Reckitt Benckiser

1 ADDENDUM TO CLINICAL STUDY REPORT TITLE PAGE

EudraCT/IND Number:	2007-004375-19
Study Number:	TH0705
Protocol Title:	A multi-centre, randomised, double-blind, parallel-group, placebo-controlled, multiple dose study of the efficacy of Strepsils Original throat lozenges in the relief of sore throat due to upper respiratory tract infection
Study Phase:	IV
Date First Subject Enrolled:	06 November 2007
Date Last Subject Completed:	19 February 2008
Report Date:	11 Jul 2014 (Date of Final CSR: 17 July 2008)
Principal Investigator:	Dr Moyra Anderson BSc MB MCh BAO MRCGP, Old School Surgery, 54 Station Road, Greenisland, Carrickfergus, BT38 8TP, Northern Ireland
Study Conduct Statement:	This study was conducted in accordance with ICH Good Clinical Practice and the ethical principles contained within the Declaration of Helsinki, as referenced in EU Directive 2001/20/EC and with and with US Good Clinical Practice Regulations (21 CFR 50, 21 CFR 54, 21 CFR 56, and 21 CFR 312). Documents defined by ICH GCP as “essential documents” will be archived in the RB company archive in Hull, HU8 7DS, UK

Reviewed and Agreed by:

Clinical Project Manager function:		**Statistician:**	
Mr Christopher Morris BSc (Hons) Reckitt Benckiser Healthcare (UK) Ltd.	Date	Mr Gary Smith MSc Reckitt Benckiser Healthcare (UK) Ltd.	Date
Addendum Report Author:		**R&D Category Manager; URT/Strepsils**	
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Reviewed and Approved by:

R&D Senior Clinical Manager, Health		**Global Medical Director**	
Dr Sue Aspley BSc (Hons) Reckitt Benckiser Healthcare (UK) Ltd	Date	Dr Bernard Ng MD MBA Reckitt Benckiser Healthcare (UK) Ltd	Date

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2 ADDENDUM TO STUDY REPORT

The purpose of this addendum is to discuss the potential impact of the choice of placebo on the results and conclusions.

Following production of the original Clinical Study Report (CSR) for TH0705 the study Sponsor, RB, has completed a review of the blinding implications of the placebo used in TH0705. This document is an addendum to the original CSR and expands upon the details included in the original report with respect to potential discernible flavour differences between the placebo and the Strepsils Original Lozenges and discusses the impact these may have had on the results of the study.

Name of Sponsor/ Company: Reckitt Benckiser Healthcare International Ltd	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority use only)**
Name of Finished Product: Strepsil Original Lozenges	**Volume:**	
Name of Active Ingredient(s): 2, 4 –dichlorobenzylalcohol, amylmetacresol	**Page:**	
Title of Trial: A multi-centre, randomised, double-blind, parallel-group, placebo-controlled, multiple dose study of the efficacy of Strepsils Original throat lozenges in the relief of sore throat due to upper respiratory tract infection		
Investigator(s): Dr M Anderson, Dr P Steele, Dr J McBride, Dr D McNally, Dr P Conn, Dr H McGoldrick, Dr N Lavin, Dr M Redmond.		
Trial Site(s): Multi-centre study in 8 Primary Care Investigational Sites in Northern Ireland		
Publication (reference): McNally D, Simpson M, Morris C, Shephard A, Goulder M. Rapid relief of acute sore throat with AMC/DCBA throat lozenges: randomised controlled trial. Int J Clin Pract 2010; 64 (2): 194 – 207		
Studied Period: 3.5 months **Date first subject enrolled:** 06 November 2007 **Date last subject completed:** 19 February 2008		**Phase of Development:** IV
Objectives: The primary objective of this study was to determine the analgesic properties of Strepsils Original lozenges in patients with sore throat due to upper respiratory tract infection (URTI). The analgesic properties were assessed by comparing throat soreness and sore throat relief in patients treated with Strepsils Original throat lozenges or placebo. In addition to the analgesic endpoints, a functional measure, difficulty in swallowing, was also assessed. The secondary objective of this study was to determine additional patient/consumer benefits associated with Strepsils Original by measuring freedom from symptoms and by the responses to a consumer questionnaire.		
Methodology: Patients with a sore throat due to URTI, either presented opportunistically or following response to advertisements for patients in local doctors' surgeries and community pharmacies were referred to their nearest investigative site. Patients were screened at primary care investigative sites in Northern Ireland. Eligible patients (those that met the study inclusion criteria and not the exclusion criteria) were randomised. Within 1 minute of the completion of baseline assessments of throat soreness (11 – point ordinal scale), difficulty in swallowing (100mm VAS) and a two-part consumer questionnaire, patients were dosed with the assigned trial medication according to their randomisation number (active or placebo lozenge). Each patient was instructed to suck the lozenge slowly, moving the lozenge around the mouth until dissolved and not to chew or crunch the lozenge. At 5, 10, 15, 30, 45, 60, 75, 90, 105, 120 minutes post first dose, at the end of Day 1, 24 hours post first dose, and at the end of Days 2 and 3 patients completed the throat soreness and difficulty in swallowing scales along with a 7 – point categorical sore throat relief scale. One question of the consumer questionnaire concerning pain relief was completed at 5 minutes with other pain relief questions completed at 120 minutes. The second part of the consumer questionnaire concerning functional impairments was completed at baseline and repeated at the end of Day 3. In addition an overall treatment rating was completed at 120 minutes post first dose and at the end of Day 3. The first two-hour assessment period was completed under supervision in a designated area within the investigative site. No food, drink or smoking was permitted during this 2-hour period. Following completion of the two-hour assessment, patients left the investigative site with their trial medication, paracetamol (rescue medication) and patient diaries. Following discharge patients could take one lozenge every 2 – 3 hours as required for up to 3 days. At the end of Day 1, at 24 hours post first dose and at the end of Days 2 and 3, the patient was asked to		

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complete the rating scales in their diary. Between one and four days after completing the study, patients returned to the investigative site with their completed diaries, unused trial medication and rescue medication. Any adverse events (AEs) and changes in concomitant medication were recorded in the patient's CRF and any ongoing AEs were followed-up. If the patient's sore throat resolved before Day 3, they discontinued their trial medication and the reason for discontinuation i.e. no further need for study medication, was recorded at the follow-up assessment.

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

Number of Subjects: **Planned:** 310 to complete first 2 hour assessment

Entered: 314 Screened, 310 Randomised

Full Analysis 310, Per Protocol 250, Safety 310

Diagnosis and Main Criteria for Inclusion: Male and female patients aged between 18 and 75 years of age with a sore throat due to URTI of onset within 4 days of presenting were eligible for study entry. Patients had to have confirmed objective findings of a sore throat as assessed by the expanded Tonsillopharyngitis Assessment (TPA) scoring at least 5 points on the TPA and had to score at least 6 on the 11 point ordinal Throat Soreness Scale at baseline, to be dosed.

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

Test Product: Strepsils Original Throat Lozenges red in colour with an aniseed flavour containing 1.2 mg, 2, 4 – dichlororbenzyl alcohol and 0.6 mg amylmetacresol. Un-intagliated. Batch No. BN0126986.

Duration of Treatment: Up to 3 days

Reference Therapy: Shape and colour matched non-medicated sugar-based lozenge with a bland sweet flavour. Batch No. BN0126989

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

Criteria for Evaluation:

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

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

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

Statistical Methods: All statistical tests were performed using a two-tailed 5% overall significance level, unless stated otherwise. The null hypothesis at all times was that the two

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treatments were equivalent. All comparisons between the treatments were reported with 95% confidence intervals for the difference. For each statistical test, an observed significance level was quoted.

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

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

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

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

Concomitant medications ongoing at randomisation were coded using the ATC level 2 categories from the WHO dictionary Enhanced March 2007 Version. All adverse events were listed and tabulated by treatment, severity, relationship to therapy and primary system organ class according to Version 11.0 of MedDRA.

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SUMMARY & CONCLUSIONS

EFFICACY RESULTS:

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

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

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

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

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

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

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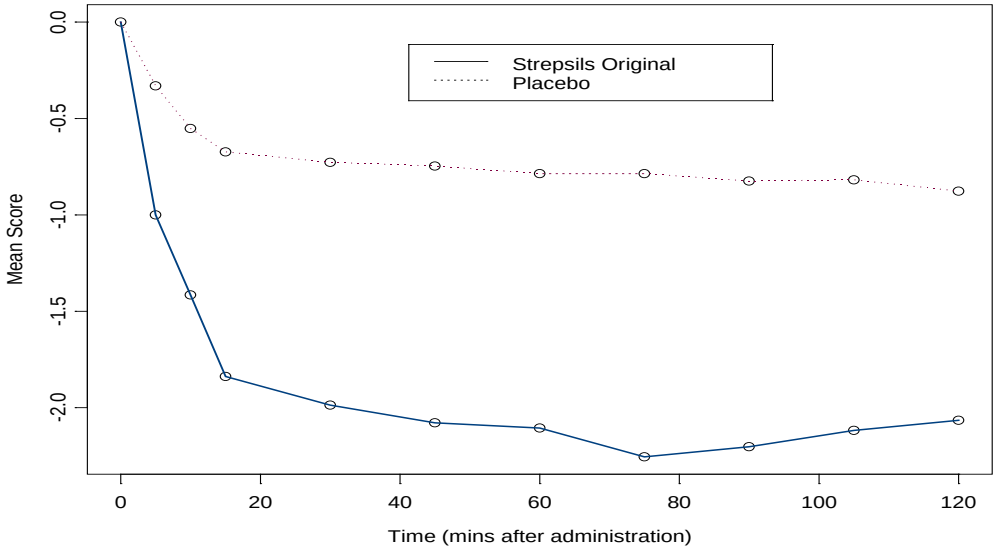
Figure 1: **Mean change from baseline in throat soreness from 5 to 120 minutes post first dose – Full Analysis Set**

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



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Key secondary efficacy variable data are summarised in Table 2.

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

Variable	Strepsils Original n	Strepsils Original LS mean[a]	Placebo n	Placebo LS mean[a]	Diff.[b]	95% CI	P
Throat Soreness (measured on a 11 point scale where 0 = not sore, 10 = very sore)							
AUC from baseline to 2 hours for change from baseline in throat soreness	154	-1.94	154	-0.69	-1.26	-1.54, -0.97	<0.0001
Change from baseline in throat soreness at end of Day 3	148	-4.02	150	-2.15	-1.87	-2.40, -1.34	<0.0001
Sore Throat Relief (measured on 7 point scale where 0 = no relief, 1 = slight relief, 2 = mild relief, 3 = moderate relief, 4 = considerable relief, 5 = almost complete relief, 6 = complete relief)							
AUC from baseline to 2 hours for sore throat relief	154	1.99	154	0.72	1.28	1.04, 1.52	<0.0001
Sore throat relief at 2 hours	153	1.93	154	0.84	1.09	0.78, 1.40	<0.0001
Sore throat relief at end of Day 3	148	3.37	152	1.79	1.58	1.15, 2.01	<0.0001
Difficulty in Swallowing (measure on 100 mm VAS where 0mm = not difficult, 100mm = very difficult)							
AUC from baseline to 2 hours for change from baseline in difficulty in swallowing	151	-14.4	152	-3.8	-10.6	-13.4, -7.8	<0.0001
Change from baseline in difficulty in swallowing at 2 hours	150	-15.0	149	-3.8	-11.1	-15.0, -7.3	<0.0001
Change from baseline in difficulty in swallowing at end of Day 3	142	-33.1	147	-15.9	-17.2	-22.4, -12.0	<0.0001
Overall Treatment Rating (measured on 11 point scale where 0 = poor, 10 = excellent)							
Overall Treatment Rating – 2 hours	153	5.49	153	2.75	2.74	2.15, 3.32	<0.0001
Overall Treatment Rating – end of Day 3	148	5.72	151	2.89	2.83	2.23, 3.43	<0.0001

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

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

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 5 minutes and lasted for at least 2 hours with the Strepsils Original Lozenges. The degree of demulcency provided by the placebo lozenge may have been influenced by the chosen composition of the lozenge (no flavour or tartaric acid). Throat soreness, pain relief and difficulty in swallowing all implied that peak effect was 75 minutes after initial dosing.

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

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

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

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

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

SAFETY RESULTS:

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

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

CONCLUSION:

The choice of placebo has the potential to affect the differences seen between placebo and active treatment. Despite this it can be concluded that Strepsils Original Throat Lozenges provide well tolerated and fast effective relief for sore throats due to upper respiratory tract infections. Following a single dose, relief is evident at 5 minutes post dose and lasts for at least 2 hours with maximal effects at 75 minutes post dose. Patients can feel the lozenge working as soon as they swallow and feel better at 2 hours. Analgesic effects continue over the 3 day study period with additional functional benefits in swallowing, eating and talking evident at 3 days.

Date of the report: 11 Jul 2014

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Abbreviation in Full
AE	Adverse event
AMC	Amylmetacresol BP
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ATC	Anatomic Therapeutic Class
AUC	Area under the curve
BSL	Baseline
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organisation
CSR	Clinical Study Report
CV	Curriculum Vitae
Diff.	Difference
DCBA	2,4-Dichlorobenzyl alcohol
EC	Ethics Committee
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMSU	Investigational Medicinal Supplies Unit
IRB	Institutional Review Board
ITT	Intent-to-treat
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Authorities
NS	Not significant
OTC	Over-The-Counter
PP	Per Protocol
RB	Reckitt Benckiser

Abbreviation	Abbreviation in Full
RBHI	Reckitt Benckiser Healthcare International
SAE	Serious adverse event
SE	Standard Error
SD	Standard Deviation
SDV	Source Data Verification
SE	Standard Error
SPID	Sum of the Pain Intensity Differences
TOTPAR	Total Sum of Pain Relief
TPA	Tonsillopharyngitis Assessment
UK	United Kingdom (of Great Britain and Northern Ireland)
URTI	Upper Respiratory Tract Infection
VAS	Visual Analogue Scale
WHO	World Health Organisation
yrs	Years

9 DISCUSSION AND OVERALL CONCLUSIONS

9.1 Discussion

9.1.1 Discussion on Placebo and Impact Assessment

Strepsils Original lozenges are a standard formulation in routine production and widely registered and marketed around the world. In this study the objectives were to investigate the analgesic and consumer benefits of the complete lozenge, building upon the results of an earlier study (BH5013) used to generate the sample size calculation for this study. The placebo was consistent with the placebo used in the previous study (BH5013) and was developed to provide a control for demulcent effects only. Flavouring systems and excipients can promote salivation enhancing the soothing and efficacious properties of lozenges[1, 2, 3, 4], so the placebo was the same colour, size and shape as the Strepsils Original throat lozenge but without the characteristic aniseed flavour and without tartaric acid (a fruit acid that stimulates saliva production).

It can be argued that the lack of flavour in the placebo throat lozenge would have 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. However, the patient information sheet for trial patients clearly identified Strepsils Original as the test product and, with the use of Strepsils Original in the community within the UK, a number of study participants may have been familiar with the flavour of the active product so might have concluded that the familiar taste was an active lozenge rather than a similar tasting placebo or might have recognised that the placebo was not the same as a familiar Strepsils. This might have had an influence on their subjective rating scores. This is supposition but the potential was there for this to introduce bias into the study and inflate the active-control treatment difference. For the primary efficacy endpoint the difference between the LS means for the treatments at 2 hours of -1.21 (95% CI -1.59, -0.82, p<0.0001) was greater than the difference of -0.7 observed in the previous study[5]. While the mean difference in treatment effect in this study (-1.21) was larger than that reported in the previous study (-0.7)[2], given that the earlier study recruited only 50 patients in total, the 95% confidence interval for the underlying mean difference based on the results of the previous study was (-1.5 to 0.2) and hence the results seen in this study were not completely unexpected indicating that if there is bias in the study it is consistent with the previous study. The choice of placebo had the potential to affect the differences seen between placebo and active treatments. Despite this it may be concluded that Strepsils Original Throat Lozenges provide fast, safe and effective relief for sore throats due to upper respiratory tract infections. Following a single dose, relief is evident at 5 minutes post dose and lasts for at least 2 hours with maximal effects at 75 minutes post dose. Patients can feel the lozenge working as soon as they swallow and feel better at 2 hours. Analgesic effects continue over 3 days with additional functional benefits in swallowing, eating and talking evident at 3 days.

9.2 Conclusion

The choice of placebo has the potential to affect the differences seen between placebo and active treatment. Despite this it can be concluded that Strepsils Original Throat Lozenges provide well tolerated and fast effective relief for sore throats due to upper respiratory tract infections. Following a single dose, relief is evident at 5 minutes post dose and lasts for at least 2 hours with maximal effects at 75 minutes post dose. Patients can feel the lozenge working as soon as they swallow and feel better at 2 hours. Analgesic effects continue over the 3 day study period with additional functional benefits in swallowing, eating and talking evident at 3 days.

11 REFERENCE LIST FOR ADDENDUM REPORT

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

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

3) Hartung-Brooks L. Sore Throat. On Continuing Practice, 1990; 17(1): 2–6 7)

4) Kelly F. Something for a sore throat please. Aust Pharmacist 2008: 394 – 7.

5) BH5013R. Data on File.

6) McNally D, Simpson M, Morris C, Shephard A, Goulder M. Rapid relief of acute sore throat with AMC/DCBA throat lozenges: randomised controlled trial. Int J Clin Pract 2010; 64 (2): 194 – 207

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PRINCIPAL INVESTIGATOR'S SIGNATURE

Study Number: TH0705

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

Phase: IV

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.

Dr. Damien Mc Nally

MB, Bch, BAO, MRCGP, DRCOG, Diploma in Mental Health (QUB)

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