Reckitt Benckiser

1 ADDENDUM TO STUDY REPORT TITLE PAGE

EudraCT/IND Number:	2010-020985-94
Study Number:	TH 1010
Protocol Title:	A randomised, double blind, placebo-controlled, parallel group, single dose study of the efficacy of a flavoured variant of Strepsils Throat Lozenge in the relief of dry and irritated sore throat due to upper respiratory tract infection or environmental factors.
Study Phase:	III
Date First Subject Enrolled:	02 November 2010
Date Last Subject Completed:	01 March 2011
Report Date:	05 August 2011
Principal Investigator:	Dr Alan G Wade, CPS Research, West of Scotland Science Park, Glasgow, G20 0XQ, United Kingdom
Study Conduct Statement:	This study was conducted in accordance with ICH Good Clinical Practice and the ethical principles contained within the Declaration of Helsinki (South Africa, 1996), as referenced in EU Directive 2001/20/EC 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

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2 ADDENDUM TO STUDY REPORT

Name of Sponsor/ Company: Reckitt Benckiser Healthcare International Ltd.	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority use only)**
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Name of Active Ingredient(s): 1.2 mg 2,4-dichlorobenzyl alcohol, 0.6 mg amylmetacresol	**Page:**	

Title of Trial: A randomised, double blind, placebo-controlled, parallel group, single dose study of the efficacy of a flavoured variant of Strepsils Throat Lozenge in the relief of dry and irritated sore throat due to upper respiratory tract infection or environmental factors.

Investigator(s): Dr Alan G Wade

Trial Site(s): Single centre at CPS Research, Glasgow, United Kingdom

Publication (reference): None

Studied Period: 4 months **Date first patient enrolled:** 2 November 2010 **Date last patient completed:** 1 March 2011 Note: The date of the end of trial notification submitted to the MHRA and ethics was incorrect (25 February 2011). The correct date of last patient completed is the 1st March 2011, as stated in the clinical study report.	**Phase of Development:** III

Objectives: The primary objective of this study was to determine the analgesic properties of an experimental formulation of Strepsils lozenge in patients with a dry and irritated sore throat due to upper respiratory tract infection (URTI) or environmental factors. The analgesic properties were assessed by comparing sore throat relief and throat soreness in patients treated with the Strepsils lozenge and patients treated with a placebo lozenge. In addition to the analgesic endpoints, functional measures of throat dryness and throat irritation were also assessed.

The secondary objective of this study was to determine consumer acceptability of the product via responses to a consumer questionnaire.

Methodology: This was a randomised, double blind, parallel group, single dose study comparing the efficacy of an experimental formulation of Strepsils lozenge with placebo.

Subjective rating scales for throat soreness, throat dryness, throat irritation (11-point scale) and sore throat relief (7-point scale) were used to assess efficacy. Throat soreness, throat dryness and throat irritation were assessed at screening, 0 (pre-dose) and 1, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes after dosing. Sore throat relief was assessed at all post-dose time points. A consumer questionnaire was completed at 0 (pre-dose), 1, 5, 20, 60 and 180 minutes after dosing to assess consumer acceptability and the treatment was rated at the end of the 3-hour assessment period.

Adverse events were assessed at 0 (pre-dose), 180 minutes and up to 24 hours post-dose. A patient diary was used to capture adverse event and concomitant medication information from 3 hours to up to 24 hours post-dose.

Number of Patients: **Planned:** 200 (100 in each treatment group)
Analysed: 203 (Full analysis set); 195 (Per-protocol)

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 or environmental factors, 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 scoring at least 3 points on the expanded Tonsillopharyngitis Assessment (TPA). They also had to have a sore throat, a dry throat and a scratchy, tickly or itchy throat as shown by scoring at least 6 on the throat soreness scale, 3 or less on a throat dryness scale and 5 or less on a throat irritation scale (all ordinal 0-10 scales).

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Patients with conditions, or who had taken medications, that could interfere with the assessment of sore throat analgesic activity or those with an allergy or intolerance to the study medication or any of the other constituents were excluded.

Test Product: Experimental flavoured throat lozenge containing 2, 4–dichlorobenzyl alcohol (1.2 mg) and amylmetacresol (0.6 mg), single oral dose, batch number 02172164, expiry date 9 March 2011

Patients were instructed to suck the lozenge slowly, moving it around the mouth until dissolved and not to chew or crunch it.

Duration of Treatment: Single dose (one lozenge)

Reference Therapy: Placebo: a single shape matched, non-medicated, sugar free throat lozenge, single oral dose, batch number 01945196, expiry date 9 March 2011

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the area under the curve (AUC) for the change from baseline in severity of throat soreness on swallowing (using the 11-point throat soreness scale) to 2 hours.

Secondary variables included:

The change from baseline in severity of throat soreness, throat dryness, throat irritation and sore throat relief at all time points up to 3 hours post-dose

The AUCs for the change from baseline to 3 hours in severity of throat soreness and the changes from baseline to 2 and 3 hours for throat dryness and throat irritation (using the respective 11-point scales) and sore throat relief (using the 7-point scale)

Time to onset of moderate pain relief, overall treatment rating and consumer acceptability by responses to the questions from the consumer questionnaire

Safety: The overall proportion of patients with adverse events (AEs) and serious adverse events (SAEs) was assessed in the clinic and up to 24-hour post-dose using a patient diary.

Statistical Methods:

All efficacy variables were analysed using the full analysis dataset, which consisted of all patients who were randomised to the study and took study medication. The primary analysis and secondary analysis of the AUC from 0 to 2 hours for sore throat relief were repeated using a per-protocol set.

The primary efficacy variable was analysed using Analysis of Covariance (ANCOVA) with the baseline severity of throat soreness as a covariate and a factor for treatment group.

The secondary AUC, changes from baseline and overall treatment rating variables were analysed using ANCOVA with baseline severity of throat soreness as a covariate and a factor for treatment group. Covariates for throat dryness and throat irritation were also added to the model for analyses of these variables. The time to onset of moderate pain relief was compared between treatment groups using the Cox-proportional Hazards model. Consumer questionnaire responses were analysed using a logistic regression model (binary data) or ANCOVA (non-binary data).

Safety data were analysed using the safety set which included all patients who took study medication. The proportion of patients reporting treatment emergent adverse events was compared between treatment groups using the chi-square test.

Treatment group differences were presented with 95% confidence intervals. All AUC analyses were based on actual timings and were calculated using the trapezoidal rule.

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SUMMARY & CONCLUSIONS

PATIENTS:

A total of 203 patients (101 test, 102 placebo) were randomised into the study and were treated with study medication. All 203 patients completed the study. The patients (107 males, 96 females) had a mean age of 34 years (range 16-67) and were mainly Caucasian (198, 98%). Their mean duration of sore throat was 2.2 days; 92% of patients had a sore throat due to URTI and 8% due environmental factors (as assessed by a study nurse).

The treatment groups were well-balanced for the demographic characteristics. The TPA score, and the pre-dose ratings for throat soreness, throat irritation, throat dryness were generally comparable between the two treatment groups. However, there was an imbalance in the proportion of patients describing their throats as swollen and inflamed (8% test, 20% placebo).

EFFICACY RESULTS:

The results for the primary efficacy variable and other AUC variables for throat soreness, sore throat relief, throat dryness and throat irritation are summarised in Table 1. The per-protocol analyses of the primary variable and AUC from 0 to 2 hours for sore throat relief gave similar results to those of the full analysis set.

TABLE 1 Summary statistics for AUCs from 0 to 2 and 0 to 3 hours for analgesic and functional ratings – full analysis set

Variable	Test (n=101)	Placebo (n=102)	Treatment difference	
	LS mean [a]	LS mean [a]	LSD mean difference for test – placebo (95% CI)	p-value
$AUC_{0\text{-}2h}$ for the change from baseline in throat soreness	-1.50	-1.53	0.04 (-0.34, 0.42)[b]	0.85
$AUC_{0\text{-}3h}$ for the change from baseline in throat soreness	-1.47	-1.55	0.07 (-0.32, 0.47)[b]	0.72
$AUC_{0\text{-}2h}$ for sore throat relief	2.78	2.42	0.36 (0.09, 0.63)[c]	0.0102
$AUC_{0\text{-}3h}$ for sore throat relief	2.77	2.43	0.34 (0.05, 0.63)[c]	0.02
$AUC_{0\text{-}2h}$ for the change from baseline in throat dryness [d]	1.87	1.75	0.12 (-0.27, 0.50)[c]	0.55
$AUC_{0\text{-}3h}$ for the change from baseline in throat dryness [d]	1.74	1.65	0.09 (-0.31, 0.48)[c]	0.66
$AUC_{0\text{-}2h}$ for the change from baseline in throat irritation [e]	1.55	1.27	0.28 (-0.08, 0.65)[c]	0.13
$AUC_{0\text{-}3h}$ for the change from baseline in throat irritation [e]	1.48	1.24	0.25 (-0.14, 0.63)[c]	0.21

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b A negative difference favours test lozenge.
c A positive difference favours test lozenge
d Estimated from ANCOVA model with factor for treatment and covariates for baseline throat soreness and baseline throat dryness
e Estimated from ANCOVA model with factor for treatment and covariates for baseline throat soreness and baseline throat irritation

Throat soreness measured on an 11-point scale where 0 = Not sore, 10 = Very sore
Sore throat relief measured on a 7-point scale where 1 = No relief, 2 = Slight relief, 3 = Mild relief, 4 = Moderate relief, 5 = Considerable relief, 6 = Almost complete relief, 7 = Complete relief
Throat dryness measured on an 11-point scale 0 = Completely dry, 10 = Completely moist
Throat irritation measured on an 11-point scale 0 = Completely scratchy, tickly or itchy 10 = Not at all scratchy, tickly or itchy

Key secondary efficacy variable data are summarised in Tables 2 and 3. There was significantly greater sore throat relief achieved in the test treatment group compared with

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placebo from 1 to 75 minutes post-dose, but not thereafter.

TABLE 2 **Mean ± sd changes in throat soreness from baseline and mean (± sd) sore throat relief over 3 hours post-dose**

	Throat soreness			Sore throat relief		
Minutes post-dose	Test (n)	Placebo (n)	T vs. P	Test (n)	Placebo (n)	T vs. P
0	7.12±1.44 (101)	7.13±0.99 (102)	ns			
1	-0.40±1.63 (101)	-0.40±1.27 (102)	ns	1.90±0.97 (101)	1.48±0.79 (102)	***
5	-1.37±1.92 (101)	-1.28±1.77 (101)	ns	2.52±1.04 (101)	2.00±0.88 (102)	***
10	-1.53±1.91 (101)	-1.63±1.87 (102)	ns	2.78±1.20 (101)	2.37±0.98 (102)	**
15	-1.45±1.87 (101)	-1.58±1.85 (102)	ns	2.85±1.13 (101)	2.47±1.03 (102)	*
30	-1.50±1.85 (101)	-1.49±1.66 (102)	ns	2.83±1.10 (101)	2.51±1.03 (102)	*
45	-1.65±2.09 (101)	-1.39±1.76 (102)	ns	2.88±1.19 (101)	2.46±1.05 (102)	**
60	-1.47±1.99 (101)	-1.49±1.68 (102)	ns	2.87±1.25 (101)	2.47±1.08 (102)	*
75	-1.59±1.90 (101)	-1.70±1.75 (101)	ns	2.79±1.21 (101)	2.46±1.09 (101)	*
90	-1.52±2.06 (101)	-1.74±1.85 (102)	ns	2.80±1.22 (101)	2.51±1.21 (102)	ns
105	-1.50±2.01 (101)	-1.60±1.79 (102)	ns	2.78±1.20 (101)	2.46±1.18 (102)	ns
120	-1.51±2.11 (101)	-1.66±1.82 (102)	ns	2.75±1.27 (101)	2.45±1.29 (102)	ns
135	-1.46±2.16 (101)	-1.53±1.85 (102)	ns	2.70±1.28 (101)	2.45±1.23 (102)	ns
150	-1.39±1.98 (101)	-1.64±1.83 (102)	ns	2.67±1.27 (101)	2.39±1.22 (102)	ns
165	-1.44±2.05 (100)	-1.63±2.08 (102)	ns	2.76±1.33 (100)	2.43±1.33 (101)	ns
180	-1.38±2.16 (101)	-1.39±1.90 (102)	ns	2.81±1.29 (101)	2.46±1.28 (102)	ns

ns	Test lozenge (S) vs. placebo (P) comparison not statistically significant
*	Test lozenge (S) vs. placebo (P) comparison statistically significant at 5% level
**	Test lozenge (S) vs. placebo (P) comparison statistically significant at 1% level
***	Test free lozenge (S) vs. placebo (P) comparison statistically significant at 0.1% level

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

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

There was no significant difference between treatments in the time to onset of moderate pain relief.

The changes from baseline in throat dryness, as assessed on the 11-point throat dryness scale showed that the test treatment group had significantly greater moistening than the placebo group at 1 and 5 minutes post-dose, but later differences were not significant. There was a significant improvement in throat irritation at 1, 5 and 10 minutes post-dose in the test group compared with placebo. Peak improvements in throat dryness and throat irritation were achieved with test lozenge at 5 and 10 minutes post-dose, respectively.

The throat dryness element of the consumer questionnaire supported the findings from the subjective rating scale. The responses showed that the speed of onset of a moistening/mouth watering sensation was significantly faster in the test lozenge group (n=101) than in the placebo group (n=101; Odds ratio 2.53, 95% CI 1.53 to 4.18, p=0.0003). At 1 and 5 minutes post-dose, patients in the test group had a significantly greater degree of throat hydration than those in the placebo group ($p<0.01$; $p<0.05$ respectively).

At 3 hours post-dose, patients treated with the test lozenge had a significantly greater degree of mouth watering/moistening effect (p=0.0002) and a greater degree of coating of the throat compared to placebo (p=0.03). There were also significant differences between the treatments in the moistening (p=0.011) and lubricating effects (p=0.007), with an effect felt deeper down the throat after taking the test lozenge than the placebo lozenge at 3 hours post-dose.

Patients rated test lozenges more highly as a treatment for sore throat than placebo lozenges

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at 3 hours post-dose (Table 3). Patients also began to feel more like their best overall at 1 hour with a significant difference between treatments (p=0.002) in favour of the test lozenge.

TABLE 3 Summary statistics for treatment ratings – full analysis set

Variable	Test (n=101)	Placebo (n=102)	Treatment difference	
	LS mean[a]	LS mean[a]	LSD mean difference for test – placebo (95% CI)[b]	p-value
Overall treatment rating at 3 hours	5.00	4.21	0.79 (0.01, 1.58)	0.049
Rating as a treatment for dry/irritated sore throat	5.03	4.29	0.74 (-0.03, 1.51)	0.06

a Estimated from ANCOVA model with factor for treatment and a covariate for baseline throat soreness
b A positive difference favours test lozenge
Measured on an 11-point scale where 0 = Poor, 10 = Excellent

SAFETY RESULTS:

In the test lozenge group, 10 (10%) patients reported 11 treatment emergent AEs and in the placebo group, 8 (8%) patients reported 11 AEs. There was no statistically significant difference between treatments in the proportion of patients reporting events (p=0.61). All treatment emergent events were of mild severity, except one that was of moderate severity. All of the AEs were classified as not or unlikely to be related to the study medication. Headache was the most commonly reported treatment emergent AE in both treatment groups; 6 (6%) patients reported 7 headaches in the test lozenge group and 5 (5%) reported 5 events in the placebo group. There were no SAEs or discontinuations due to AE in this study.

CONCLUSION:

There were some changes to the planned conduct of the study with respect to matching of placebo, and the fact that study nurses who administered the drug also were involved in collecting patient assessments of efficacy. Despite these changes it is considered that data from the study remain valid as there is no evidence to suggest the site staff unblinded the patients.

The experimental formulation lozenge provides fast and effective pain relief for patients with a dry and irritated sore throat due to URTI or environmental factors. Following a single dose, pain relief is evident after 1 minute with peak analgesic effect occurring at 45 minutes and superior pain relief over 3 hours compared with placebo lozenges. The test lozenges also provide rapid improvements in throat dryness and throat irritation, with peak effects at 5 and 10 minutes after intake.

The lozenges are well accepted by consumers. They have moistening and lubricating effects, which are felt deep down in the throat and are rated as a better treatment for sore throat than placebo lozenges 3 hours after intake.

The test lozenges are well tolerated and there are no apparent safety concerns regarding their use.

Date of the report: 05 August 2011, addendum 19 August 2013

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9.4 Treatments

9.4.6 Blinding

The protocol stated that "The lozenges are colour shaped and matched to maintain the study blinding" (section 11.2). The protocol also stated that the patients would be blindfolded prior to being given the investigational medicinal product (IMP, a lozenge) and that an independent member of the site staff would watch the patients put the lozenge in their mouths (section 12.3).

The following aspects of the protocol were incorrect:

1. Whilst the product and the placebo were the same colour, the test product was more opaque than the placebo.

2. The IMP administration was supervised by the study nurse who was involved in the conduct of the study and in the supervision of the patients.

These should have been reflected in the blinding (section 9.4.6) section of the clinical study report.

9.4.8 Treatment Compliance

The protocol also stated that the patients would be blindfolded prior to being given the investigational medicinal product (IMP, a lozenge) and that an independent member of the site staff would watch the patients put the lozenge in their mouths (section 12.3).

The following aspects of the protocol were incorrect:

1. Trial subjects were not blindfolded prior to being administered the IMP, but were asked to close their eyes.

2. The IMP administration was supervised by the study nurse who was involved in the conduct of the study and in the supervision of the patients.

These should have been reflected in treatment compliance (Section 9.4.8) section of the clinical study report.

9.8 Changes in the Conduct of the Study or Planned Analysis

9.8.1 Changes in the Conduct of the Study

The protocol stated that "The lozenges are colour shaped and matched to maintain the study blinding" (section 11.2). The protocol also stated that the patients would be blindfolded prior to being given the investigational medicinal product (IMP, a lozenge) and that an independent member of the site staff would watch the patients put the lozenge in their mouths (section 12.3).

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3. The IMP administration was supervised by the study nurse who was involved in the conduct of the study and in the supervision of the patients.

The protocol states "A Tonsillopharyngitis Assessment (TPA), performed by the investigator or designated sub-investigator" (section 6). However this assessment was conducted by the research nurses on the study. This has been captured in the clinical study report, was explained in the REC application, and is reflected in the delegation log.

The protocol states "200 patients (100 in each treatment group) will be recruited. It is anticipated that this will be sufficient to ensure that 170 completed patients provide 2 hour data for the primary end point (AUC from 0 to 2 hours for change from baseline in sore throat relief)"(section 10). However the site recruited 203 patients on the study.

10 STUDY PATIENTS

10.2 Protocol Deviations

The protocol stated that "The lozenges are colour shaped and matched to maintain the study blinding" (section 11.2). The protocol also stated that the patients would be blindfolded prior to being given the investigational medicinal product (IMP, a lozenge) and that an independent member of the site staff would watch the patients put the lozenge in their mouths (section 12.3).

The following aspects of the protocol were incorrect:

1. Whilst the product and the placebo were the same colour, the test product was more opaque than the placebo.

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The protocol states "200 patients (100 in each treatment group) will be recruited. It is anticipated that this will be sufficient to ensure that 170 completed patients provide 2

hour data for the primary end point (AUC from 0 to 2 hours for change from baseline in sore throat relief)"(section 10). However the site recruited 203 patients on the study.

11 EFFICACY EVALUATION

11.4.7 Efficacy Conclusions

During the conduct of the study there were changes with respect to matching of placebo, and the fact that study nurses who administered the drug also were involved in collecting patient assessments of efficacy. Despite these changes it is considered that data from the study remain valid as there is no evidence to suggest the site staff unblinded the patients.

The specific efficacy variables selected to address the primary and secondary study objectives and the conclusions are presented in Table 11.4.32.

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

The primary aim of the study was to determine the analgesic properties of an experimental formulation of Strepsils lozenge in patients with a dry and irritated sore throat due to URTI or environmental factors. The test formulation contained a significantly higher proportion of tartaric acid than currently marketed formulations of Strepsils and was designed to produce mouth-watering effects.

A total of 203 patients were randomised to treatment (101 to test lozenge and 102 to placebo lozenge) and were analysed in a full analysis set. The variability observed for the primary efficacy endpoint in this study was 1.37 (root mean square error from the ANCOVA model of the full analysis set) which was lower than predicted and suggests that with 203 patients analysed, the study was more than adequately powered.

The study population consisted of 107 males and 96 females and had a mean age of 34 years. The majority of patients had a sore throat due to URTI (92%) and 8% had a sore throat due to environmental factors, as assessed by a study nurse. The treatment groups were generally well matched in the demographic and baseline sore throat characteristics apart from an imbalance in the proportion of patients describing their throats as swollen and inflamed. The patients were considered a representative sample of the general population of patients with a dry and irritated sore throat due to URTI or environmental factors. In this study, novel scales for throat dryness and throat irritation were used to obtain patients who had significant levels of throat irritation and dryness at study entry. Hence, the population differed from those used in previous studies with Strepsils lozenges. Treatment compliance was 100% as site staff monitored patients taking the study medication and hence is unlikely to influence the outcome of the study.

There were some changes to the planned conduct of the study with respect to matching of placebo, and the fact that study nurses who administered the drug also were involved in collecting patient assessments of efficacy. Despite these changes it is considered that data from the study remain valid.

The primary analysis, comparing the AUC for the change from baseline in severity of throat soreness, from 0 to 2 hours did not find any statistically significant differences between the test lozenge and placebo. The analysis of the AUC in severity of throat soreness from 0 to 2 hours (using the 11-point Throat Soreness scale) gave LS mean reductions from baseline of -1.50 and -1.53 for the test and placebo lozenges respectively. The LS mean difference was 0.04 (95% CI -0.34 to 0.42) for the comparison of the test lozenge and the placebo lozenge. This treatment difference was considerably smaller than previously observed in comparisons between test lozenges and placebo. Similar results were obtained using a per-protocol population.

In addition, no significant differences were observed in the AUC for the change from baseline in severity of throat soreness, from 0 to 3 hours or from the changes in throat soreness from baseline at any time point.

However, the secondary analyses for sore throat relief indicated that the test lozenges provided superior pain relief compared with the placebo lozenges. Significant differences between treatment groups were observed for the AUC values for the change from baseline in sore throat relief (TOTPAR) to 2 hours ($p=0.0102$) and 3 hours ($p=0.02$). Significantly greater pain relief was achieved in the test treatment group compared with placebo from 1 to 75 minutes post-dose ($p<0.001$ at 1 and 5 minutes, $p<0.05$ or $p<0.01$ for 10 to 75 minutes). Maximal improvements in sore throat relief were achieved with the test lozenge at 45 minutes post-dose. A single dose provided effective pain relief over the 3-hour period, although the treatment differences from 90 minutes onwards were not statistically significant.

The different findings arising from the analyses of the analgesic variables of throat soreness and sore throat relief were unexpected, and both the 7-point sore throat relief and 11-point throat soreness rating scales have been used previously to assess the analgesic properties of throat medications. A study has shown that patients with sore throats can independently assess patient reported outcomes (PROs) for pain on swallowing, swollen throat and difficulty swallowing[16], although a close correlation would have been expected between throat soreness and sore throat relief. Nevertheless the fact that patients were asked to assess "soreness" specifically on swallowing as opposed to pain relief which was elicited as a passive experience may explain this anomaly.

Analyses indicated that there was a significant interaction between the treatment group and baseline throat soreness with greater reductions with the test lozenge than the placebo lozenge in patients with more severe throat soreness at baseline. A similar interaction was evident with severity of throat irritation. These findings may indicate that patients with more severe symptoms at baseline could benefit more from treatment with the test lozenge. The analyses may also indicate that the

additional inclusion criteria of dry and irritated throat may have changed the overall sensitivity of the population to treatment.

Patients entered the study with a known dry and irritated sore throat at baseline, as verified by their baseline scores on the 11-point rating scales for throat dryness and throat irritation. Although the scale for throat dryness had been used in previous in-house consumer studies, the scale for throat irritation was used for the first time in this study. Both scales were useful PRO measures for assessing throat dryness and throat irritation, although further work is need to validate the scales.

The test lozenges had both a rapid moistening and a calming effect on dry and irritated sore throats, as shown by the significantly greater moistening effect at 1 and 5 minutes post-dose and improvement in throat irritation at 1, 5 and 10 minutes post-dose compared with placebo. Maximal improvements in throat dryness and throat irritation are achieved with the test lozenge at 5 and 10 minutes post-dose, respectively.

These early moistening/lubricating sensations experienced by patients with a dry and irritated sore throat are supported by the responses to the consumer questionnaire. At 1 and 5 minutes post-dose, the test lozenges provided a significantly greater degree of throat hydration than placebo lozenges ($p<0.01$; $p<0.05$ respectively). The onset of a moistening/mouth watering sensation was also significantly faster with test lozenges compared with placebo ($p=0.0003$), with half of the patients taking test lozenges had experienced this sensation within 5 seconds compared to 26% taking placebo.

The moistening and lubricating effect of the test lozenges was also evident at later assessment times, long after the lozenge had dissolved in the mouth. At 3 hours post-dose, patients reported a significantly greater degree of mouth watering/moistening effect compared to placebo ($p=0.0002$). In addition to the moistening effect, the test lozenges provided a greater degree of coating of the throat than placebo lozenges at 3 hours post-dose ($p=0.03$). The moistening effect was felt deeper down the throat after taking the test lozenge than placebo lozenges at 3 hours post-dose ($p=0.011$), as was the lubricating effect ($p=0.007$). However, despite the superior deep down moistening and lubricating effect of the test lozenges at 3 hours post-dose, there was no significant difference between treatment groups in pain relief felt deeper down in the throat at this time. Furthermore, the pain relieving, moistening and lubricating actions of the test lozenges did not translate into improved functioning, with no significant differences between the treatment groups in the talking, swallowing, reading and concentrating variables on the functional impairment scale.

Patients did start to feel better after taking the test lozenges with the consumer questionnaire responses indicating that they began to feel more like their best overall at 1 hour post-dose ($p=0.002$), although there was no significant difference between the treatment groups at 3 hours post-dose.

The test lozenges were rated as a better treatment for sore throat than placebo lozenges at 3 hours post-dose. There was also a trend towards superiority in their rating of the test lozenge as a treatment of a dry/irritated sore throat (p=0.06).

There were no safety issues highlighted by this study with the test lozenges to indicate any change in the well-established safety profile of Strepsils. The test lozenges were tolerated as well as placebo lozenges with no significant differences between the treatment groups in the proportion of patients reporting an AE. All but one of the reported AEs was of mild intensity and no Aes were classified as severe. The most commonly reported treatment emergent AE in both treatment groups was headache and most Aes were related to the patient's URTI such as headache, cough, sinus congestion and runny nose. The potential risk to patients from taking the test lozenges is considered low.

Although the test lozenge showed some signs of benefit in a population with dry and irritated sore throat, the overall effect was marginal. It is possible that the enhanced mouth watering effects of an experimental formulation containing a high proportion of tartaric acid diminished the analgesic effects of 2, 4–dichlorobenzyl alcohol (1.2 mg) and amylmetacresol (0.6 mg) (AMC/DCBA) locally in the throat.

13.2 Conclusion

There were some changes to the planned conduct of the study with respect to matching of placebo, and the fact that study nurses who administered the drug also were involved in collecting patient assessments of efficacy. Despite these changes it is considered that data from the study remain valid as there is no evidence to suggest the site staff unblinded the patients.

The experimental formulation lozenge provides fast and effective pain relief for patients with a dry and irritated sore throat due to URTI or environmental factors. Following a single dose, pain relief is evident after 1 minute with peak analgesic effect occurring at 45 minutes and superior pain relief over 3 hours compared with placebo lozenges. The test lozenges also provide rapid improvements in throat dryness and throat irritation, with peak effects at 5 and 10 minutes after intake.

The lozenges are well accepted by consumers. They have moistening and lubricating effects, which are felt deep down in the throat and are rated as a better treatment for sore throat than placebo lozenges 3 hours after intake.

The test lozenges are well tolerated and there are no apparent safety concerns regarding their use.