Reckitt Benckiser

1 STUDY REPORT TITLE PAGE

EudraCT Number:	2008-006413-25
Study Number:	GA0821
Protocol Title:	A single-centre randomised, partially blind, single dose, crossover study investigating the onset of action of soothing and cooling after taking Gaviscon Peppermint liquid, Double Action Gaviscon liquid, Gaviscon Instants Oral Powder, compared to a control in subjects with heartburn following a refluxogenic meal, using the 2-stopwatch technique.
Study Phase:	IV
Date First Subject Enrolled:	07 January 2009
Date Last Subject Completed:	09 February 2009
Report Date:	24 June 2009
Principal Investigator:	Dr S Febbraro, MD, Principal Investigator, Simbec Research Limited, Merthyr Tydfil, CF48 4DR Tel 01443 690977
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. Documents defined by ICH GCP as “essential documents” will be archived in the RB company archive in Hull, UK

Reviewed and Agreed by:

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Reckitt Benckiser Healthcare (UK) Ltd

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Reckitt Benckiser Healthcare (UK) Ltd

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

2 SYNOPSIS

Name of Sponsor/ Company: Reckitt Benckiser Healthcare (UK) Limited	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority use only)**
Name of Finished Product: Gaviscon Peppermint Liquid Gaviscon Double Action Liquid Gaviscon Instants Oral Powder Fresh Tropical	**Volume:**	
Name of Active Ingredient(s): Sodium alginate/calcium carbonate/sodium bicarbonate	**Page:**	

Title of Trial: A single-centre randomised, partially blind, single dose, crossover study investigating the onset of action of soothing and cooling after taking Gaviscon Peppermint liquid, Double Action Gaviscon liquid, Gaviscon Instants Oral Powder, compared to a control in subjects with heartburn following a refluxogenic meal, using the 2-stopwatch technique.

Investigator(s): Dr S Febbraro, MD

Trial Centre(s): Simbec Research Limited, Merthyr Tydfil, CF48 4DR

Publication (reference): None

Studied Period: 1 month **Date first subject enrolled:** 07 Jan 2009 **Date last subject completed:** 09 Feb 2009	**Phase of Development:** IV

Objectives: The primary objective of this study was to determine the time to onset of action in terms of providing a perceived soothing effect and a perceived cooling effect in the throat/oesophagus (foodpipe), compared to the control.

The secondary objectives were to determine the subject's willingness to use the product(s) again and replace their "current therapy."

Methodology: Potential participants were screened and eligible subjects scheduled to commence the treatment visits at least 48 hours after screening. Subjects were randomised to receive each of the 4 treatments with a minimum of 2 days and a maximum of 7 days between doses. On each dosing day, subjects attended the unit in the morning, were provided with a light breakfast and fasted for four hours. They were then provided with a standardised refluxogenic meal (fat content of 60%) and remained supine after consumption. When subjects experienced heartburn of at least moderate severity on a self-rating scale, they received their allocated study medication. At dosing, two stopwatches were started and subjects were asked to stop one of these as soon as they perceived any soothing effect and were asked to stop the other as soon as they perceived any cooling effect. Thirty minutes after dosing, subjects were asked if they would be willing to use the product again, if they would be willing to replace their current therapy and if they had experienced any adverse effects. Stopwatch times were censored at 30 minutes i.e. soothing and cooling times were recorded as 30 minutes if the relevant stopwatch had not been stopped by 30 minutes after dosing. Subjects returned for a post study evaluation a minimum of 3 days and a maximum of 7 days after their last treatment visit.

Number of Subjects: **Planned:** 45

Analysed: 45

Diagnosis and Main Criteria for Inclusion: Those with self-rated at least moderate heartburn within 60 minutes following ingestion of a standardised refluxogenic meal at the screening visit.

Age: ≥ 18 years ≤ 65 years

Sex: Male and female subjects were eligible for entry.

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Status: Members of the Simbec Volunteer Panel who stated (self-rated) that they had a tendency to experience symptoms of heartburn related to reflux, following some meals.

Subjects who gave written informed consent.

Key exclusion criteria:

Those who had experienced any gastrointestinal bleeding within the last 12 months.

Those with difficulty in swallowing.

Those with a history and/or symptom profile suggestive of Zollinger-Ellison syndrome, gastric carcinoma, previous or current peptic ulcer disease, pernicious anaemia, Barrett's oesophagus or systemic sclerosis.

Those with known hypophosphataemia or phenylketonuria.

Those with severe constipation or history of colonic stenosis.

Those who had taken any antacids, H_2 antagonists, motility stimulants/prokinetics or other medicines for relief of symptoms of acid reflux disease within the previous 24 hours prior to screening.

Those who had taken proton pump inhibitors within the previous 48 hours prior to screening.

Those with any previous history of allergy or known intolerance to any of the study drugs or following formulation constituents, sodium alginate, calcium carbonate, potassium bicarbonate, or hydroxybenzoate (parabens).

Those who were receiving treatment for their upper gastrointestinal problems or gastro-oesophageal reflux disease from their GP.

Test Product: Product A: Gaviscon Peppermint liquid, containing 500mg sodium alginate, 267mg sodium bicarbonate, and 160 mg calcium carbonate per 10ml dose, 150ml suspension in bottle, PL 00063/0127. 10ml administered orally, batch no. 811282

Product B: Gaviscon Double Action Liquid, containing 500mg sodium alginate, 213mg sodium bicarbonate, and 325mg calcium carbonate per 10ml dose, 150 ml suspension in bottle, PL 00063/0156. 10ml administered orally, batch no. 80881

Product C: Gaviscon Instants Oral Powder Fresh Tropical, containing 500mg sodium alginate 267mg sodium hydrogen carbonate, and 160mg calcium carbonate per 1.428g sachet dose, PL 00063/0367. One sachet administered orally, batch no. 01080/193

Duration of Treatment: Single dose of each treatment

Reference Therapy: Product D: Control, containing 50.10mg lactose, 30.00mg mannitol, 15.00mg maize starch, 2.00mg povidone K30, 1.48mg citric acid anhydrous granular, 0.75mg magnesium stearate, and 0.67mg sodium citrate per 100mg tablet. One tablet administered sublingually, batch no. 06001/334

Name of Sponsor/ Company: Reckitt Benckiser Healthcare (UK) Limited	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority use only)**
Name of Finished Product: Gaviscon Peppermint Liquid Gaviscon Double Action Liquid Gaviscon Instants Oral Powder Fresh Tropical	**Volume:**	
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Criteria for Evaluation:

Efficacy: The primary efficacy endpoints were the times to first perceived soothing and cooling effects in the throat/oesophagus (foodpipe) using a stopwatch. The secondary efficacy endpoints were:

- Willingness to use the product again to treat heartburn (yes/no)
- Willingness to replace current therapy with this product (yes/no)

Safety: Safety was assessed in terms of the overall proportion of subjects with treatment emergent adverse events. Adverse events were recorded in the CRF by the Investigator or designee after asking subjects "Have you had any symptoms or complaints since your last visit?" at the beginning of each treatment visit before dosing and at the post study visit. At 30 minutes after dosing, they were asked if they had experienced any symptoms or complaints since they were last asked. Spontaneously reported adverse events were also recorded. Vital signs were monitored.

Statistical Methods: The times to first perceived soothing and cooling effects were summarised by treatment using the number of subjects assessed, the number of subjects with censored data, mean, standard deviation, minimum and maximum (where enumerable). Kaplan-Meier medians and their 95% confidence intervals were also computed. The Kaplan-Meier survival curves for each treatment were also presented.

The times to first perceived soothing and cooling effects were compared between treatments using a Cox regression model adjusted for repeated events (using SAS Proc Phreg). The design factors, treatment sequence and study period were included in the model using the *strata* statement. If a statistically significant overall difference between treatments was demonstrated then pairwise comparisons of each of the three active treatments *vs* control were also evaluated.

For the secondary endpoints, the 'willingness to use the product again to treat heartburn' and 'willingness to replace current therapy with this product' were summarised by treatment using frequency distributions. Additionally, comparisons between treatments overall were made using a logistic regression model adjusted for correlated observations (using SAS Proc Genmod). If a statistically significant overall difference between treatments was demonstrated then pairwise comparisons of each of the three active treatments *vs* control were also evaluated.

All hypothesis tests were performed using the 5% level of significance. No adjustments were made for multiple comparisons.

Descriptive statistics (n, mean, standard deviation, minimum, median and maximum) were calculated for vital signs parameters at pre-study and post-study, for laboratory data at pre-study (biochemistry and haematology) and for the continuous variables age, height, weight and BMI by gender and overall. Additionally, the incidence of treatment emergent adverse events was compared between treatment groups using a Chi-Square test for all adverse events by preferred term, for adverse events classified by the investigator as definitely/probably/possibly related to study medication and also for severe adverse events.

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SUMMARY & CONCLUSIONS

SUBJECT DISPOSITION: Sixty-four subjects were screened and 45 subjects were included in the study and randomised to treatment sequence. Forty-five subjects completed the first two treatment visits, one subject was withdrawn prior to treatment at Visit 3 and one subject was not dosed at Visit 4 because they failed to report at least moderate heartburn after consuming the refluxogenic meal. Thus 43 subjects received all four treatments, one subject received only Treatments A, B and C and one subject received only Treatments C and D.

DEMOGRAPHY: The 45 subjects randomised to treatment sequence comprised 17 males and 28 females with an overall mean age of 35.7 years, mean height 169.5 cm, mean weight 75.8 kg and mean BMI of 26.2 kg/m^2.

EFFICACY RESULTS: The Kaplan-Meier median times to first perceived soothing effect were 2.26 minutes (95% CI 1.55, 3.15) for Gaviscon product A, 2.12 minutes (95% CI 1.58, 3.08) for Gaviscon product B and 2.97 minutes (95% CI 2.25, 4.05) for Gaviscon product C. No subject times were censored for product B and C, while two times were censored for product A. The Kaplan-Meier median time for the control product D, which was a sublingual tablet, was indeterminate due to the high number of censored times (31 censored times). The time to obtaining a perceived soothing effect was statistically significantly shorter for all three Gaviscon products ($p<0.0001$ in each case) compared with control.

The Kaplan-Meier median times to first perceived cooling effect were 1.08 minutes (95% CI 0.58, 1.95) for Gaviscon product A, 0.83 minutes (95% CI 0.55, 1.23) for Gaviscon product B and 3.95 minutes (95% CI 2.33, 11.22) for Gaviscon product C. No subject times were censored for product B, while four times and 14 times were censored for products A and C respectively. The negative control group had 33 censored times and therefore the Kaplan-Meier median time was indeterminate. The time to obtaining a perceived cooling effect was statistically significantly shorter for all three Gaviscon products ($p<0.0001$ in each case) compared with control.

For Gaviscon products A, B and C, statistically significantly more subjects (79.5% (LS adjusted value 81.1%; lower 95% CL 68.0%), 93.2% (LS adjusted value 94.9%; lower 95% CL 86.4%), and 51.1% (LS adjusted value 50.8%; lower 95% CL 38.6%) respectively) said they would be willing to use the product again, compared to the negative control (6.8% (LS adjusted value 5.8%; lower 95% CL 2.4%), ($p<0.0001$ in each case). For products A, B, and C, statistically significantly more subjects (38.6% (LS adjusted value 37.7%; lower 95% CL 26.1%), 56.8% (LS adjusted value 56.7%; lower 95% CL 43.6%), and 26.7% (LS adjusted value 26.3%; lower 95% CL 17.0%) respectively) said they would be willing to replace their current therapy with the product, compared to the negative control (2.3%, LS adjusted value 2.1%; lower 95% CL 0.4%), ($p = 0.0034$ for product A, $p = 0.0004$ for product B, and $p = 0.0137$ for product C).

SAFETY RESULTS: Twelve subjects reported a total of 13 treatment emergent adverse events. All events resolved with no sequelae. Four were mild, eight were moderate and one (headache) was classed as severe. Eleven events were categorised by the Investigator as not related or as unlikely to be related to treatment. One event (abdominal pain) was classed as possibly related to treatment. One event (flatulence) was classed as probably related to treatment. No events were classed as definitely related to treatment. There were no serious adverse events and there were no clinically significant changes in vital signs.

CONCLUSION: The Gaviscon treatments showed a statistically significantly earlier onset of action in terms of perceived soothing and cooling effects in the throat/oesophagus (foodpipe) than the control. The reported Kaplan-Meier median times for soothing for Gaviscon Peppermint liquid and Gaviscon Double Action were approximately 3 minutes and for Gaviscon Instants Oral Powder was approximately 4 minutes. Cooling effects were perceived more

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quickly than soothing effects with Gaviscon Peppermint liquid and Gaviscon Double Action, achieving onset time within 2 minutes. Based on the subjective responses, more than half of the subjects would be willing to use the Gaviscon Peppermint liquid and Gaviscon Double Action again, which was statistically significantly more than the number of subjects who would consider reusing the control. Fewer subjects were willing to replace their current therapy with the Gaviscon treatments, but these proportions were nonetheless statistically significantly more than the proportion willing to consider the sublingual tablet as an alternative therapy. With respect to the objective methodology, this study substantiated the claims of onset of action in terms of soothing and cooling in the throat/oesophagus (foodpipe) for Gaviscon Peppermint liquid and Gaviscon Double Action.

Date of the report: 24 June 2009

3 TABLE OF CONTENTS

3.1 List of Tables and Figures Contained in the Body of the Report

3.2 List of Appendices

All subjects in this study received study medication from one batch, so this appendix is not present.

16.1.7 Randomisation scheme and codes (subject identification and treatment assigned)

16.1.8 Audit certificates

16.1.9 Documentation of statistical methods

16.1.10 Documentation of inter-laboratory standardisation methods and Quality assurance procedures if used

Multiple laboratories were not used for analyses in this study, so this appendix is not present.

16.1.11 Publications based on the study

None of the data from this study has been published at present, so this appendix is not present. However, there is an intention to publish the data from this study.

16.1.12 Important publications referenced in the report

None of the publications referenced in the report is appended.

16.2 SUBJECT DATA LISTINGS

16.2.1 Discontinued Subjects

16.2.2 Protocol Deviations

16.2.3 Subjects excluded from the analyses

16.2.4 Demographic data

16.2.5 Compliance and/or drug concentration data.

16.2.6 Individual efficacy response data.

16.2.7 Adverse event listings (each subject)

16.2.8 Listing of individual laboratory measurements by subject

16.3 CASE REPORT FORMS

16.3.1 CRFs for deaths, other serious adverse events and withdrawals for adverse events.

No subjects died, experienced other serious adverse events or withdrew because of adverse events, so no CRFs are appended.

16.3.2 Other CRFs submitted – no other CRFs are appended

16.4 INDIVIDUAL SUBJECT DATA LISTINGS (US ARCHIVAL LISTINGS)

The information required for this Appendix is not applicable for this study. It will be provided as a report addendum if required by a regulatory authority.

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Abbreviation in Full
AE	Adverse Event
ANOVA	Analysis of Variance
CFR	Code of Federal Regulations
CRF	Case Report Form
CV	Curriculum Vitae
EC	Ethics Committee
ECG	Electrocardiogram
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hg	Mercury
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMSU	Investigational Material Supplies Unit
ITT	Intention to Treat
IRB	Institutional Review Board
kg	kilogram
LREC	Local research ethics committee
LS	Least squares
m	metre
mg	milligram
ml	millilitre
OTC	Over the Counter
PAGB	The Proprietary Association of Great Britain
RB	Reckitt Benckiser Healthcare (UK) Ltd
SAE	Serious Adverse Event
SDV	Source Data Verification

5 ETHICS

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

The name and full address of the single IEC consulted is provided in Appendix 16.1.3.

The study protocol together with subject information and consent documents were reviewed and approved by South East Wales Local Research Ethics Committee (LREC) on 08 December 2008.

5.2 Ethical Conduct of the Study

This study was conducted in accordance with the Declaration of Helsinki (South Africa, 1996), as referenced in EU Directive 2001/20/EC. It complied with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

5.3 Subject Information and Consent

Copies of a representative subject information sheet and a blank consent form (Version 1, dated 04 November 2008) are provided in Appendix 16.1.3.

Before entering the study, the investigator or designated physician explained the nature of the study, its purpose, procedures, expected duration and potential risks to the subjects. Subjects who were considered by the investigator to be suitable for entry into the study were given the opportunity to read the subject information sheet and consent form, and to ask questions. If they were happy with, and understood the information, they were asked to sign the consent form. The investigator also signed the form. The subject was given a copy of the information sheet and signed consent form. No protocol-related procedures were performed prior to the subject signing the consent form.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Appendix 16.1.4 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 principal investigator is also included in the Appendix.

The study was carried out at Simbec Research Limited under the guidance of the Principal Investigator, Dr S Febbraro. Some study-related activities were delegated to suitably qualified Simbec personnel. Analyses of clinical laboratory samples were performed by the Bioanalytical Unit and statistical analysis was performed by the Statistical Analysis Group at Simbec Research Ltd.

The study drug supplies were packed and shipped to Simbec Research Ltd by the Investigational Material Supplies Unit (IMSU), Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS. Study project management tasks and writing of the study clinical report were conducted by Dr K Sarratt, Clinical Project Manager, RB. Monitoring was contracted to Mrs. Ann Ring. RB was responsible for the expedited reporting of any serious adverse events occurring during the study, to the relevant Regulatory Authorities.

7 INTRODUCTION

Gaviscon® is an alginate-based reflux suppressant that offers relief to those that suffer from heartburn symptoms. It comes in a number of over the counter (OTC) and prescribable presentations/formulations to offer consumer choice of flavours and dosing formats. In an effort to support the market research derived consumer claims, Reckitt Benckiser performed a sensorial based clinical trial to generate data to substantiate the claims of “soothes within X minutes” and “cools within X minutes” for Gaviscon Peppermint liquid, Gaviscon Double Action liquid, and Gaviscon Instants Oral Powder, using the 2-stopwatch technique.

The 2-stopwatch technique was shown to be a valid method in the heartburn indication based on the pilot study in which subjects were asked to stop one of the stopwatches when they first perceived a soothing effect and the other stopwatch when they first perceived a cooling effect from the administered treatment.[1] Similarly, in this definitive randomised, crossover, single dose study, the 2-stopwatch technique was used to assess the onset of action in terms of soothing and cooling compared to a control. The choice of a sublingual tablet as a negative control was appropriate for comparison because it did not give any sensorial benefit as shown in the pilot study; and it was envisaged that an oral placebo or any type of oral product of any description that can readily enter the oesophagus through the mouth may impart some kind of soothing or cooling effect.[1] In addition, the study was partially blinded, which was achieved by blocking out the label on the study medication and having a member of Simbec staff who was not associated with the study administer the study medication. The sublingual tablet was open-label.

The population studied was a sample of the community-based population who had the tendency to suffer from heartburn symptoms following some meals and had access to OTC medications like Gaviscon®. In this sensorial based study, the subjects were provided with a refluxogenic meal to induce the symptoms of heartburn. Gaviscon Peppermint liquid and Gaviscon Double Action liquid were spoon administered by a member of Simbec staff not associated with the study, at a 10ml dose and by an oral route as specified in the product licence. The Gaviscon Instants Oral Powder sachet was cut open by a member of Simbec staff not associated with the study and given to the subject directly from the sachet. The powder from the sachets was swallowed by an oral route as specified in the product licence. The control treatment was also administered by a member of Simbec staff

not associated with the study who provided each subject with one tablet to be placed under the tongue.

8 STUDY OBJECTIVES

The primary objective of this study was to determine the time to onset of action in terms of providing a perceived soothing effect and a perceived cooling effect in the throat/oesophagus (foodpipe), compared to the control.

The secondary objectives of this study were to determine the subject's willingness to use the product(s) again and replace their "current therapy."

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan – Description

The study protocol is included as Appendix 16.1.1. The case report form (CRF) is included as Appendix 16.1.2.

This was a single-centre, randomised, partially blind, single dose, crossover sensorial based study in subjects who displayed symptoms of heartburn following a refluxogenic meal.

The subject population studied were community-based subjects who experienced postprandial heartburn, but who were otherwise reasonably healthy. Forty-five subjects were to be included in the study. Each subject attended two screening visits, the second of which took place at least 48 hours after the first screening visit and was used to identify those subjects who experienced at least moderate heartburn within 60 minutes of consumption of a standardised refluxogenic meal containing 60% fat. Those who experienced moderate heartburn were invited to attend four treatment visits (with a washout of 2-7 days between treatments) and one post study visit (3-7 days after the final treatment visit). Each treatment visit required attendance at Simbec at approximately 8.00am. Subjects were screened for presence of ethanol and drugs of abuse and female subjects were pregnancy tested. Subjects then received a light breakfast and fasted for at least four hours. They were then provided with a standardised refluxogenic meal containing 60% fat and asked to remain supine after consumption of the meal. If they experienced heartburn of at least moderate severity on the self-rating scale within 60 minutes of finishing the study meal, they were dosed in a sitting position with their allocated study medication for that visit. Subjects who did not experience heartburn of at least moderate severity within 60 minutes of completing their meal were not dosed at that treatment visit.

Allocation of treatments to visits was based on a Latin Square design using four allocation schemes i.e. four different schedules for allocating treatments to visits. The assignment of the allocation schemes to the subject was randomised by the RB Statistician according to a computer-generated randomisation schedule. The randomisation schedule was checked by a statistician not involved in the analysis of

the study. On entry to the study, subjects were allocated a unique subject number in numerical sequence. Study treatments were allocated at each study visit according to the allocation sequence assigned to the subject number.

Treatments studied were:

Product A: Gaviscon Peppermint liquid, contains 500mg sodium alginate, 267mg sodium bicarbonate, 160mg calcium carbonate per 10ml dose, 300ml suspension in bottle, PL 00063/0127, Batch No: 811282, expiry date 10 September 2009

Product B: Gaviscon Double Action Liquid, contains 500mg sodium alginate, 213mg sodium bicarbonate, and 325mg calcium carbonate per 10ml dose, 300ml suspension in bottle, PL 00063/0156, Batch No: 808881, expiry date 10 September 2009

Product C: Gaviscon Instants Oral Powder Fresh Tropical, contains 500mg sodium alginate, 267mg sodium hydrogen carbonate, and 160mg calcium carbonate per 1.428g sachet dose, oral powder in sachet, PL 00063/0367, Batch No: 01080/193, expiry date 10 September 2009

Product D: Control, contains 50.10mg lactose, 30.00mg mannitol, 15.00 mg maize starch, 2.00mg povidone K30, 1.48mg citric acid anhydrous granular, 0.75mg magnesium stearate, and 0.67mg sodium citrate per 100mg tablet, Batch No: 06001/334, expiry date 10 September 2009

Subjects were provided with two stopwatches, which were started by the study staff at the time the subject was dosed. One of these was used to record the time to first perceived soothing effect in the throat/oesophagus (foodpipe), and the other to record the time to first perceived cooling effect in the throat/oesophagus (foodpipe). Subjects were instructed (before treatment was administered) to stop the soothing effect stopwatch when they first perceived any soothing effect and to stop the cooling effect stopwatch when they first perceived a cooling effect. The treatment study period was 30 minutes. At the end of the treatment study period, subjects were asked if they would be willing to use the product again, if they would be willing to replace their current therapy with the product, and if they experienced any adverse effects. A washout period of at least 2 and no more than 7 days was required between each of the treatment visits.

The post study visit took place between 3 and 7 days after the last treatment visit.

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

This was a study to determine the onset of action in terms of first perceived soothing and cooling effects of three Gaviscon formulations compared to a control in the treatment of moderate, self-rated heartburn. The same negative control as was used

in the pilot study, a sublingual tablet, was chosen since it was unlikely to provide soothing and cooling effects in subjects with heartburn. The sublingual tablet was open-label. Two of the Gaviscon formulations were in liquid form and the other was in powder form, hence complete blinding of the study was not feasible. However, partial blinding through block-out labels was implemented for the Gaviscon formulations. It was considered that partial blinding would not cause any bias to the study.

The use of a crossover design enabled each subject to act as their own control and so minimised variability in that respect. Other measures taken to control bias and variability included the use of standardised meals, standardised fluid intake, standardised study procedures, adequate washout periods between treatments, control of posture, limitations on allowed concomitant medications and exclusion of those with other diseases or a serious condition associated with their heartburn. The overall study duration was short and there were at least 2 but no more than 7 days between treatments, so the likelihood of a carryover effect was low. The dose of each active treatment studied was the dose currently licensed OTC in the United Kingdom and elsewhere. Therefore any differences seen would reflect attributes of the products currently used at appropriate doses, not attributes associated with unlicensed doses.

9.3 Selection of Study Population

Subjects were recruited from the Simbec database of volunteers who responded to direct advertising for the study. The advertising made it clear that a response to the advert was voluntary as was participation in the study. The advert also specified that subjects should suffer from heartburn following meals, but should not be receiving treatment for it from their General Practitioner (GP).

9.3.1 Inclusion Criteria

Only subjects to whom all of the following conditions apply were to be included:

1) Age: ≥ 18 years ≤ 65 years
2) Sex: Male and female subjects were eligible for entry.
3) Status: Members of the Simbec Volunteer Panel who stated (self-rated) that they had a tendency to experience symptoms of heartburn related to reflux, following some meals.
4) Primary diagnosis: Those with self-rated at least moderate heartburn within 60 minutes following ingestion of a standardised refluxogenic meal at the screening visit.
5) Subjects who gave written informed consent.

9.3.2 Exclusion Criteria

Subjects to whom any of the following conditions applied were excluded:

1) Those who suffered a recent, significant unexplained weight loss of 6-7kg in the last 6 months.
2) Those who experienced any gastrointestinal bleeding within the last 12 months.
3) Those with difficulty in swallowing.
4) Those with a history and/or symptom profile suggestive of Zollinger-Ellison syndrome, gastric carcinoma, previous or current peptic ulcer disease, pernicious anaemia, Barrett's oesophagus or systemic sclerosis.
5) Those with known hypophosphataemia or phenylketonuria.
6) Those with severe constipation or history of colonic stenosis.
7) Those who had taken any antacids, H_2 antagonists, motility stimulants/prokinetics or other medicines for relief of symptoms of acid reflux disease within the previous 24 hours prior to Screening Visit 2.
8) Those who had taken proton pump inhibitors within the previous 48 hours prior to Screening Visit 2.
9) Those with a history of drug, solvent or alcohol abuse.
10) Those with any previous history of allergy or known intolerance to any of the study drugs or following formulation constituents, sodium alginate, calcium carbonate, sodium carbonate, potassium bicarbonate, or hydroxybenzoate (parabens).
11) Those who had a history of cardiovascular disorders or show evidence of clinically significant cardiovascular disease.
12) Those with any previous history or allergy or known intolerance to lactose, soya, or wheat.
13) Those who were receiving treatment for their upper gastrointestinal problems or gastro-oesophageal reflux disease from their General Practitioner (GP).
14) Those unable in the opinion of the Investigator to comply fully with the study requirements.
15) Those who were currently participating in a clinical study or who had participated in any other clinical study within the last 30 days.
16) Those who had previously participated in this randomised study.
17) Woman of childbearing potential, who were pregnant or lactating, seeking pregnancy or failing to take adequate contraceptive precautions, (i.e. an oral or injectable contraceptive, an approved hormonal implant or topical patch, an intrauterine device, abstinence [were the subject to become sexually active, she was to agree to use a double barrier method] or condoms/diaphragm and spermicide). A woman of childbearing potential was defined as any female who was less than 2 years post-menopausal or had not undergone an hysterectomy or surgical sterilisation, e.g. bilateral tubal ligation, bilateral ovariectomy (oophorectomy).
18) Those who were on steroids or non-steroidal anti-inflammatory drugs.
19) Those who were diabetic.

9.3.3 Removal of Subjects from Therapy or Assessment

The Investigator could withdraw a subject from the study at any time. Reasons for removing a subject from the study included but were not limited to:

- adverse events that in the judgement of the Investigator may have caused severe or permanent harm (significant clinical deterioration was an adverse event)
- violation of the study protocol
- in the Investigator's judgement, it was in the subject's best interest
- subject declined further study participation

The primary reason for withdrawal was documented as one of the following: adverse events; lack of efficacy; lost to follow-up; withdrawal of consent; protocol violation; death or other. The Investigator was to make reasonable attempts to contact subjects who were lost to follow-up - a minimum of two documented telephone calls or a letter was considered reasonable.

If a subject was withdrawn prematurely from the study, the following assessments were to be carried out:

- Vital Signs
    - blood pressure (after sitting for 5 minutes; mmHg)
    - heart rate (radial pulse counted for 30 seconds after resting for 5 minutes; beats/minute)
    - oral temperature (ºC).
- Physical examination
- Review of concomitant medication
- Review of adverse events

9.4 Treatments

9.4.1 Treatments Administered

The following medication was supplied:

Product A: Gaviscon Peppermint liquid, contains 500mg sodium alginate, 267mg sodium bicarbonate, 160mg calcium carbonate per 10ml dose, 300ml suspension in bottle, PL 00063/0127, Batch No: 811282, expiry date 10 September 2009

Product B: Gaviscon Double Action Liquid, contains 500mg sodium alginate, 213mg sodium bicarbonate, and 325mg calcium carbonate per 10ml dose, 300ml

suspension in bottle, PL 00063/0156, Batch No: 808881, expiry date 10 September 2009

Product C: Gaviscon Instants Oral Powder Fresh Tropical, contains 500mg sodium alginate, 267mg sodium hydrogen carbonate, and 160mg calcium carbonate per 1.428g sachet dose, oral powder in sachet, PL 00063/0367, Batch No: 01080/193, expiry date 10 September 2009

Product D: Control, contains 50.10mg lactose, 30.00mg mannitol, 15.00 mg maize starch, 2.00mg povidone K30, 1.48mg citric acid anhydrous granular, 0.75mg magnesium stearate, and 0.67mg sodium citrate per 100mg tablet, Batch No: 06001/334, expiry date 10 September 2009

A volume of 10ml of products A and B was administered orally on a single occasion for each product. One sachet of product C was administered orally on a single occasion. One tablet of product D was administered sublingually on a single occasion.

In addition to the above, Maalox suspension, commercial formulation, containing dried aluminium hydroxide gel 220mg and magnesium hydroxide 195mg in 5ml, PL0050/5002, batch number 084, expiry date September 2010, was supplied by Simbec and a single dose of 10ml administered orally to those subjects who required symptomatic relief after experiencing heartburn during the second screening visit and throughout the treatment visits.

9.4.2 Identity of Investigational Product(s)

All drug supplies apart from the Maalox suspension were packed and labelled to GMP standards by the Investigational Material Supplies Unit (IMSU), Reckitt Benckiser Healthcare UK Ltd, Dansom Lane, Hull HU8 7DS, UK. The Gaviscon products were supplied as blinded and the control as open label. They were shipped directly from the IMSU to Simbec Research Ltd.

9.4.3 Method of Assigning Subjects to Treatment Groups

A detailed description of the randomisation method, including how it was executed, is presented in Appendix 16.1.7.

Each subject received each of the four study treatments over the course of the four study visits. Allocation of treatments to visits was based on a Latin Square design using four allocation schemes i.e. four different schedules for allocating treatments to visits. The assignment of allocation schemes to subjects was randomised by the RB Statistician according to a computer-generated randomisation schedule. The randomisation schedule was checked by a statistician not involved in the analysis of the study. On entry to the study, subjects were allocated a unique subject number in numerical sequence. Study treatments were allocated at each study visit according to the allocation sequence assigned to the subject number.

9.4.4 Selection of Doses in the Study

This was a single dose study, each treatment being given once at a treatment visit. All products were administered orally. The doses used were those currently approved in the UK for non-prescription Gaviscon.

9.4.5 Selection of Timing of Dose for Each Subject

Each subject was dosed according to the randomisation list. Drug was administered by Simbec staff not directly involved with the study when the subject indicated that they were experiencing at least moderate heartburn after their refluxogenic meal. The refluxogenic meal was provided at approximately 13.00. Dosing occurred within 60 minutes after the meal. If a subject did not experience at least moderate heartburn within that time they were not dosed with the study medication.

9.4.6 Blinding

In order to maintain the partial blinding of the study, the Gaviscon treatments (test products A, B and C) had a blocked-out label. The randomised treatment allocation schedule was an open list and was prepared using the treatment codes A, B, C and D. At each visit the member of Simbec staff not directly involved with the study either dispensed the liquid treatment, gave a sachet of powder, or gave a sublingual tablet as allocated for the subject/visit by reference to the randomisation list.

9.4.7 Prior and Concomitant Therapy

Concomitant therapies were defined as prescribed medications, physical therapy, and over-the-counter preparations, including herbal preparations licensed for medicinal use, other than study medication and supplementary medication that the subject received during the course of the study.

The Investigator recorded any medications given in treatment of adverse events on the concomitant medication page in the subject's case report form. Any medication taken by the subject during the course of the study was also recorded on this form. Any changes in concomitant therapy during the study were documented, including cessation of therapy, initiation of therapy and dose changes.

The use of the following treatments was not permitted:

- Antacids, H_2 antagonists, motility stimulants or other medicines for relief of symptoms of acid reflux disease 24 hours prior to enrolment in the study or during the study

- Proton pump inhibitors 48 hours prior to enrolment into the study or during the study

Subjects who used these therapies during the study were to be withdrawn from the study.

No drinking or eating was allowed other than what was provided by Simbec during the treatment visits. No alcohol was allowed from 48 hours prior to the treatment visits. Smoking was not allowed during the treatment visits.

9.4.8 Treatment Compliance

Simbec personnel (appropriately trained staff not involved with the study) administered 10ml of each Gaviscon liquid treatment to the subject using a spoon. The Gaviscon powder was administered directly from the sachet. The sublingual tablet (control - product D) was administered sublingually. Any subject who did not comply with the required form of administration was withdrawn from the study. Subjects were observed on each dosing occasion.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flowchart

The efficacy and safety assessments are summarised in Table 9.5.1.

Table 9.5.1 Flowchart of Study Procedures

Study Period	Pre-study Screening		Treatment Visit				Post Study Visit (3-7 days after visit 4)
	Visit 1	Visit 2	Treatment 1 Day 1	Treatment 2 Day 2	Treatment 3 Day 3	Treatment 4 Day 4	
Informed Consent	X						
Medical History	X						X
Concomitant Medication	X						X
Vital Signs (inc 12 lead ECG)	X						X
Physical Examination	X						X
Haematology	X						
Biochemistry	X						
Serum pregnancy test (females only)	X						
Urinalysis	X						
Drugs of abuse test	X		X	X	X	X	
Eligibility decision	X						
Refluxogenic Meal		X	X	X	X	X	
Severity rating of heartburn (pre-treatment)		X	X	X	X	X	
Rescue Medication		X					
Dosing			X	X	X	X	
Onset of first perceived soothing and cooling effects (by stopwatch)			X	X	X	X	
Willingness to use product again			X	X	X	X	
Willingness to replace current therapy			X	X	X	X	
Adverse Events			X	X	X	X	X
Washout Period (2-7 days)*			X	X	X		

*Washout Periods occurred after the treatment visit.

All assessments were conducted by the Investigator or a delegated individual qualified by education and experience to perform the delegated task(s), or where patients completed the assessments they were supervised by the Investigator or delegated individual.

Medical History & Current Medical Status: A medical history was taken at Pre-study Screening Visit 1 and the subject's current status as having self rated moderate heartburn confirmed at Pre-study Screening Visit 2. Smoking, alcohol and Drugs of Abuse History and Use were collected at screening as specified in the protocol.

Demographics: Gender, race (categorised as Caucasian, Asian, Afro-Caribbean, Other), date of birth, height (cm), weight (kg) and body mass index (kg/m^2) were collected at Pre-study Screening Visit 1.

Concomitant Medication (and history at pre-study): At the first screening visit the medication and therapy history of the subjects was recorded along with current medication usage and concomitant therapy in the previous 2 days. At study treatment visits, any unscheduled visits and at the post-study visit, subjects were asked about any concomitant medication used since the previous visit.

Vital signs (inc 12-lead ECG): Blood pressure (five minutes sitting, mm Hg), 12 lead ECG, heart rate (beats/minute) and oral temperature (°C) were assessed at Pre-study Screening Visit 1 and at the Post-study Visit.

Physical Examination: A standard physical examination was conducted at Pre-study Screening Visit 1 and the Post-study Visit. Clinically significant findings were documented in the CRF.

Haematology: The following were assessed from blood samples obtained at Pre-study Screening Visit 1: Haemoglobin (g/dL), Red cells (10^{12}/L), Haemotocrit (ratio L/L), Mean cell volume (fl), Mean cell haemoglobin (pg), Mean cell haemoglobin concentration (g/L), White cells (10^9/L), Platelets (10^9/L), Differential white cell count (10^9/L), neutrophils, lymphocytes, monocytes, basophils and eosinophils.

Biochemistry: The following were assessed from blood samples obtained at Pre-study Screening Visit 1: sodium (mmol/L), potassium (mmol/L), urea (mmol/L), creatinine (µmol/L), uric acid (mmol/L), glucose (mmol/L), calcium (mmol/L), inorganic phosphorus (mmol/L) total bilirubin (µmol/L), alkaline phosphatase (ALP, IU/L), alanine transaminase (ALT, IU/L),, gamma glutamyl transferase (GGT, IU/L), α-hydroxybutyrate dehydrogenase (HBD, IU/L), creatine kinase (IU/L), total protein (g/L), albumin (g/L), cholesterol (mmol/L), triglycerides (mmol/L).

Urinalysis: The following tests were conducted using urine samples obtained at Pre-study Screening Visit 1: dip-stick test for pH, protein, glucose, ketones, bilirubin, blood, free haemoglobin, urobilinogen. If abnormal results were found, microscopy and culture were conducted.

Drugs of Abuse and Urine Alcohol: A urine sample was screened for drugs of abuse (opiates, amphetamine, cannabinoids, cocaine, barbiturates, benzodiazepines and methadone) and alcohol at baseline, and prior to dosing at each treatment visit.

Viral Serology: Testing for hepatitis B surface antigen, hepatitis C antibody, and HIV screening was conducted on a blood sample obtained at screening. Results were reported as positive or negative.

Pregnancy testing: Women of child-bearing potential had a serum pregnancy test using the standard pregnancy testing method of the unit. This was performed at screening. In addition, at each treatment visit, prior to dosing, women were tested for pregnancy using urine.

Efficacy assessments: A standardised refluxogenic meal containing 60% fat was provided after a four hour fast. Subjects self-rated any heartburn experienced after consumption of this meal on a scale of none, mild, moderate or severe. When they considered themselves to have moderate heartburn, they were dosed with their allocated study treatment. On dosing, two stopwatches were started which subjects had received previous instructions to stop when they first perceived any soothing and any cooling. Subjects were asked 30 minutes after dosing whether they would use the product again and whether they would replace their current therapy with the product.

Adverse Events: All adverse events reported spontaneously by the subject or in response to questioning or observation by the Investigator were recorded in the subject's case report form. The Investigator or a designated deputy asked the subject: "Are you experiencing any symptoms or complaints?" at the baseline visit and "Have you had any symptoms or complaints since you were last asked?" at each treatment visit at the 30 minute assessment time. They were also asked this question when they attended the post study follow-up visit.

All adverse events (including clinically significant laboratory abnormalities) were followed up wherever possible to resolution or until the Investigator believed there would be no further change, whichever was the earlier.

Each adverse event was recorded according to the criteria given below "Relationship to study medication" was determined by the Investigator or by a medically qualified Co-investigator.

The rating systems used to determine the severity and relationship to study medication are given in Table 9.5.2.

Table 9.5.2 Rating Systems used to Determine Adverse Event Severity and Relationship to Study Medication

Variable	Category	Definition
Severity		Severity was determined by the Investigator. For symptomatic AEs the following definitions were applied but medical experience and judgement was also used in the assessment of severity.
	Mild	The AE did not limit usual activities; the subject might have experienced slight discomfort.
	Moderate	The AE resulted in some limitation of usual activities; the subject might have experienced significant discomfort.
	Severe	The AE resulted in an inability to carry out usual activities; the subject might have experienced intolerable discomfort or pain.
Relationship to study medication	Definite	An AE that followed an anticipated response to the study medication; and that was confirmed by both improvement upon stopping the study medication (dechallenge), and reappearance of the reaction on repeated exposure (rechallenge)
	Probable	An AE that followed a reasonable temporal sequence from administration of the study medication, that was an anticipated response to the study medication; and that could not have been reasonably explained by the known characteristics of the subject's clinical state or concomitant therapy
	Possible	An AE that followed a reasonable temporal sequence from administration of the study medicines; that might have been an anticipated response to the study medication; but that could have been produced by the subject's clinical state or concomitant therapy.
	Unlikely	An AE that did not follow an anticipated response to the study medication; which may have been attributable to other than the study medication, and that was more likely to have been produced by the subject's clinical state or concomitant therapy.
	None	An AE that was known beyond all reasonable doubt to be caused by the subject's state or concomitant therapy.

9.5.2 Appropriateness of Measurements

Key assessments of efficacy and safety parameters were made using standard, widely used, published and reliable methodologies. In this study, supportive efficacy questions of subject perception were also asked.

9.5.3 Primary Efficacy Variable(s)

The primary efficacy endpoints were the times to first perceived soothing and cooling effects in the throat/oesophagus (foodpipe), assessed using a stopwatch. For a subject/visit at which a soothing or cooling effect was not reported within 30 minutes, the result was reported as censored at 30 minutes.

9.5.4 Drug Concentration Measurements

Drug concentrations were not measured in this study.

9.6 Data Quality Assurance

This was a single-centre study and the same laboratory was used for all analyses. Laboratory results were subject to Quality Assurance procedures at Simbec Research Ltd.

The CRF was in a format familiar to Simbec Research staff, and a Study Initiation meeting was held to discuss the study-specific aspects of the trial. At this meeting study staff was briefed in detail on the RB adverse event and concomitant medication recording procedures. A Pre-Study Briefing Meeting was held by the Simbec Research project manager, to train all nursing staff and personnel involved in the study on study-specific procedures.

100% of the CRFs were monitored to check for completion errors, and 100% Source Data Verification was carried out on the following items:

- Subject identity (date of birth, gender, initials, BMI, subject A number)
- Subject screening number
- Subject number
- Consent signatures
- Date of consent
- Visit dates
- Dose administration
- GP Update/Printout Letter
- Smoking and alcohol status
- Medical status of subject (clinically significant medical history and other disorders)
- ECGs
- Laboratory results
- Medical history
- Subject eligibility (inclusion/exclusion criteria)
- Vital signs
- Physical examination
- AEs
- Concomitant medication

The following aspects of this study were subject to a GCP compliance audit, conducted by the GCP auditor at Simbec:

Study database
Study report
Master CRF

Audit certificates are included in Appendix 16.1.8.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

A copy of the final statistical analysis plan is presented as Appendix 16.1.9.

Data sets to be analysed:

Safety Population (Safety): All subjects who were recruited to the study and received at least one dose of study medication. This population was used for summaries of demography and safety.

Intention to Treat Population (ITT): All subjects who were recruited to the study, received at least one dose of study medication and had efficacy data for at least one treatment visit other than that for the control. This population was used for summaries of efficacy data.

Planned Statistical Analyses:

As per the protocol, the times to first perceived soothing and cooling effects were to be summarised by treatment using the number of subjects assessed, number of subjects with censored data, mean, standard deviation, minimum and maximum values (where enumerable). Kaplan-Meier medians and their 95% confidence intervals were to be computed for each parameter.

The times to first perceived soothing and cooling effects were to be compared between treatments using Kaplan-Meier survival curves and the proportional hazards model. If a statistically significant overall between treatment difference was demonstrated, then pairwise comparisons of each of the three active treatments vs control were also to be evaluated.

The secondary efficacy endpoints were to be summarised by treatment using frequency distributions. These parameters were to be compared between treatments overall using a chi-square test for independence. If a statistically significant overall between treatment difference was demonstrated, then pairwise comparisons of each of the three active treatments vs control would also be evaluated.

All hypothesis tests were to be performed using the 5% level of significance. No adjustments were to be made for multiple comparisons.

All treatment emergent adverse events were listed and tabulated by treatment, severity, relationship to therapy and primary system organ class according to the latest version of MedDRA available at the time of database lock. In counting the number of events reported, a continuous event, i.e. an event which was reported more than once and which did not cease, was counted only once; non-continuous adverse events reported several times by the same patient were counted as multiple events. Events present immediately prior to first dose of study medication that did not worsen in severity, were not included. Events with start dates during follow-up were not considered treatment emergent and were listed separately.

Differences between treatment groups in the proportion of subjects reporting treatment emergent adverse events were compared using the chi-square test.

9.7.2 Determination of Sample Size

In a similar previous crossover study in 20 subjects, post-study review of the data revealed that the Kaplan-Meier medians for the time to onset of soothing for Gaviscon Peppermint liquid and Gaviscon Double Action were 1.37 minutes (95% CI 0.83, 2.90) and 1.17 minutes (95% CI 0.80, 2.65), respectively. In the same study the Kaplan-Meier medians for the time to onset of cooling for Gaviscon Peppermint liquid and Gaviscon Double Action were 0.57 minutes and 0.45 minutes, respectively. While methods do not exist to assess the power of a study to provide Kaplan-Meier medians with a prospectively defined level of precision, assuming that the results of the current study would mirror those of the previous study, it was considered that a study in 40 subjects would be sufficient to substantiate the claims "soothes within 3 minutes" and "cools within 2 minutes" for Gaviscon Peppermint liquid and Gaviscon Double Action, and potentially for Gaviscon Instants Oral Powder, which had not been tested previously, using the upper 95% confidence limits for the Kaplan-Meier medians.

Post-study review of the data for the previous study also indicated that a study in 40 subjects would have in excess of 90% power to demonstrate that the onset of soothing and cooling was statistically significantly shorter for Gaviscon Peppermint liquid and Gaviscon Double Action, and potentially for Gaviscon Instants Oral Powder, compared to control, when assessed using survival analysis methodology.

9.8 Changes in the Conduct of the Study or Planned Analysis

9.8.1 Changes in the Conduct of the Study

No changes were made in the conduct of the study.

9.8.2 Changes in the Planned Statistical Analysis of the Study

The following changes to the planned statistical analysis as described in the protocol and captured in the signed statistical analysis plan were made:

In addition to the Kaplan-Meier medians, Kaplan-Meier survival curves for each treatment were also presented.

Instead of comparing the times to first perceived soothing and cooling effects between treatments using the Kaplan-Meier survival curves and the proportional hazard model, the effects were compared between treatments using a Cox regression model adjusted for each repeated events (using SAS Proc Phreg). The design factors, treatment sequence and study period were included in the model using the *strata* treatment.

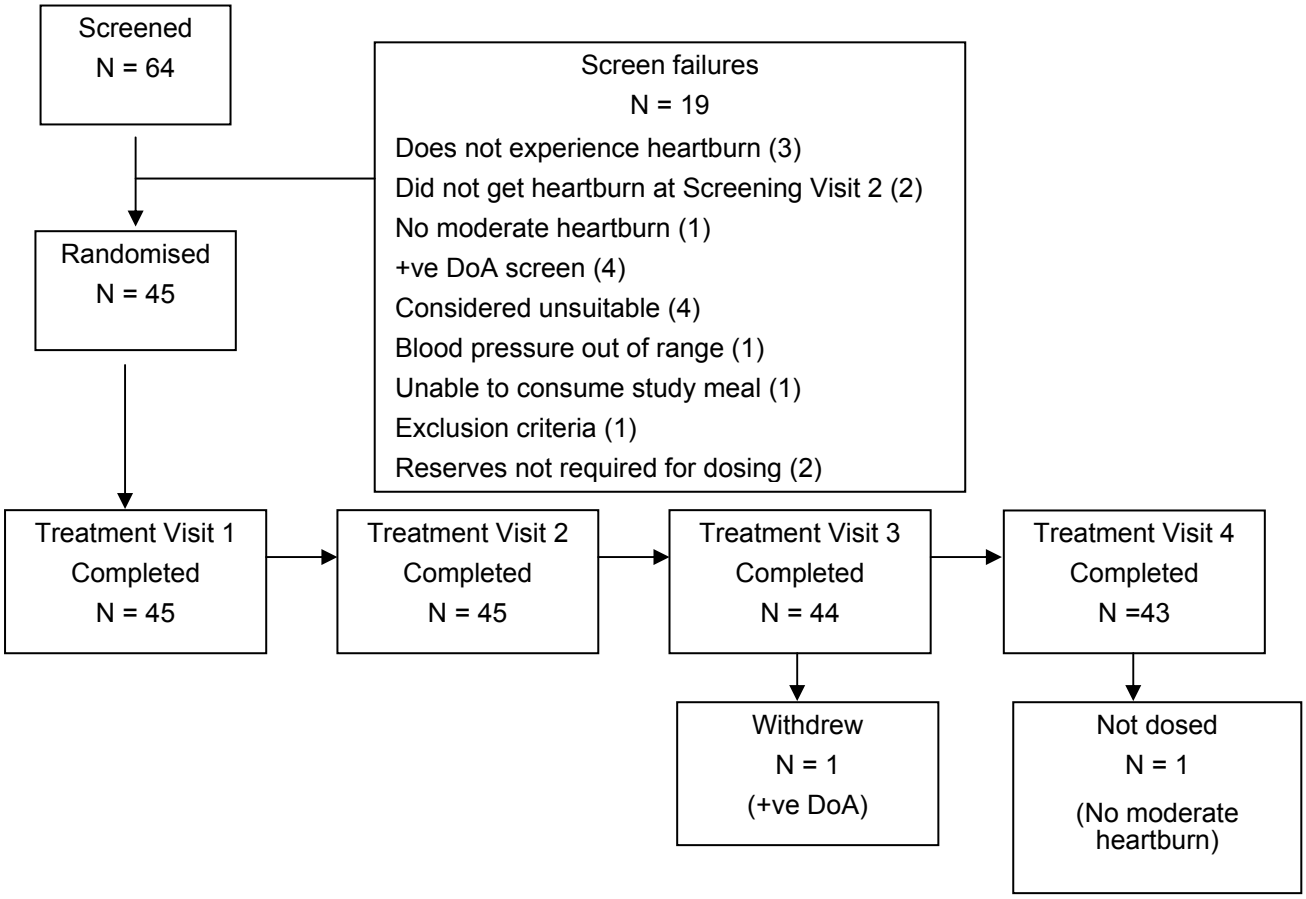
For the secondary endpoints, comparisons between treatments overall were made using a logistic regression model adjusted for correlated observations (using SAS Proc Genmod). The parameters were not compared between treatments overall using a chi-square test for independence.

10 STUDY SUBJECTS

10.1 Disposition of Subjects

A listing of all subjects discontinued from the study after enrolment is provided in Appendix 16.2.1. A flow chart illustrating the disposition of study subjects is shown in Figure 10.1.1.

Figure 10.1.1: Disposition of Subjects



10.2 Protocol Deviations

A listing of individual subjects who deviated from the protocol is presented in Appendix 16.2.2.

11 EFFICACY EVALUATION

11.1 Data Sets Analysed

Appendix 16.2.3 contains a tabular listing of all subjects included in the efficacy analysis and visit dates for all the screened subjects, which also gives screening numbers and, where appropriate, subject (randomisation) numbers. Subjects who were screened but not randomised were excluded from the efficacy analysis. For this partially blinded study, the strategy for the inclusion/exclusion of data in the data sets analysed was included in the statistical analysis plan for the study and finalised following discussions of evaluability held prior to the database being locked.

All 45 subjects who were randomised to treatment received at least one dose of study medication and were included in the Safety Population used for summaries of demography and safety.

All 45 subjects who were randomised to treatment received at least one dose of study medication and had efficacy data for at least one treatment visit other than that for the control and were included in the ITT Population used for summaries of efficacy data.

11.2 Demographic and Other Baseline Characteristics

Details of demographic and baseline characteristics, including baseline laboratory values and all concomitant medication for all individual randomised subjects are presented in by-subject tabular listings in Appendix 16.2.4.

11.2.1 Demographics

A summary of the demographics of the subjects based on the safety population is shown in Table 11.2.1:

Table 11.2.1 Summary of subject demographic data in study GA0821

Variable		Male	Female	All
AGE (YRS)	N	17	28	45
	MEAN	30.4	39.9	35.7
	SD	6.4	12.3	11.2
	MIN	22	19	19
	MEDIAN	30	38	34
	MAX	42	65	65
HEIGHT (CM)	N	17	28	45
	MEAN	179.9	163.1	169.5
	SD	6.0	7.2	10.6
	MIN	168	150	150
	MEDIAN	180	163	168
	MAX	189	184	189
WEIGHT (KG)	N	17	28	45
	MEAN	88.7	68.0	75.8
	SD	14.2	12.1	16.3
	MIN	62.8	52.2	52.2
	MEDIAN	92.0	66.2	70.9
	MAX	116.2	95.2	116.2
BMI (KG/M^2)	N	17	28	45
	MEAN	27.3	25.5	26.2
	SD	3.6	4.2	4.0
	MIN	20.6	18.7	18.7
	MEDIAN	28.1	25.1	26.1
	MAX	32.5	39.5	39.5

One subject was Afro-Caribbean and the rest were Caucasian.

11.2.2 Medical History, Physical Examination and Vital Signs

Details of Medical History, Physical Examination Findings, ECG Results and Vital Signs are provided by subject number in Appendix 16.2.4.

For subjects included in the study, there were no medical history findings or physical examination findings that were considered to breach the eligibility criteria for participation in this study. All past medical histories and abnormal physical findings at screening were considered not to be clinically significant.

Subject 20 had a minor pre and post study ECG abnormality, which the Investigator considered to be not clinically significant. Subjects 7 and 11 had abnormal ECG readings upon review at the post study but these were considered not clinically significant.

There were no clinically meaningful findings in recordings of pulse, blood pressure and oral temperature. Some of the subjects had their vital signs repeated at pre-study and post-study visits. A summary of vital signs pre and post study is provided in Section 14.3.

11.2.3 Previous Medications and Contraceptive Use

Details of current and previous medications on entry to the study are listed in Appendix 16.2.4.

Nineteen of the 28 female subjects were taking contraceptive products. Ten of these were taking oral contraceptive pills, three had intrauterine devices, two had implanted subcutaneous products, and four had intramuscular injections. Subject 4 used the Mirena Coil for hormone replacement. Subject 16 was taking Salbutamol for treatment of asthma. Subject 1 took Paracetamol as needed for the relief of menstrual pain prior to study treatment. Subject 37 was taking Liviel for menopausal symptoms. Several subjects took one dose of Maalox (10ml), the rescue medication during screening visit 2 for symptomatic relief of heartburn.

11.2.4 Concomitant Medications

Details of medications taken during the study are listed in Appendix 16.2.4.

Subjects 6, 16, and 29 took Paracetamol, Veganin, and Cocodamol, respectively, for treatment of a headache. Paracetamol was also taken by subjects 7, 23, and 42 for treatment of a backache, sore throat and toothache, respectively. Subject 9 took one dose of Temazepam, a sedative, for wisdom tooth removal. A single dose of Maalox, the rescue medication, was taken by a number of subjects on days where they were treated with the negative control.

11.3 Measurements of Treatment Compliance

All subjects were administered the study treatments by a member of Simbec staff not associated with the study and were observed during dosing. Mouth inspections were performed at each dosing visit to ensure compliance.

11.4 Efficacy Results

Details of efficacy assessments recorded during the study are listed by subject and study visit in Appendix 16.2.6.

11.4.1 Analysis of Efficacy

11.4.1.1 Primary Endpoints (time to first perceived soothing and cooling effects)

The times to first perceived soothing effect and cooling effect with each treatment are summarised below in Table 11.4.1 and 11.4.2, respectively.

Table 11.4.1 Time (minutes) to first perceptible soothing effect in study GA0821

Product	N	No. Censored	Mean	SD	Minimum	Maximum	KM Median	KM 95% CI	PH p-value
Product A	44	2	4.21	6.48	0.18	30.00	2.26	1.55 – 3.15	< 0.0001 *
Product B	44	0	3.72	5.09	0.27	27.83	2.12	1.58 – 3.08	< 0.0001 *
Product C	45	0	3.98	3.49	0.53	17.75	2.97	2.25 – 4.05	< 0.0001 *
Product D	44	31	23.96	10.15	1.38	30.00	N/a	N/a – N/a	< 0.0001 **

** Overall Comparison of All Treatments
* Pairwise Comparison vs Control

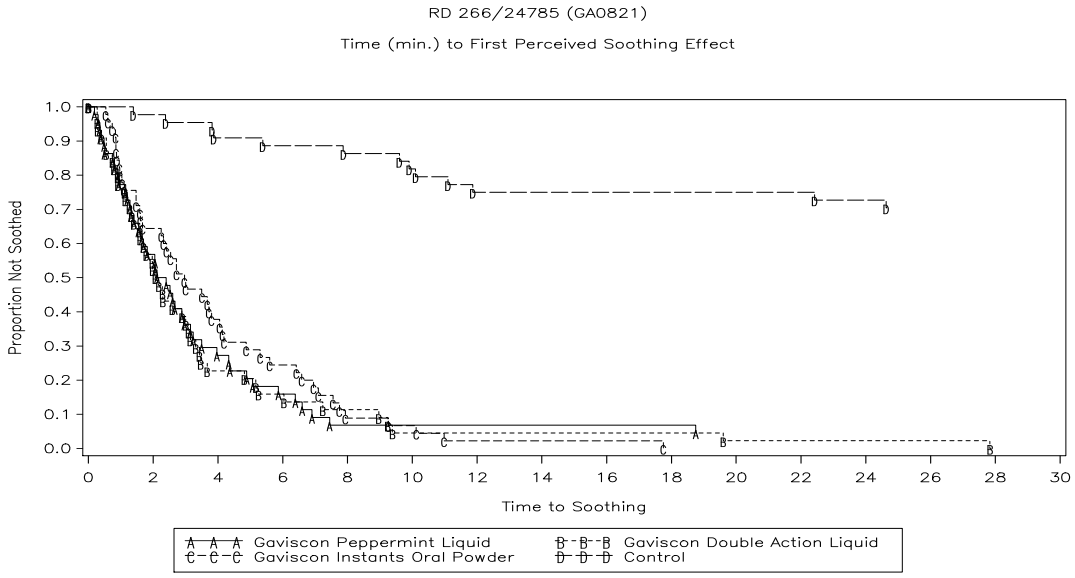


Figure 11.4.1 Kaplan-Meier curves for time (minutes) to first perceived soothing effect for Products A, B, C and D

The Kaplan-Meier median times to first perceptible soothing effect experienced by most subjects for all three Gaviscon products, A (2.26; 95% CI 1.55, 3.15), B (2.12; 95% CI 1.58, 3.08) and C (2.97; 95% CI 2.25, 4.05), were within three minutes after dosing. Two subjects for product A did not experience a soothing effect within the 30 minutes, resulting in censored times. The negative control product D had censored times for 31 of the 44 subjects i.e. a much greater proportion of subjects did not experience a soothing effect within 30 minutes compared to the three Gaviscon products. The overall difference between treatments in time to first perceived soothing was statistically significant ($p<0.0001$) and the times for each Gaviscon product were statistically significantly shorter compared to control ($p<0.0001$).

Table 11.4.2 Time (minutes) to first perceptible cooling effect in study GA0821

Product	N	No. Censored	Mean	SD	Minimum	Maximum	KM Median	KM 95% CI	PH p-value
Product A	44	4	4.88	9.23	0.15	30.00	1.08	0.58 – 1.95	< 0.0001 *
Product B	44	0	1.95	4.04	0.10	25.85	0.83	0.55 – 1.23	< 0.0001 *
Product C	45	14	11.96	12.83	0.20	30.00	3.95	2.33 – 11.22	< 0.0001 *
Product D	44	33	24.51	10.05	2.32	30.00	N/a	N/a – N/a	< 0.0001 **

** Overall Comparison of All Treatments
* Pairwise Comparison vs Control

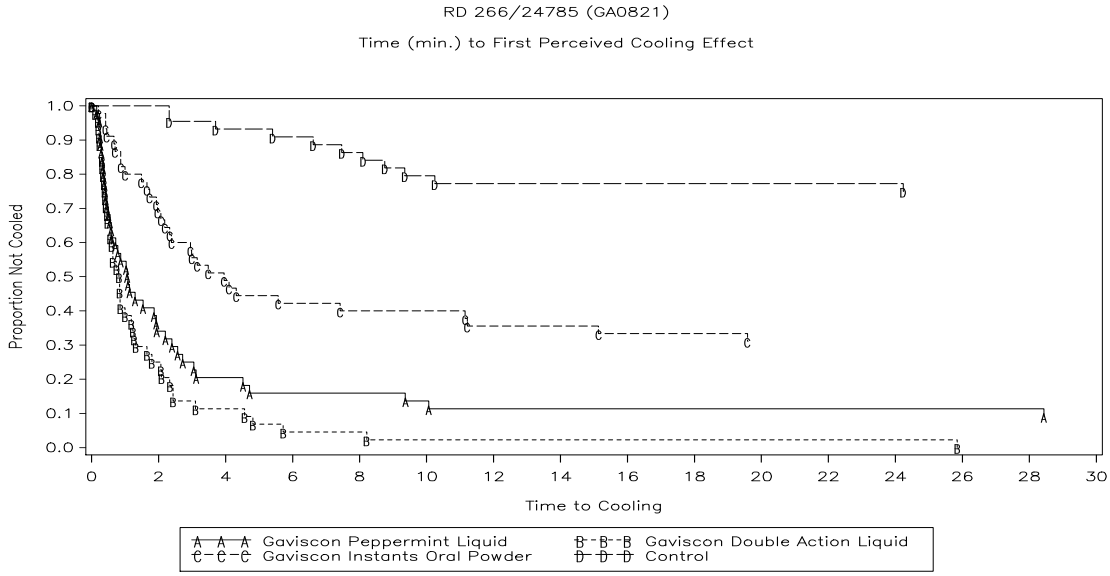


Figure 11.4.2 Kaplan-Meier curves for time (minutes) to first perceived cooling effect for Products A, B, C and D

The Kaplan-Meier medians for time after dosing to first perceived cooling effect were 1.08 minutes (95% CI 0.58, 1.95) and 0.83 minutes (95% CI 0.55, 1.23) for Gaviscon products A and B respectively. Product C had a higher Kaplan-Meier median time of 3.95 minutes (95% CI 2.33, 11.22) with fourteen subjects having censored times, compared to four subjects for product A and no subjects for product B. As seen with soothing, the negative control product D had a much greater proportion (33 of 44 subjects) of subjects who did not experience a cooling effect within 30 minutes compared to the three Gaviscon products. The overall difference between treatments in time to first perceived cooling was statistically significant ($p<0.0001$) and the times for each Gaviscon product were statistically significantly shorter compared to control ($p<0.0001$).

11.4.1.2 Secondary Endpoint (subjective assessments)

The subjective assessments of whether subjects would be willing to use the product again to treat their heartburn and replace their current therapy with the product are summarised in Table 11.4.3.

Table 11.4.3 Subjective assessments in study GA0821

	Response n (%, adjusted %, lower 1-sided 95% CL for adjusted %)	Product A	Product B	Product C	Product D
Willingness to use Product Again to Treat Heartburn (p < 0.0001 **)	Yes	35 (79.5, 81.1, 68.0)	41 (93.2, 94.9, 86.4)	23 (51.1, 50.8, 38.6)	3 (6.8, 5.8, 2.4)
	No	9 (20.5)	3 (6.8)	22 (48.9)	41 (93.2)
		p <0.0001 *	p<0.0001 *	p<0.0001 *	
Willingness to Replace Current Therapy with this Product (p< 0.0001 **)	Yes	17 (38.6, 37.7, 26.1)	25 (56.8, 56.7, 43.6)	12 (26.7, 26.3, 17.0)	1 (2.3, 2.1, 0.4)
	No	27 (61.4)	19 (43.2)	33 (73.3)	43 (97.7)
		P=0.0034 *	P=0.0004 *	p=0.0137 *	

** Overall Comparison of All Treatments

* Pairwise Comparison vs Control

For Gaviscon products A, B, and C, 79.5% (LS adjusted value 81.1%; lower 95% CL 68.0%), 93.2% (LS adjusted value 94.9%; lower 95% CL 86.4%), and 51.1% (LS adjusted value 50.8%; lower 95% CL 38.6%), respectively, said they would be willing to use the products again. While there was a larger number that would use products A and B, compared to C, more than half of the subjects gave a positive response for each Gaviscon product. There was a statistical significant overall difference ($p<0.0001$) between the treatment groups. Based on the adjusted percentages, there was a statistical significant difference ($p<0.0001$) between each Gaviscon product and the control. Only 3 (6.8%; LS adjusted value 5.8%; lower 95% CL 2.4%) subjects expressed a willingness to use control product D again.

In terms of replacing their current therapy with one of the Gaviscon products, more than half said they would be willing to do so with product B, Gaviscon Double Action 56.8% (LS adjusted value 56.7%; lower 95% CL 43.6%). For product A, 38.6% (LS adjusted value 37.7%; lower 95% CL 26.1%) said they would be willing to replace their current therapy with this product, Gaviscon Peppermint liquid. For product C, Gaviscon Instants Oral, 26.7% (LS adjusted value 26.3%; lower 95% CL 17.0%) of the subjects said they would be willing to replace their current therapy with this product. Only one subject said they would be willing to replace their current therapy with the negative control product D. Statistically significantly more subjects were willing to replace their current therapy with a Gaviscon product compared to the control (for product A, $p = 0.0034$; for product B, $p = 0.0004$; and for product C, $p = 0.0137$).

11.4.2 Analytical Issues

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

11.4.2.1 Adjustments for Covariates

No adjustments were made for covariates therefore this section is not applicable.

11.4.2.2 Handling of Dropouts or Missing Data

Subject 16 has missing data for Treatment Visits 3 and 4 as a result of testing positive for drugs of abuse prior to Treatment Visit 3. Subject 13 has missing data for Treatment Visit 4 as a result of not experiencing heartburn of moderate severity at that visit. These results were treated as missing in the analysis. It is considered that with so few missing items of data there will be no impact on the results of the study.

11.4.2.3 Interim Analyses and Data Monitoring

No interim analyses were performed and there was no data monitoring, therefore this section is not applicable.

11.4.2.4 Multi-centre Studies

This was a single centre study therefore this section is not applicable.

11.4.2.5 Multiple Comparison/Multiplicity

No adjustment for multiple comparisons was made in this study. However, given the clear differentiation between active and control treatments in this study, this has no qualitative effect on the results.

11.4.2.6 Use of an “Efficacy Subset” of Subjects

No efficacy subsets of subjects were created, therefore this section is not applicable.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

This study was not designed to test equivalence therefore this section is not applicable.

11.4.2.8 Examination of Subgroups

No sub-groups were examined in this study therefore this section is not applicable.

11.4.3 Tabulation of Individual Response Data

In addition to tables giving summarised data for efficacy variables, relevant individual subject data are presented in by-subject tabular listings in Appendix 16.2.6.

No individual response data are presented in the body of the report.

11.4.4 Drug Dose, Drug Concentration and Relationships to Response

This was not a dose response study and fixed doses of study medication were used, therefore this section is not applicable.

11.4.5 Drug-Drug and Drug-Disease Interactions

No drug/drug or drug/disease interactions were seen in this study and so this section is not applicable.

11.4.6 By-subject Displays

Group mean data represent the principal analysis in this study and so this section is not applicable.

11.4.7 Efficacy Conclusions

It was clear from the study that the Gaviscon products had a statistically significantly faster onset of action in terms of providing perceived soothing and cooling effects within 30 minutes compared to the control, a sublingual tablet with no actives. However, some subjects did perceive a soothing and cooling effect from the control. Gaviscon Double Action had a faster onset of action for soothing and cooling than the other two Gaviscon products. As seen in the pilot study the time to a cooling effect was perceived more rapidly than soothing for Gaviscon Peppermint liquid and Gaviscon Double Action, but not for Gaviscon Instants Oral Powder.

It was anticipated, based on the previous pilot study that Gaviscon Peppermint liquid and Gaviscon Double Action would give soothing and cooling times (based on the Kaplan-Meier medians) within 3 minutes and 2 minutes, respectively. Based on the results and using the upper 95% confidence limits, it can be said that on average, Gaviscon Peppermint liquid and Gaviscon Double Action soothes within 3.15 minutes and 3.08 minutes, respectively, while Gaviscon Instants Oral Powder soothes within 4.05 minutes. In terms of cooling, Gaviscon Peppermint liquid and Gaviscon Double Action provide a cooling effect within 2 minutes (using the upper 95% confidence limits); however, this was not the case with Gaviscon Instants Oral Powder which showed a cooling effect within 12 minutes.

According to the subjective assessments and looking at the lower 95% confidence limit, more than half of the subjects were willing to use Gaviscon Peppermint liquid and Gaviscon Double Action again, which was significantly more than for control sublingual tablet, with the greatest willingness being for Gaviscon Double Action. Although statistically significantly different from the control, many subjects who were willing to use the Gaviscon products again were not willing to replace their current

therapy with the products, especially in the cases of Gaviscon Peppermint liquid and Gaviscon Instants Oral Powder.

Overall, this study was successful in substantiating claims for Gaviscon Peppermint liquid and Gaviscon Double Action of being able to provide soothing and cooling effects within a few minutes for those that suffer from heartburn.

12 SAFETY EVALUATION

All subjects who received at least one dose of study medication are included in the safety analysis.

12.1 Extent of Exposure

Forty-three subjects received a single dose of all four study medications, one subject received single doses of all three active study medications (but not control) and one subject received a single dose of Treatment C and control only. Thus 44 subjects received Treatment A (Gaviscon Peppermint liquid), 44 subjects received Treatment B (Gaviscon Double Action), 45 subjects received Treatment C (Gaviscon Instants Oral Powder) and 44 subjects received Treatment D (Control).

12.2 Adverse Events (AEs)

All adverse events for each subject, including the same event on several occasions are listed in Appendix 16.2.7, giving both the original terms used by the investigator and the preferred terms according to MedDRA Version 11.0 dictionary.

The tables that follow describe adverse events occurring after the initiation of treatment with study medication. Only treatment emergent AEs are included in the summary tables. Three subjects reported four adverse events before dosing, which are included in the listing in Appendix 16.2.7 but not in the following tables.

12.2.1 Brief Summary of Events

Twelve subjects reported a total of 13 treatment emergent adverse events. All events resolved with no sequelae. Four were mild, eight were moderate and one (headache) was classed as severe. Eleven events were categorised by the Investigator as not related or as unlikely to be related to treatment. One event (abdominal pain) was classed as possibly related to treatment. One event (flatulence) was classed as probably related to treatment. No events were classed as definitely related to treatment. There were no serious adverse events and there were no clinically significant changes in vital signs.

12.2.2 Display of Adverse Events

A summary by treatment of the 13 treatment emergent adverse events that occurred in the study categorised by MedDRA body system and preferred term is provided in Table 12.2.2.1.

Table 12.2.2.1 **Summary of Adverse Events by Body System and Preferred Term in study GA0821 (safety population)**

Number of Reports / Number of Subjects (% brackets)

MedDRA Primary SOC	MedDRA Preferred Term	A (n=44)	B (n=44)	C (n=45)	D (n=44)
Gastrointestinal disorders	ABDOMINAL PAIN	0 / 0	0 / 0	1 / 1 (2.2)	0 / 0
	FLATULENCE	0 / 0	1 / 1 (2.3)	0 / 0	0 / 0
	TOOTHACHE	0 / 0	0 / 0	1 / 1 (2.2)	0 / 0
Musculoskeletal and connective tissue disorders	BACK PAIN	0 / 0	0 / 0	0 / 0)	1 / 1 (2.3)
	NECK PAIN	0 / 0	0 / 0	0 / 0	1 / 1 (2.3)
Nervous system disorders	HEADACHE	1 / 1 (2.3)	1 / 1 (2.3)	2 / 2 (4.4)	2 / 2 (4.5)
Respiratory, thoracic and mediastinal disorders	PHARYNGOLARYNGEAL PAIN	0 / 0	0 / 0	1 / 1 (2.2)	0 / 0
Surgical and medical procedures	WISDOM TEETH REMOVAL	0 / 0	1 / 1 (2.3)	0 / 0	0 / 0

One AE occurred after treatment with product A (Gaviscon Peppermint liquid), three after treatment with product B (Gaviscon Double Action Liquid), five after treatment with product C (Gaviscon Instants Oral Powder), and four after treatment with product D (Control).

Table 12.2.2.2 summarises the adverse events by severity and preferred term.

Table 12.2.2.2 Summary of Adverse Events by Severity and Preferred Term in study GA0821 (safety population)

			Number of Events		
MedDRA Primary SOC	MedDRA Preferred Term	Product	Mild	Moderate	Severe
Gastrointestinal disorders	ABDOMINAL PAIN (p=1.0000)	C	0	1	0
	FLATULENCE (p=1.0000)	B	1	0	0
	TOOTHACHE (p=1.0000)	C	0	1	0
Musculoskeletal and connective tissue disorders	BACK PAIN (p=1.0000)	D	0	1	0
	NECK PAIN (p=1.0000)	D	0	1	0
Nervous system disorders	HEADACHE (p=0.3994)	A	0	1	0
		B	0	1	0
		C	0	1	1
		D	2	0	0
Respiratory, thoracic and mediastinal disorders	PHARYNGOLARYNGEAL PAIN (p=1.0000)	C	0	1	0
Surgical and medical procedures	WISDOM TEETH REMOVAL(p=1.0000)	B	1	0	0

p-values are based on treatment comparisons of the number of severe adverse events, for each preferred term.

One subject (Subject 38) experienced one severe adverse event of headache associated with product C (Gaviscon Instants Oral Powder). This event occurred 3 hours post dosing and lasted for 40 minutes. It was considered unlikely to be related to treatment. The subject recovered completely. All other events were of mild or moderate severity. All resolved with no sequelae.

Table 12.2.2.3 summarises the adverse events by treatment and relationship to therapy.

Table 12.2.2.3 Summary of Adverse Events by Treatment and Relationship to Therapy in study GA0821 (safety population)

			Number of Events				
MedDRA Primary SOC	MedDRA Preferred Term	Product	Definite	Probable	Possible	Unlikely	None
Gastrointestinal disorders	ABDOMINAL PAIN (p=0.3994)	C	0	0	1	0	0
	FLATULENCE (p=0.3855)	B	0	1	0	0	0
	TOOTHACHE (p=1.0000)	C	0	0	0	0	1
Musculoskeletal and connective tissue disorders	BACK PAIN (p=1.0000)	D	0	0	0	0	1
	NECK PAIN (p=1.0000)	D	0	0	0	0	1
Nervous system disorders	HEADACHE (p=1.0000)	A	0	0	0	1	0
		B	0	0	0	1	0
		C	0	0	0	2	0
		D	0	0	0	1	1
Respiratory, thoracic and mediastinal disorders	PHARYNGOLARYNGEAL PAIN (p=1.0000)	C	0	0	0	1	0
Surgical and medical procedures	WISDOM TEETH REMOVAL(p=1.0000)	B	0	0	0	0	1

p-values are based on treatment comparisons of the number of subjects with definite, probable or possible adverse events, for each preferred term

Overall two events in two subjects were considered to have a causal (definite, probable or possible) relationship to study medication. Subject 1 experienced abdominal pain, possibly related to treatment with product C (Gaviscon Instants Oral Powder). Subject 2 experienced flatulence, probably related to treatment with product B (Gaviscon Double Action Liquid).

No subject was withdrawn due to any adverse event.

12.2.3 Analysis of Adverse Events

Adverse events were reported following each of the treatments and there were no statistically significant differences in incidence between treatments.

12.3 Other Serious Adverse Events (SAEs) and other Significant Adverse Events

There were no deaths, other serious or significant adverse events in this study.

12.4 Clinical Laboratory Evaluation

Haematology, biochemistry and urinalysis clinical laboratory evaluations were performed only at pre-study screening. No clinically significant abnormalities were found at screening.

12.4.1 Listing of Individual Laboratory Measurements by Subject and each Clinically Significant Abnormal Laboratory Value

No abnormal laboratory value was deemed by the Investigator to be clinically significant. A listing of individual laboratory measurements by subject is given in Appendix 16.2.8. A summary of the pre-study haematology and biochemistry data is given in Sections 14.3.1 and 14.3.2, respectively. Out of range values for haematology, biochemistry and urinalysis are shown in Tables 12.4.1, 12.4.2 and 12.4.3 below, respectively.

Table 12.4.1 Out of range haematology values at screening in study GA0821 (Safety population)

Subject	Visit	Parameter	Result	Low Range	High Range	Units
3	Pre-Study	Eosinophils (X10 9.L-1)	0.5	0.0	3.0	10**9/L
4	Pre-Study	MCH (pg)	33.6	26.5	33.1	PG
4	Pre-Study	MCHC (g.L-1)	351	320	350	G/L
7	Pre-Study	RBC (X10 12.L-1)	4.31	4.45	5.67	10**12/L
8	Pre-Study	RBC (X10 12.L-1)	3.97	3.99	5.14	10**12/L
9	Pre-Study	Eosinophils (X10 9.L-1)	0.4	0.0	0.3	10**9/L
9	Pre-Study	Platelets (X10 9.L-1)	414	169	357	10**9/L
11	Pre-Study	MCH (pg)	34.5	27.5	33.6	PG
11	Pre-Study	MCV (fL)	97.6	80.6	96.4	FL
12	Pre-Study	Haemoglobin (g.L-1)	154	120	152	G/L
12	Pre-Study	MCH (pg)	33.5	26.5	33.1	PG
15	Pre-Study	Lymphocytes (X10 9.L-1)	3.4	1.0	3.1	10**9/L
15	Pre-Study	Platelets (X10 9.L-1)	371	152	351	10**9/L
16	Pre-Study	Haematocrit (L.L-1)	0.384	0.396	0.493	L/L
16	Pre-Study	Haemoglobin (g.L-1)	130	136	171	G/L
16	Pre-Study	RBC (X10 12.L-1)	4.16	4.45	5.67	10**12/L
16	Pre-Study Rpt	Haemoglobin (g.L-1)	135	136	171	G/L
16	Pre-Study Rpt	Platelets (X10 9.L-1)	365	152	351	10**9/L
16	Pre-Study Rpt	RBC (X10 12.L-1)	4.38	4.45	5.67	10**12/L
18	Pre-Study	Platelets (X10 9.L-1)	382	169	357	10**9/L
19	Pre-Study	Monocytes (X10 9.L-1)	0.8	0.2	0.7	10**9/L

19	Pre-Study	Platelets (X10 9.L-1)	493	169	357	10**9/L
20	Pre-Study	Lymphocytes (X10 9.L-1)	3.6	1.0	3.1	10**9/L
25	Pre-Study	Haematocrit (L.L-1)	0.352	0.362	0.450	L/L
25	Pre-Study	Platelets (X10 9.L-1)	385	169	357	10**9/L
25	Pre-Study	RBC (X10 12.L-1)	3.88	3.99	5.14	10**12/L
26	Pre-Study	RBC (X10 12.L-1)	3.86	3.99	5.14	10**12/L
29	Pre-Study	Haematocrit (L.L-1)	0.482	0.362	0.450	L/L
29	Pre-Study	Haemoglobin (g.L-1)	166	120	152	G/L
29	Pre-Study	RBC (X10 12.L-1)	5.15	3.99	5.14	10**12/L
33	Pre-Study	Haematocrit (L.L-1)	0.454	0.362	0.450	L/L
33	Pre-Study	Haemoglobin (g.L-1)	158	120	152	G/L
34	Pre-Study	Lymphocytes (X10 9.L-1)	3.8	1.1	3.5	10**9/L
34	Pre-Study	Platelets (X10 9.L-1)	414	169	357	10**9/L
36	Pre-Study	Lymphocytes (X10 9.L-1)	3.6	1.0	3.1	10**9/L
36	Pre-Study	Platelets (X10 9.L-1)	352	152	351	10**9/L
38	Pre-Study	Haemoglobin (g.L-1)	133	136	171	G/L
42	Pre-Study	Platelets (X10 9.L-1)	435	169	357	10**9/L
43	Pre-Study	Basophils (X10 9.L-1)	0.2	0.0	0.1	10**9/L
43	Pre-Study	Eosinophils (X10 9.L-1)	0.4	0.0	0.3	10**9/L
43	Pre-Study	MCH (pg)	24.8	26.5	33.1	PG
43	Pre-Study	MCHC (g.L-1)	316	320	350	G/L

Table 12.4.2 Out of range biochemistry values at screening in study GA0821 (Safety population)

Subject	Visit	Parameter	Result	Low Range	High Range	Units
1	Pre-Study	Cholesterol (mmol.L-1)	5.27	0.0	5.2	MMOL/L
2	Pre-Study	Total Bilirubin (umol.L-1)	25.9	3.6	22.0	UMOL/L
2	Pre-Study	Creatinine (umol.L-1)	54.3	56.0	92.2	UMOL/L
3	Pre-Study	Albumin (g.L-1)	51.8	39.3	48.5	G/L
3	Pre-Study	Creatinine (umol.L-1)	52.1	56.0	92.2	UMOL/L
3	Pre-Study	Total Protein (g.L-1)	81.7	66.1	81.1	G/L
4	Pre-Study	Calcium (mmol.L-1)	2.19	2.24	2.66	MMOL/L
5	Pre-Study	ALP (IU.L-1)	291.1	84.6	253.4	IU/L
5	Pre-Study	Cholesterol (mmol.L-1)	6.60	0.0	5.2	MMOL/L
5	Pre-Study	Creatinine (umol.L-1)	54.4	56	92.2	UMOL/L
5	Pre-Study	Potassium (mmol.L-1)	5.35	3.85	5.2	MMOL/L
6	Pre-Study	ALT (IU.L-1)	117.4	13.0	67.2	IU/L
6	Pre-Study	GGT (IU.L-1)	121.1	10.0	69.7	IU/L
6	Pre-Study Rpt	ALT (IU.L-1)	74.3	13.0	67.2	IU/L
6	Pre-Study Rpt	GGT (IU.L-1)	93.2	10.0	69.7	IU/L
7	Pre-Study	Total Protein (g.L-1)	82.4	66.7	80.8	G/L
8	Pre-Study	ALT (IU.L-1)	32.9	8.9	32.6	IU/L
8	Pre-Study	Total Bilirubin (umol.L-1)	2.5	3.6	22.0	UMOL/L
8	Pre-Study	Creatinine (umol.L-1)	49.2	56.0	92.2	UMOL/L
10	Pre-Study	ALT (IU.L-1)	108.4	13.0	67.2	IU/L
10	Pre-Study	Total Bilirubin (umol.L-1)	3.8	4.9	33.9	UMOL/L
10	Pre-Study	Cholesterol (mmol.L-1)	6.04	0.0	5.2	MMOL/L
11	Pre-Study	GGT (IU.L-1)	9.7	10.0	69.7	IU/L
12	Pre-Study	Cholesterol (mmol.L-1)	5.25	0.0	5.2	MMOL/L
13	Pre-Study	Creatinine (umol.L-1)	51.8	56.0	92.2	UMOL/L
13	Pre-Study	Sodium (mmol.L-1)	143.1	135.4	142.5	MMOL/L
14	Pre-Study	Albumin (g.L-1)	51.2	42.0	50.5	G/L
14	Pre-Study	Cholesterol (mmol.L-1)	5.61	0.0	5.2	MMOL/L
14	Pre-Study	Creatinine (umol.L-1)	65.5	73.4	113.8	UMOL/L
16	Pre-Study	Total Bilirubin (umol.L-1)	4.3	4.9	33.9	UMOL/L
16	Pre-Study	Cholesterol (mmol.L-1)	6.81	0.0	5.2	MMOL/L
16	Pre-Study	Phosphorus (mmol.L-1)	1.44	0.78	1.41	MMOL/L
17	Pre-Study	Cholesterol (mmol.L-1)	5.72	0.0	5.2	MMOL/L
17	Pre-Study	Urea (mmol.L-1)	6.7	2.3	6.4	MMOL/L

18	Pre-Study	Albumin (g.L-1)	49.5	39.3	48.5	G/L
18	Pre-Study	GGT (IU.L-1)	6.7	7.8	46.8	IU/L
18	Pre-Study	Sodium (mmol.L-1)	144.2	135.4	142.5	MMOL/L
18	Pre-Study	Urea (mmol.L-1)	8.2	2.3	6.4	MMOL/L
19	Pre-Study	Cholesterol (mmol.L-1)	5.99	0.0	5.2	MMOL/L
19	Pre-Study	Creatinine (umol.L-1)	52.7	56.0	92.2	UMOL/L
19	Pre-Study	Triglycerides (mmol.L-1)	2.60	0.0	2.3	MMOL/L
20	Pre-Study	GGT (IU.L-1)	72.3	10.0	69.7	IU/L
20	Pre-Study	HBD (IU.L-1)	205.8	70.0	180	IU/L
20	Pre-Study	Triglycerides (mmol.L-1)	5.50	0.0	2.3	MMOL/L
21	Pre-Study	Total Bilirubin (umol.L-1)	3.9	4.9	33.9	UMOL/L
21	Pre-Study	Cholesterol (mmol.L-1)	5.37	0.0	5.2	MMOL/L
21	Pre-Study	Creatinine (umol.L-1)	70.9	73.4	113.8	UMOL/L
22	Pre-Study	ALP (IU.L-1)	61.8	84.6	253.4	IU/L
23	Pre-Study	Cholesterol (mmol.L-1)	7.93	0.0	5.2	MMOL/L
23	Pre-Study	Phosphorus (mmol.L-1)	1.55	0.87	1.44	MMOL/L
23	Pre-Study Rpt	Cholesterol (mmol.L-1)	7.39	0.0	5.2	MMOL/L
24	Pre-Study	Cholesterol (mmol.L-1)	5.23	0.0	5.2	MMOL/L
24	Pre-Study	Sodium (mmol.L-1)	143.2	135.4	142.5	MMOL/L
25	Pre-Study	Cholesterol (mmol.L-1)	6.54	0.0	5.2	MMOL/L
25	Pre-Study	Total Protein (g.L-1)	82.9	66.1	81.1	G/L
26	Pre-Study	Total Bilirubin (umol.L-1)	1.9	3.6	22.0	UMOL/L
26	Pre-Study	Creatinine (umol.L-1)	48.6	56	92.2	UMOL/L
27	Pre-Study	Phosphorus (mmol.L-1)	0.84	0.87	1.44	MMOL/L
28	Pre-Study	Albumin (g.L-1)	49.3	39.3	48.5	G/L
28	Pre-Study	Cholesterol (mmol.L-1)	5.55	0.0	5.2	MMOL/L
28	Pre-Study	GGT (IU.L-1)	6.7	7.8	46.8	IU/L
29	Pre-Study	Albumin (g.L-1)	51.5	39.3	48.5	G/L
29	Pre-Study	ALT (IU.L-1)	38.8	8.9	32.6	IU/L
29	Pre-Study	Cholesterol (mmol.L-1)	6.12	0.0	5.2	MMOL/L
30	Pre-Study	Calcium (mmol.L-1)	2.22	2.24	2.66	MMOL/L
30	Pre-Study	Glucose (mmol.L-1)	3.3	3.8	5.5	MMOL/L
30	Pre-Study	Triglycerides (mmol.L-1)	2.70	0.0	2.3	MMOL/L
31	Pre-Study	Cholesterol (mmol.L-1)	6.35	0.0	5.2	MMOL/L
31	Pre-Study	Creatinine (umol.L-1)	67.9	73.4	113.8	UMOL/L
31	Pre-Study	Sodium (mmol.L-1)	144.8	136	144.3	MMOL/L
31	Pre-Study	Triglycerides (mmol.L-1)	2.50	0.0	2.3	MMOL/L
32	Pre-Study	Cholesterol (mmol.L-1)	5.32	0.0	5.2	MMOL/L
32	Pre-Study	GGT (IU.L-1)	9.2	10.0	69.7	IU/L
32	Pre-Study	Sodium (mmol.L-1)	144.5	136	144.3	MMOL/L

33	Pre-Study	Cholesterol (mmol.L-1)	5.59	0.0	5.2	MMOL/L
33	Pre-Study	Creatinine (umol.L-1)	46.6	56.0	92.2	UMOL/L
33	Pre-Study	Sodium (mmol.L-1)	144.5	135.4	142.5	MMOL/L
34	Pre-Study	ALP (IU.L-1)	272.5	84.6	253.4	IU/L
34	Pre-Study	ALT (IU.L-1)	42.2	8.9	32.6	IU/L
34	Pre-Study	Cholesterol (mmol.L-1)	6.09	0.0	5.2	MMOL/L
34	Pre-Study	Creatine Kinase (IU.L-1)	276.5	35.1	227.9	IU/L
34	Pre-Study	GGT (IU.L-1)	129.4	7.8	46.8	IU/L
34	Pre-Study	Total Protein (g.L-1)	81.8	66.1	81.1	G/L
34	Pre-Study	Urea (mmol.L-1)	9.3	2.3	6.4	MMOL/L
34	Pre-Study Rpt	Cholesterol (mmol.L-1)	5.43	0.0	5.2	MMOL/L
34	Pre-Study Rpt	GGT (IU.L-1)	88.9	7.8	46.8	IU/L
34	Pre-Study Rpt	Total Protein (g.L-1)	82.0	66.1	81.1	G/L
35	Pre-Study	Albumin (g.L-1)	51.4	42.0	50.5	G/L
35	Pre-Study	Cholesterol (mmol.L-1)	5.96	0.0	5.2	MMOL/L
36	Pre-Study	Cholesterol (mmol.L-1)	5.61	0.0	5.2	MMOL/L
36	Pre-Study	Total Protein (g.L-1)	84.3	66.7	80.8	G/L
37	Pre-Study	ALT (IU.L-1)	46.2	8.9	32.6	IU/L
37	Pre-Study	Cholesterol (mmol.L-1)	5.76	0.0	5.2	MMOL/L
37	Pre-Study	Creatinine (umol.L-1)	47.5	56	92.2	UMOL/L
38	Pre-Study	ALP (IU.L-1)	122.8	124.9	294.3	IU/L
38	Pre-Study	Total Bilirubin (umol.L-1)	4.6	4.9	33.9	UMOL/L
39	Pre-Study	Albumin (g.L-1)	53.0	42.0	50.5	G/L
39	Pre-Study	Sodium (mmol.L-1)	145.2	136.0	144.3	MMOL/L
39	Pre-Study	Total Protein (g.L-1)	81.4	66.7	80.8	G/L
40	Pre-Study	Sodium (mmol.L-1)	143.2	135.4	142.5	MMOL/L
41	Pre-Study	Albumin (g.L-1)	53.4	39.3	48.5	G/L
41	Pre-Study	Cholesterol (mmol.L-1)	5.48	0.0	5.2	MMOL/L
41	Pre-Study	Total Protein (g.L-1)	87.2	66.1	81.1	G/L
42	Pre-Study	ALP (IU.L-1)	267.6	84.6	253.4	IU/L
42	Pre-Study	Sodium (mmol.L-1)	142.8	135.4	142.5	MMOL/L
43	Pre-Study	Total Bilirubin (umol.L-1)	2.1	3.6	22.0	UMOL/L
43	Pre-Study	Creatinine (umol.L-1)	49.1	56.0	92.2	UMOL/L
45	Pre-Study	Creatinine (umol.L-1)	66.8	73.4	113.8	UMOL/L
45	Pre-Study	Total Protein (g.L-1)	81.6	66.7	80.8	G/L

Table 12.4.3 Out of range urinalysis values at screening in study GA0821 (Safety population)

Subject	Visit	Parameter	Result	Normal Range
8	Pre-Study	pH	8.5	5.0 -> 8.0
9	Pre-Study	Ketone	+	Negative
12	Pre-Study	pH	8.5	5.0 -> 8.0
13	Pre-Study	Protein	Trace	Negative
14	Pre-Study	pH	8.5	5.0 -> 8.0
25	Pre-Study	Blood	+	Negative
28	Pre-Study	Protein	Trace	Negative
39	Pre-Study	pH	8.5	5.0 -> 8.0
41	Pre-Study	pH	8.5	5.0 -> 8.0
41	Pre-Study	Blood	Trace	Negative
42	Pre-Study	Blood	++	Negative

12.4.2 Evaluation of Each Laboratory Parameter

The active moiety of the study medications used in this study has been licensed for use in man for many years. Their safety profile is very well established. For this reason, laboratory evaluations were not conducted during the study and no further data are presented here.

12.5 Vital Signs, Physical Findings and other Observations Related to Safety

Vital sign and ECG data are presented in full in Appendix 16.2.4. A summary of all vital signs data pre- and post- study is provided in Section 14.3.3. All vital signs and ECG parameters were either within normal ranges or were considered not clinically significant by the investigating physician. No changes were noted during the post-study physical examination, and no pregnancy occurred during the study.

12.6 Safety Conclusions

There were no clinically significant safety issues identified during the conduct of the study. There was a very low incidence of adverse events.

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

This sensorial based study employed the adapted 2-stopwatch technique that was shown to be effective in a previous pilot study[1] for assessing the onset of sensorial effects – soothing and cooling – in the throat/oesophagus (foodpipe) in the heartburn indication. Subjects dosed as a result of experiencing heartburn of moderate severity after consuming a refluxogenic meal, stopped the stopwatches when they first perceived a soothing effect and when they first perceived a cooling effect. As noted in the results, the Gaviscon treatments demonstrated statistically significantly faster onset of action than the control sublingual tablet. The control however did illicit some responses which is suggestive of a placebo effect. The sublingual tablet was not a placebo in the true sense of the word since it was different in appearance to the test medications and contained different excipients but no active ingredients. A greater number of subjects reported censored times with the control, 31/44 (70%) for soothing and 33/44 (75%) for cooling, which is comparable to what was seen in the pilot study. Therefore it is clearly apparent from the results that the overall size of the effect, if any, was not detrimental in determining the onset of action in terms of perceived soothing and cooling effects.

The Gaviscon liquid treatments had shorter Kaplan-Meier median times to perceived cooling than Gaviscon Instants Oral Powder, which had a reported Kaplan-Meier median time of 11.22 minutes at the 95% upper confidence limit, and also had marginally shorter times to perceived cooling than to perceived soothing. The liquid formulations contain peppermint whereas the powder contains mint and passionfruit flavours. As stated in the discussion of the pilot study, peppermint is known to have a cooling effect in the oral cavity, and associated compounds such as menthol are known to modulate both warm and cold receptor activity[1,2]. The mint of the powder may have been somewhat masked by the fruit flavour or just the combination of the two resulted in fewer subjects perceiving cooling in a particularly short time. In addition, based on the subjective feedback, the powder was the least favoured compared to the other two Gaviscon treatments in terms of the subjects' willingness to use it again and replace their current therapy with it.

Although statistically significantly better than that for control, the low positive response in the Gaviscon treatments for replacement of current therapy could be misleading because the study did not record the subjects' current therapy. If the subject was already taking one of the Gaviscon treatments then they may have been less likely to want to replace their current therapy. It would perhaps have been better to record the subject's current therapy at screening for these results to have some relevance.

The ultimate purpose of the study was to substantiate claims of onset of action in terms of soothing and cooling for Gaviscon treatments compared to a control and this study achieved that. The study however made no attempt to show that these effects were clinically meaningful, which has been defined in pain studies as a 1 or 2 point

change from baseline in pain using approved scales[3-5]. Therefore, in terms of future studies, it would be useful to examine or show a difference in heartburn severity and relief from baseline after dosing with Gaviscon products to demonstrate clinical significance. The information from these studies can then be used to further support the efficacy of the products.

13.2 Conclusion

The Gaviscon treatments showed a statistically significantly earlier onset of action in terms of perceived soothing and cooling effects in the throat/oesophagus (foodpipe) than the control. The reported Kaplan-Meier median times for soothing for Gaviscon Peppermint liquid and Gaviscon Double Action were approximately 3 minutes while those for Gaviscon Instants Oral Powder were approximately 4 minutes. Cooling effects were perceived more quickly than soothing effects with Gaviscon Peppermint liquid and Gaviscon Double Action, with an average onset time within 2 minutes. Based on the subjective responses, more than half of the subjects would be willing to use the Gaviscon Peppermint liquid and Gaviscon Double Action again, which was statistically significantly more than would consider reusing the control. Relatively few subjects were willing to replace their current therapy with any of the Gaviscon treatments, but this was significantly more than the one subject who would consider the sublingual tablet as an alternative therapy. With respect to the objective methodology, this study substantiated the claims of onset of action in terms of soothing and cooling in the throat/oesophagus (foodpipe) for Gaviscon Peppermint liquid and Gaviscon Double Action.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

No additional demographic data is presented here.

14.2 Efficacy Data

No additional efficacy data is presented here.

14.3 Safety Data

14.3.1 Summary of Haematology Data

A summary of pre-study haematology data are provided in table 14.3.1 below:

Table 14.3.1 Summary of Haematology Data for Study GA0821 (Safety population)

Visit	Parameter	N	Mean	SD	Minimum	Median	Maximum
Pre-Study	Basophils (X10 9.L-1)	45	0.06	0.05	0.0	0.1	0.2
Pre-Study	Eosinophils (X10 9.L-1)	45	0.21	0.11	0.0	0.2	0.5
Pre-Study	Haematocrit (L.L-1)	45	0.4202	0.0338	0.352	0.417	0.482
Pre-Study	Haemoglobin (g.L-1)	45	142.9	12.8	120	142	166
Pre-Study	Lymphocytes (X10 9.L-1)	45	2.31	0.60	1.4	2.3	3.8
Pre-Study	MCH (pg)	45	30.60	1.84	24.8	30.8	34.5
Pre-Study	MCHC (g.L-1)	45	339.9	8.2	316	342	353
Pre-Study	MCV (fL)	45	89.99	4.25	78.4	90.1	97.6
Pre-Study	Monocytes (X10 9.L-1)	45	0.45	0.14	0.2	0.4	0.8
Pre-Study	Neutrophils (X10 9.L-1)	45	4.55	1.21	2.6	4.3	8.0
Pre-Study	Platelets (X10 9.L-1)	45	293.1	68.1	179	286	493
Pre-Study	RBC (X10 12.L-1)	45	4.680	0.447	3.86	4.72	5.64
Pre-Study	WBC (X10 9.L-1)	45	7.71	1.62	4.9	7.5	12.0

14.3.2 Summary of Biochemistry Data

A summary of pre-study biochemistry data are provided in the table below:

Table 14.3.2 Summary of Biochemistry Data for Study GA0821 (Safety population)

Visit	Parameter	N	Mean	SD	Minimum	Median	Maximum
Pre-Study	Albumin (g.L-1)	45	47.66	2.76	41.6	47.8	53.4
Pre-Study	ALP (IU.L-1)	45	182.73	49.79	61.8	176.0	291.1
Pre-Study	ALT (IU.L-1)	45	30.18	21.44	9.6	24.4	117.4
Pre-Study	Total Bilirubin (mmol.L-1)	45	7.24	3.84	1.9	6.8	25.9
Pre-Study	Calcium (mmol.L-1)	45	2.407	0.083	2.19	2.40	2.58
Pre-Study	Cholesterol (mmol.L-1)	45	5.11	1.02	3.0	5.2	7.9
Pre-Study	Creatine Kinase (IU.L-1)	45	136.18	95.58	41.1	96.0	421.8
Pre-Study	Creatinine (mmol.L-1)	45	68.18	12.74	46.6	67.6	96.4
Pre-Study	GGT (IU.L-1)	45	29.08	26.25	6.7	23.5	129.4
Pre-Study	Glucose (mmol.L-1)	45	4.75	0.38	3.3	4.7	5.5
Pre-Study	HBD (IU.L-1)	45	138.28	23.49	91.8	140.2	205.8
Pre-Study	Potassium (mmol.L-1)	45	4.616	0.296	3.97	4.61	5.35
Pre-Study	Sodium (mmol.L-1)	45	141.84	1.58	138.5	141.9	145.2

Pre-Study	Phosphorus (mmol.L-1)	45	1.179	0.174	0.84	1.20	1.55
Pre-Study	Total Protein (g.L-1)	45	77.48	3.74	68.7	77.8	87.2
Pre-Study	Triglycerides (mmol.L-1)	45	1.304	0.889	0.20	1.10	5.50
Pre-Study	Uric Acid (mmol.L-1)	45	0.278	0.073	0.15	0.25	0.43
Pre-Study	Urea (mmol.L-1)	45	5.07	1.27	3.3	4.9	9.3

14.3.3 Summary of Vital Signs

Pre and post study vital signs are presented in table 14.3.3 below:

Table 14.3.3 Summary of Vital Signs for Study GA0821 (Safety population)

Variable		Pre-Study	Post-Study	Change
SITTING SBP	N	45	45	45
(MMHG)	MEAN	129.8	129.8	0.0
	SD	11.8	11.1	11.0
	MIN	96	101	-39
	MEDIAN	131	131	0
	MAX	158	153	20
SITTING DBP	N	45	45	45
(MMHG)	MEAN	77.7	74.3	-3.4
	SD	7.5	8.7	7.0
	MIN	65	56	-19
	MEDIAN	79	74	-2
	MAX	90	93	12
SITTING	N	45	45	45
PULSE (BPM)	MEAN	70.8	73.0	2.1
	SD	8.7	11.5	8.6
	MIN	51	49	-15
	MEDIAN	72	71	1
	MAX	88	98	26
TEMP. (C)	N	45	45	45
	MEAN	36.28	36.33	0.06
	SD	0.36	0.37	0.41
	MIN	35.4	35.7	-1.0
	MEDIAN	36.2	36.3	0.1
	MAX	37.2	37.3	1.1

14.4 Displays of Adverse Events

No additional displays of adverse events are provided here.

14.4.1 Listings of Deaths, other Serious and Significant Adverse Events

There were no deaths, other serious and significant adverse events in this study

14.4.2 Narratives of Deaths, other Serious and certain other Significant Adverse Events

There were no deaths, other serious and significant adverse events in this study

14.4.3 Clinically Significant Abnormal Laboratory Value Listing (each subject)

No abnormal laboratory value was deemed by the Investigator to be clinically significant.

15 REFERENCE LIST

1) GA0706 Clinical Study Report, Reckitt Benckiser, Data on File.
2) Eccles R. Menthol and related cooling compounds. J Pharm Pharmacol 1994; 46: 618-630.
3) Farrar JT, Young JP, LaMoreaux,L et al. Clinical importance of changes in chronic pain intensity measured on an 11 point numerical pain rating scale. Pain 2001; 94(2): 149-158.
4) Farrar JT, Berlin JA, Strom BL. Clinically important changes in acute pain outcome measures: a validation study. J Pain Sympt Man 2003; 25(5) 406-411.
5) Salaffi F, Stancati A, Silvestri CA, et al. Minimum clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. Eur J Pain 2004; 8(4): 283-291.