opaque blister packs and a third party oversight of administration employed to maintain blinding. Each patient was to be blindfolded and provided with one throat lozenge by a research staff member not subsequently involved with the assessment/oversight of that patient. The intention was to ensure the patient and the staff supervising their assessments remained blinded to the treatment they had received. Patients had been told they would be randomly assigned to receive either a warming, cooling or placebo throat lozenge but they would be asked questions to cover both warming and cooling. The placebo throat lozenge provided an adequate control to which to compare the overall effects of the Strepsils Cool and Strepsils Warm formulations.

9.2 Selection of Study Population

Patients were those with a sore throat due to URTI who attended a GP referral practice or attended CPS Research directly after responding to media advertising. For patients that rang CPS Research in response to advertising, some initial screening took place over the telephone according to a pre-determined script. Advertising identified that the research was investigating new Strepsils products and participants received a payment of £50 and their travel expenses for taking part.

9.4.1 Treatments Administered

The following medications were administered:

i Un-intagliated Strepsils Cool Throat lozenges, containing 1.2 mg DCBA and 0.6 mg AMC, white to pale yellow in colour with a mentholated flavour

ii Un-intagliated Strepsils Warm Throat lozenges, containing 1.2 mg DCBA and 0.6 mg AMC, red to purple in colour with a spicy warming fruit flavour

iii Non-medicated sugar-based placebo throat lozenges, red in colour with a bland, sweet flavour

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

9.4.2 Identity of Investigational Product(s)

The identities of the medications supplied in the study were:

i Strepsils Cool Throat lozenges: Batch No. 8M024

ii Strepsils Warm Throat lozenges: Batch No. 8M025

iii Non-medicated sugar-based placebo throat lozenges: Batch No. 0172727

The manufacture and primary packing of Strepsils Cool throat lozenges and Strepsils Warm throat lozenges were contracted out to Pharmapac, Wirral UK by RBHI (Nottingham, UK). Un-intagliated lozenges were packed into opaque PVD/PVdC blister material and packed into plain white cartons. Each carton contained 2 x 8 lozenge blisters. The placebo throat lozenges were manufactured and primary packed by RBHI (Nottingham, UK). The placebo throat lozenges were also packed into opaque PVD/PVdC blister material and packed into plain white cartons. Each carton contained 2 x 12 lozenge blisters. All were produced according to Good Manufacturing Practice (GMP) standards.

All investigational product supplies were secondary packed and labelled to GMP standards by the IMSU, Reckitt Benckiser Healthcare UK Ltd, Dansom Lane, Hull HU8 7DS, UK. This involved the production of specific patient packs containing 2 lozenges each. The original blister packs were cut down to size and labelled in accordance with the protocol and clinical trial requirements. Given the difference in primary blister packs the blister formats supplied for the trial were not matched.

9.4.3 Method of Assigning Patients to Treatment Groups

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

Drug supplies were packed and labelled by the IMSU, according to a computer produced randomisation schedule generated by the RBHI statistician not involved

with the statistical analysis of the study and checked by a RBHI co-worker. At screening, patients were allocated a unique patient (screening) number.

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

All drug supplies were stored at CPS and only taken to the satellite GP practices by the research team as required, i.e. when patients were to be seen at the GP practices. Patients randomised at the GP practices were allocated the next randomisation in numerical sequence of the supplies available on site at that time.

9.4.6 Blinding

Strepsils products are normally intagliated with S on each side of the lozenge. To help with blinding, specific batches of Strepsils Cool and Strepsils Warm were produced un-intagliated. To address the issue that the lozenges were not identical in appearance a third party blinding method was employed. The intention was that each patient was to be blindfolded and provided with their allocated treatment by a member of the investigational staff who was not involved in their study assessments. The dosing person watched the patient put the throat lozenge in their mouth. Once the throat lozenge has been put in the mouth the blindfold was removed.

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

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

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

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

9.8.1 Changes to the Conduct of the Study

To ensure that visual differences in the lozenges did not result in data bias, staff administering the investigational products were to be independent of the investigational staff who were involved in the study assessments. None of the monitoring visit reports document a review of the methods used for independent dosing and assessment and best practice was not followed with respect to documenting delegation of responsibilities of the research staff. Monitoring was only conducted at CPS and not at any of the satellite GP practices. Subsequent review of the individual CRFs indicated that investigational staff who had been involved with dosing of some patients were not involved in the study assessments for those patients however were involved with the assessments of patients dosed by other investigational staff. Blinding of the research staff was therefore not maintained throughout the study period but was maintained on a patient-by-patient basis. . There were differences in the blister pack appearances and although the lozenges were packed in opaque blister material the colours could be seen through the packaging. It is unclear whether the staff monitoring the study remained blinded throughout the study. However, as monitoring visit reports state that drug accountability was performed, it is concluded that the blinding of the monitor(s) checking accountability was not maintained.

10 CSR Section - Study Patients

10.1 Disposition of Patients

A total of 225 patients were randomised into the study (77 patients received the Strepsils Warm throat lozenge, 74 patients received the Strepsils Cool throat lozenge and 74 patients received a placebo throat lozenge) between 12th January 2009 and 20th February 2009. The number of patients screened to achieve 225 patients randomised is unknown. All patients completed the study.

The majority of the patients were directed to CPS Research for their study assessments (166 randomised patients). In addition 49 patients were randomised at Rutherglen GP Practice, 7 randomised at Waverley GP Practice and 3 randomised at Chapelhall GP Practices. Randomisation by centre and treatment group is summarised in Table 10.1.1

Table 10.1.1 Randomisation by Centre and Treatment Group

Centre	Treatment Group		
	Strepsils Warm	Strepsils Cool	Placebo Throat Lozenge
CPS Research	57	52	57
Rutherglen	17	18	14
Waverley	2	3	2
Chapelhall	1	1	1
TOTAL	77	74	74

In accordance with the statistical analysis plan Waverley and Chapelhall centres were pooled for formal statistical analysis.

13 CSR SECTION - DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

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

The primary efficacy results from this study are summarised in Table 13.1.1 with overall treatment ratings at 2 hours summarised in Table 13.1.2 along with the equivalent results from the previous two studies, BH5013 and TH0705. The results are broadly consistent with the results seen in the previous two studies. The analysis of the area under the change from baseline curve (AUC) in severity of throat soreness from 0 to 2 hours (using the 11-point Throat Soreness Scale) in the current study revealed LS mean reductions from baseline of –2.06 , –1.78 and -0.98 for Strepsils Cool throat lozenge, Strepsils Warm throat lozenge and placebo throat lozenge respectively, and LS mean differences of 1.08 (95%CI -1.56, -0.60) for the comparison of Strepsils Cool throat lozenge and placebo throat lozenge and 0.80 (95%CI -1.27, -0.33) for the comparison of Strepsils Warm throat lozenge and placebo throat lozenge. These active-control differences lie within those observed

between Strepsils original and the placebo throat lozenge in the previous studies TH0705 (-1.26, 95%CI -1.54, -0.97) and BH5013 (-0.76, 95% CI - 1.42, -0.09)[12].

However there were study conduct issues that merit further discussion as they may have impacted on the results seen in this study. This study was described as multi-centre and, although Patients were seen at three GP practices as well as CPS, unlike TH0705 which was a multicentre GP study, all patients were managed by the central research team at CPS. In this respect it can almost be considered as a single centre study with variability being minimised by utilising a central study team yet the variability seen in the present study was not significantly less than TH0705 and was more than that observed in BH5013 (Table 13.1.1).

Blinding of the study was compromised as the independent dosing of patients by someone independent from the research team was not implemented. This meant the study staff could differentiate between the three lozenges. 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 it can be argued that the lack of flavour and smell with the placebo throat lozenge would have unblinded the patients. Advertisements for trial patients identified that new variants of Strepsils were being trialled which may have set patient expectations of the lozenges. However the study was a parallel group study and there was no opportunity for one trial patient to try more than one treatment. The aim of the placebo throat lozenge was to control for demulcency only as flavouring systems and excipients can promote salivation enhancing the soothing and efficacious properties of lozenges.

Table 13.1.1 Comparison of AUC from Baseline to 2 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

Study	Parameter	Placebo Lozenge	Strepsils Original	Strepsils Cool	Strepsils Warm
BH5013	N	25	25		
	Female: Male	16:9	20:5		
	Mean Age (yrs)	36.9	45.0		
	BSL Throat Soreness	7.3	7.7		
	Mean Total Change from BSL[a]	-3.7	-9.4		
	P value		0.044		
	Difference in LS mean AUC 0 – 2 hrs ± SD[b]		-0.76 ± 1.09		
	95 % CI		-1.42, -0.09		
TH0705	N	155	155		
	Female: Male	105:50	105:50		
	Mean Age (yrs) ± SD	35.9 ± 14.2	36.3 ± 14.0		
	BSL Throat Soreness ± SD	7.2 ± 1.2	7.1 ± 1.1		
	Mean AUC 0 – 2 hrs ± SD	-0.73 ± 1.14	-1.97 ± 1.49		
	LS Mean	-0.69[c]	-1.94[c]		
	Difference		-1.26[c]		
	95% CI		-1.54, -0.97[c]		
	P value		<0.0001[c]		
TH0817	N	74		74	77
	Female: Male	43:31		45:29	45:32
	Mean Age (yrs) ± SD	32.6 ± 13.2		32.4 ± 14.7	30.3 ± 12.2
	BSL Throat Soreness ± SD	6.81 ± 1.57		6.81 ± 1.24	6.91 ± 1.02
	Mean AUC 0 – 2 hrs ± SD	1.00 ± 1.61		2.07 ± 1.47	1.83 ± 1.50
	LS Mean	-0.98		-2.06	-1.78
	Difference			-1.08	-0.80
	95% CI			-1.56, -0.60	-1.27, -0.33
	P value			<0.0001	0.001

[a] Analysis summed changes from baseline rather than AUC

[b] Used for sample size calculation for present study TH0817 (21 Sugar Lozenge / 24 Strepsils Original with TPA ≥ 3)

[c] Results for 154 patients/group

Table 13.1.2 Comparison of Overall Lozenge Rating at 2 hours

Study	Parameter	Placebo Lozenge	Strepsils Original	Strepsils Cool	Strepsils Warm
BH5013	N	25	25		
	Mean	3.7 ± 2.5	4.5 ± 2.7		
	P value		NS		
TH0705	N	154	154		
	LS Mean	2.75	5.49		
	Difference		2.74		
	95% CI		2.15, 3.32		
	P value		<0.0001		
TH0817	N	74		74	77
	LS Mean	2.14		5.15	4.71
	Difference			3.00	2.57
	95% CI			2.11, 3.90	1.68, 3.45
	P value			<0.0001	<0.0001

In order to address the blinding concerns the Sponsor has investigated the organoleptic (flavour) data to look for unusual patterns in responses that might suggest unblinding (see Appendix 1). A number of patients receiving warm or placebo throat lozenges reported cooling sensations while a number of patients receiving cool or placebo throat lozenges reported warming sensations. These data coupled with an examination of outliers data suggests that there was no systematic unblinding of the study.

However, the choice of placebo and the wide use of Strepsils in the community within the UK did have potential to introduce bias during this, and the other trials, and inflate the active-control treatment difference. It should be noted that the Strepsils variants used in this study were novel and not available on the market, unlike Strepsils Original used in the previous two studies (BH5013 and TH0705). Despite this the study results do still support the effectiveness of the Strepsils lozenges as a symptomatic treatment for sore throats providing fast and sustained relief with the different variants conferring different sensorial benefits to cater for different patient preferences.

Therefore although there may be a question over the absolute treatment differences over and above placebo, overall the risk/benefit conclusions that can be drawn from the data in relation to the new Strepsils variants remain unaffected.

Throat soreness, pain relief, difficulty in swallowing and throat numbness single dose data indicated that effects over and above that of the placebo throat lozenge control

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

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

In addition the consumer questionnaire indicated that at two hours post dose patients taking both Strepsils throat lozenges were happier in relation to their throat and began to feel more like their best overall, and over 50% of patients felt better than before they took the throat lozenge. The sensorial experience of a cooling sensation was clearly evident with over 60% of patients feeling a cooling sensation within 5 seconds from the Strepsils Cool throat lozenge. Similarly the Strepsils Warm throat lozenge provided a warming sensation that over 60% of patients felt within 30 seconds. Both throat lozenges were significantly superior to the placebo throat lozenge ($p<0.001$) in terms of their perceived ability to sooth, coat and provide comfort to the throat.

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

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

13.2 Conclusion

There is no evidence to suggest that systematic unblinding occurred during the study but choice of placebo did have the potential to affect the differences seen between placebo and active treatments. Despite this it can be concluded that Strepsils Cool throat lozenges and Strepsils Warm throat lozenges provide safe and fast relief for sore throats due to upper respiratory tract infections. Following a single dose, relief is evident from 1 minute post dose and lasts for at least 2 hours with maximal effects from 15 minutes post dose. Patients can feel relief as soon as they swallow and feel better at 2 hours.

14 REFERENCE LIST FOR ERRATUM REPORT

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12) Reanalysis of BH5013 data for sample size calculation. Data on File.

APPENDICES

Appendix 1: Sensorial data analysis

At numerous time points subjects were asked sensorial questions around the warming and cooling flavours. The following are examples of questions asked during the study and the resulting data is presented below the question.

'At one minute post dose how quickly did you feel the cooling sensation'
Table 14.2.55'

46.8% of patients randomized to the warming lozenge reported they felt a cooling sensation.
26% of patients randomized to the placebo lozenge reported they felt a cooling sensation.

'At one minute post dose how deep down in the throat was the cooling felt'
Table 14.2.56

44.2% of patients randomized to the warming lozenge reported they felt cooling.
26% of patients randomized to the placebo lozenge reported they felt a cooling sensation.

'Did you feel warming relief from the first moment you swallowed'
Table 14.2.57

16.2% of patients randomized to a cooling lozenge reported they felt warming
13.7% of patients randomized to a placebo lozenge reported they felt warming.
The same patients went on to answer the same question after 2 hours.

'Did you feel warming relief after two hours'
Table 14.2.58

16.2% of patients randomized to a cooling lozenge reported they felt warming
13.7% of patients randomized to a placebo lozenge reported they felt warming.

An examination has also been made of outliers in this study. From the studentised residuals from the ANOVA model, there were 13/224 (5.8%) with an absolute value > 1.971 and 4/224 (1.8%) with an absolute value > 2.598 which are reasonable consistent with the expected 5% and 1% and suggest nothing untoward in the data.

Reckitt Benckiser

PRINCIPAL INVESTIGATOR'S SIGNATURE

Study Number: TH0817

Report Title: A multi-centre, randomised, double blind, placebo-controlled, parallel group, single dose study of the efficacy of two flavour variants of Strepsils throat lozenges in the relief of sore throat due to upper respiratory tract infection.

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.

[redacted]

[redacted]

Date

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