Reckitt Benckiser

1 CLINICAL STUDY REPORT ERRATUM TITLE PAGE

EudraCT/IND Number:	2010-020985-94
Study Number:	TH1010
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 Patient Enrolled:	02nd November 2010
Date Last Patient Completed:	01st March 2011
Original Report Date:	05th August 2011
Addendum to Report Date:	19th August 2013
Erratum Report Date:	18th November 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 conducted in accordance with conditions and principles of Good Clinical Practice as referenced in UK SI 2004/1031, the ethical principles contained within the Declaration of Helsinki (South Africa, 1996 and, as referenced in EU Directive 2001/20/EC. Documents defined by ICH GCP as "essential documents" will be archived in the RB company archive in Hull UK

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

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:	**Volume:**	
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 Wade, Dr Gordon Crawford		
Trial Site(s): Single centre at CPS Research, Glasgow, United Kingdom		
Publication (reference): None		
Studied Period: 4 months **Date first subject enrolled:** 2 November 2010 **Date last subject completed:** 1 March 2011		**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), 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 Subjects: **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). Patients with conditions, or who had taken medications, that could interfere with the		

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Name of Finished Product:	**Volume:**	
Name of Active Ingredient(s): 1.2 mg 2,4-dichlorobenzyl alcohol, 0.6 mg amylmetacresol	**Page:**	

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 Products:

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.

Assessment Period: 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, 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.

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:	**Volume:**	
Name of Active Ingredient(s): 1.2 mg 2,4-dichlorobenzyl alcohol, 0.6 mg amylmetacresol	**Page:**	

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 general 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_{0-2h} for the change from baseline in throat soreness	-1.50	-1.53	0.04 (-0.34, 0.42)[b]	0.85
AUC_{0-3h} for the change from baseline in throat soreness	-1.47	-1.55	0.07 (-0.32, 0.47)[b]	0.72
AUC_{0-2h} for sore throat relief	2.78	2.42	0.36 (0.09, 0.63)[c]	0.0102
AUC_{0-3h} for sore throat relief	2.77	2.43	0.34 (0.05, 0.63)[c]	0.02
AUC_{0-2h} for the change from baseline in throat dryness [d]	1.87	1.75	0.12 (-0.27, 0.50)[c]	0.55
AUC_{0-3h} for the change from baseline in throat dryness [d]	1.74	1.65	0.09 (-0.31, 0.48)[c]	0.66
AUC_{0-2h} for the change from baseline in throat irritation [e]	1.55	1.27	0.28 (-0.08, 0.65)[c]	0.13
AUC_{0-3h} 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

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Name of Active Ingredient(s): 1.2 mg 2,4-dichlorobenzyl alcohol, 0.6 mg amylmetacresol	**Page:**	

significantly greater sore throat relief achieved in the test treatment group compared with 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

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Name of Finished Product:	**Volume:**	
Name of Active Ingredient(s): 1.2 mg 2,4-dichlorobenzyl alcohol, 0.6 mg amylmetacresol	**Page:**	

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 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, erratum 18 November 2014

3 TABLE OF CONTENTS

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS FOR ERRATUM REPORT

Abbreviation	Abbreviation in Full
AE	Adverse event
ANCOVA	Analysis of covariance
AUC	Area under the curve
CPS	Community Pharmacology Services
CSR	Clinical Study Report
DMP	Data Management Plan
EU	European Union
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
LS	Least Square
QC	Quality control
RB	Reckitt Benckiser
SAE	Serious adverse event
TPA	Tonsillopharyngitis Assessment
UK	United Kingdom (of Great Britain and Northern Ireland)
URTI	Upper Respiratory Tract Infection

5 INTRODUCTION TO STUDY REPORT ERRATUM

Following production of the original Clinical Study Report (CSR) and the subsequent Addendum for TH1010 an internal audit highlighted a variety of issues that were not adequately described either in the original CSR or addressed in the Addendum. Also highlighted were many typographical and/or grammatical type errors. This document is an erratum to the addenda that was written following the finalisation of the original CSR and provides updates, corrections and comments to address the findings from the internal audit. The following information is presented as amended CSR sections using the same numbering system as appears in the CSR.

1 TITLE PAGE

Both the original CSR title page and the addendum title page give a statement of compliance that reads:

"This study was conducted in accordance with ICH Good Clinical Practice and the ethical principles contained within the Declaration of Helsinki (South Africa, 1996), as referenced in EU Directive 2001/20/EC. Documents defined by ICH GCP as "essential documents" will be archived in the RB company archive in Hull UK."

This statement should have read:

"This study was conducted in accordance with conditions and principles of Good Clinical Practice as referenced in UK SI 2004/1031, the ethical principles contained within the Declaration of Helsinki (South Africa, 1996 and, 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."

Note – The corrected version of the statement has been used on the title page of this erratum.

2 SYNOPSIS & TITLE PAGE FOOTER

During the audit it was noted that the sponsor name was not consistent throughout all documentation. The study contract was reviewed, and for this study, the name is Reckitt Benckiser Healthcare International Ltd. However since this study has been completed the name has changed and hence the company name of the signatories is Reckitt Benckiser Healthcare (UK) Ltd, whilst the name on study documentation and in the synopsis header of this document remain Reckitt Benckiser Healthcare International Ltd.

7 INTRODUCTION

It has been noted in the introduction of the CSR that there is mention of 2.1% Tartaric acid that was not specifically mentioned in the protocol in the same way. It is stated in the CSR as being included as part of the formulation of the lozenge to produce an extreme mouth-watering effect. The protocol does state Tartaric acid in the excipient list and patients were to be excluded if they had a known allergy to it. It was also stated in the Protocol Introduction (Section 6) that the aim of the study was to produce a mouth-watering or lubricating sensation to provide specific relief from dry and irritated sore throat.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan – Description

It was noted during the audit that there was an incomplete sentence within section 9.1 of the Final Study Report. The sentence in question was located within the fourth paragraph of the section and originally read as:

"Pre-screening of patients responding to advertising was conducted by telephone using a standardised script before patients."

Although this Study Report underwent a QC Check, this error was not picked up. The QC Process has been updated and is now more rigorous, to pick up such errors in future.

The amended text for section 9.1, paragraph 4 is detailed below:

"Pre-screening of patients responding to study specific advertising was conducted by telephone using a standardised script. Patients who were successfully pre-screened were invited to attend the investigational site (CPS Research premises) at a given time, if they consented to take part in the study."

9.1.1. Flowchart of Study Procedures

It was noted during the audit that the consent procedure was not documented within section *9.1 – Overall Study Design and Plan – Description.* The informed consent procedure was documented in section *9.1.1 – Flowchart of Study Procedures* in tabular format. A full description of the informed consent process is documented in section *5.3 – Patient Information and Consent.*

9.5.1 Efficacy and Safety Measurements Assessed and Flowchart

The audit findings for this section indicated that there was an 'oddly worded sentence' used within the text. Although this Study Report underwent a QC Check, this error was not picked up. The QC Process has been updated and is now more rigorous, to pick up such errors in future.

The original and amended sentence for section 9.5.1 is detailed below as well as their locations within the section:***Paragraph 4, Sentence 1 – Females Only***

Original Wording: "*At the screening visit, female patients were asked if they might be pregnant, if they are lactating or seeking pregnancy, if they were taking adequate contraceptive precautions, if they had at least 2 years post-menopausal, if they had been sterilised or had had a hysterectomy.*"

Amended Wording: "*At the screening visit, female patients were asked if they might be pregnant, if they are lactating or seeking pregnancy, if they were taking adequate contraceptive precautions, if they* ***were*** *at least 2 years post-menopausal* ***or*** *if they had been sterilised or had* ***undergone*** *a hysterectomy.*"

11 EFFICACY EVALUATION

11.1 Data Sets Analysed

It was noticed during the audit that there was an incorrect reference to an appendix within this section. The original text stated that:

"Appendix 16.2.3 contains a tabular listing of all patients excluded from the efficacy analysis and the reasons for exclusion"

The text should have referred to Appendix Listing 16.2.2.1 which is the table titled "Patient data listing of patients excluded from the per-protocol set".

11.2.1 Demographic and Baseline Data

It was noted during the audit that a sentence was repeated twice within the section. Although this Study Report underwent a QC Check, this error was not picked up. The QC Process has been updated and is now more rigorous, to pick up such errors in future.

The details of the repeated sentence are listed below for reference:

Paragraph 1, Sentence 3

"the treatment groups were well balanced for the demographic variables"

Paragraph 2, Sentence 5

"the treatments were balanced with respect to all variables."

11.2.3 Medical History

It was noted during the audit that there were no comments regarding the imbalance between the treatment groups. A Senior Medical Advisor has since commented on the imbalance of the groups with the following comments:

"The primary endpoint would not be affected by the imbalance since GI and musculoskeletal conditions would not have an impact on the sore throat pain scale"

The comments were provided after review of the relevant study sections and Table 14.1.4 entitled "Relevant On-Going Medical History".

11.2.4 Pre-dose Efficacy Data

It was noted during the audit that there were no comments regarding the imbalance between the treatment groups. A Senior Medical Advisor has since commented on the imbalance of the groups with the following comments:

"The imbalance in the nature of the sore throat (scratchy vs. swollen and inflamed) would not impact the primary endpoint due to the nature of the primary endpoint where only pain is measured, and the duration of the measurement (3 hours).

The comments were provided after review of the relevant study sections.

11.4.1.2 Secondary Endpoints

Table 11.4.30 Consumer questionnaire: Whether throat felt as moist as normal at 3 hours post-dose – Full analysis set

The text preceding table 11.4.30 was found to contain an incomplete sentence which is detailed below:

"Table 11.4.30 presents details of the patient assessment of whether their throat felt as normal at 3 hours post-dose"

This sentence should have read:

"Table 11.4.30 presents details of the patient assessment of whether their throat felt as moist as normal at 3 hours post-dose"

Although this Study Report underwent a QC Check, this error was not picked up. The QC Process has been updated and is now more rigorous, to pick up such errors in future.

11.4.2 Analytical Issues

It was noted during the audit that there were a number of typographical errors within the text. The typographical errors are detailed below:

Paragraph 1, Sentence 1

"Detailed documentation of statistical methods, as the final Statistical Analysis Plan, is presented in Appendix 16.1.9"

This sentence should have read:

"Detailed documentation of statistical methods, as ***per*** *the final Statistical Analysis Plan, is presented in Appendix 16.1.9"*

Paragraph 2, Sentence 1

"There was ***a*** *slight evidence of non-normality for the analyses involving the primary endpoint, the AUC for the change from baseline in throat soreness at 2 hours and also for TOTPAR at 2 hours with the Shapiro-Wilk tests being statistically significant for both treatment groups."*

This sentence should have read:

"There was slight evidence of non-normality for the analyses involving the primary endpoint, the AUC for the change from baseline in throat soreness at 2 hours and also for TOTPAR at 2 hours with the Shapiro-Wilk tests being statistically significant for both treatment groups."

Although this Study Report underwent a QC Check, these errors were not picked up. The QC Process has been updated and is now more rigorous, to pick up such errors in future.