SIGNATURE PAGE

Document Name : GA0706 Final Report 11-Jul-2008

Document Title :

Document Version : 0.1; CURRENT; Most-Recent; For Approval

Date (GMT)	Signed by
09/Nov/2015 12:50:03	EmField
Justification	Clinical Approver

Justification	

Justification	

Justification	

Justification	

Justification	

Justification	

Reckitt Benckiser

1 STUDY REPORT TITLE PAGE

EudraCT Number:	2007-005821-31
Study Number:	GA0706
Protocol Title:	A single-centre randomised, partially blind, single dose, crossover pilot study investigating the use of stopwatches to assess the onset of action of soothing and cooling of Gaviscon Peppermint liquid, Double Action Gaviscon liquid, Gaviscon Advance liquid, and a control in subjects with heartburn following a refluxogenic meal.
Study Phase:	IV
Date First Subject Enrolled:	21 January 2008
Date Last Subject Completed:	21 February 2008
Report Date:	11 July 2008
Principal Investigator:	Dr PM Dewland, BSc, MA, MBBS, FFPM, DCPSA , Medical Director 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:

Clinical Project Manager:

Dr K Sarratt BSE PhD — 30 July 2008 (Date)

Reckitt Benckiser Healthcare (UK) Ltd

Statistician:

Mr J Sykes, BSc MSc CStat — 30 July 08 (Date)

Reckitt Benckiser Healthcare (UK) Ltd

R & D Manager:

Dr I Jolliffe, BPharm (Hons), MRPharmsS, PhD — 27th July 08 (Date)

Reckitt Benckiser Healthcare (UK) Ltd

Report Writer:

Dr I A Gibb BSc PhD MICR — 27 July 08 (Date)

Insight Clinical Consulting Ltd

Reviewed and Approved by:

Clinical Project Manager

Mr D Crossley BSc MRPharmS — 30 July 2008 (Date)

Reckitt Benckiser Healthcare (UK) Ltd

Global Medical Director:

Dr P Berry MB, ChB, MPH — 4 August 2008 (Date)

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 Sachets Gaviscon Advance Aniseed Flavour Gaviscon Double Action Liquid	**Volume:**	
Name of Active Ingredient(s): Sodium alginate/calcium carbonate/sodium bicarbonate/potassium bicarbonate	**Page:**	
Title of Trial: A single-centre randomised, partially blind, single dose, crossover pilot study investigating the use of stopwatches to assess the onset of action of soothing and cooling of Gaviscon Peppermint liquid, Double Action Gaviscon liquid, Gaviscon Advance liquid, and a control in subjects with heartburn following a refluxogenic meal		
Investigator(s): Dr PM Dewland, BSc., MA, MBBS, FFPM, DCPSA		
Trial Centre(s): Simbec Research Limited, Merthyr Tydfil, CF48 4DR		
Publication (reference): None		
Studied Period: 1 month **Date first subject enrolled:** 21 Jan 2008 **Date last subject completed:** 21 Feb 2008		**Phase of Development:** IV
Objectives: The primary objective of this study was to pilot the stopwatch technique for determining the onset of action of products that provide a perceived soothing effect in the throat/oesophagus (foodpipe) during heartburn. The secondary objectives of this study were to evaluate the time to first perceived cooling effect in the throat/oesophagus (foodpipe); the description of an "instant" benefit from the product; the ability of the product to make the mouth/throat feel fresher; and the subject's willingness to use the product again.		
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. Five minutes after dosing, subjects were asked if they would describe any benefit they had felt from the product as "instant". Thirty minutes after dosing, subjects were asked if they would be willing to use the product again and if they had experienced any adverse effects and if their mouth/throat felt any fresher after the treatment. 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:** 20 **Analysed:** 20		

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 Sachets Gaviscon Advance Aniseed Flavour Gaviscon Double Action Liquid	**Volume:**	
Name of Active Ingredient(s): Sodium alginate/calcium carbonate/sodium bicarbonate/potassium bicarbonate	**Page:**	

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 ≤ 80 years

Sex: Male and female subjects were eligible for entry.

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

Test Product: Product A: Gaviscon Peppermint liquid in sachets, containing 500mg sodium alginate, 267mg sodium bicarbonate, and 160 mg calcium carbonate per 10ml dose, 10ml suspension in sachet, NL 15334. 10ml administered orally, batch no. 732491

Product B: Gaviscon Advance Aniseed Flavour, containing 1000mg sodium alginate and 200mg potassium bicarbonate per 10ml dose, 300 ml suspension in bottle, PL 00063/0097. 10ml administered orally, batch no. 728581

Product C: Gaviscon Double Action Liquid, containing 500mg sodium alginate 213mg sodium bicarbonate, and 325mg calcium carbonate per 10ml dose, 300ml suspension in bottle, PL 00063/0156. 10ml administered orally, batch no. 716481

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. 397280

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 Sachets Gaviscon Advance Aniseed Flavour Gaviscon Double Action Liquid	**Volume:**	
Name of Active Ingredient(s): Sodium alginate/calcium carbonate/sodium bicarbonate/potassium bicarbonate	**Page:**	

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the time to first perceived soothing effect in the throat/oesophagus (foodpipe) using a stopwatch. The secondary efficacy endpoints were:

- Time to first perceived cooling effect in the throat/oesophagus (foodpipe) using a stopwatch
- Would you describe any benefit you felt from this product as "instant" (yes/no)?
- Did the product make your mouth/throat feel fresher (yes/no)?
- Willingness to use the product to treat heartburn again (yes/no)

Safety: Safety was assessed in terms of the overall proportion of subjects with 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: No formal statistical comparisons were made. The time to first perceived soothing effect was summarised by treatment using the number of subjects assessed, the number of subjects with censored and uncensored data and either the mean standard deviation, minimum, median and maximum (if all subjects provide uncensored data) or the median and minimum (when censored data were reported). Where there were no censored observations an upper one-sided 95% confidence limit for the mean time to first perceived soothing effect was computed.

The number and percentage of subjects who had a time to first perceived soothing effect of no more than 5 seconds were summarised by treatment. The lower one-sided 95% confidence limit for the percentage of subjects who had a time to first perceived soothing effect of no more than 5 seconds was computed using exact methods and summarised by treatment.

The secondary endpoint amount of time to first perceived cooling effect in the throat/oesophagus (assessed using a stopwatch) was summarised using the same methods as for time to perceived soothing effect.

The three remaining parameters 1) "instant" benefit 2) mouth/throat freshness and 3) willingness to use product to treat heartburn were summarised by treatment using a frequency distribution. For each parameter the lower one-sided 95% confidence limit for the percentage of subjects who gave a positive response was computed using exact methods and summarised by treatment.

Descriptive statistics (n, mean, standard deviation, minimum, median and maximum) were calculated for vital signs parameters at pre-study and post-study 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.

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 Sachets Gaviscon Advance Aniseed Flavour Gaviscon Double Action Liquid	**Volume:**	
Name of Active Ingredient(s): Sodium alginate/calcium carbonate/sodium bicarbonate/potassium bicarbonate	**Page:**	

SUMMARY & CONCLUSIONS

EFFICACY RESULTS: The median times to first perceived soothing effect were 1.37 minutes for Gaviscon formulation A, 1.34 minutes for Gaviscon formulation B and 1.17 minutes for Gaviscon formulation C. No subject times were censored in any of these three treatment groups. In contrast, the negative control which was a sublingual tablet, had a median time to first perceived soothing effect of 30 minutes and 16 subjects had times censored at 30 minutes. No subject perceived a soothing effect within 5 seconds of dosing with any treatment.

The median times to first perceived cooling effect were 0.57 minutes for Gaviscon formulation A, 1.03 minutes for Gaviscon formulation B and 0.45 minutes for Gaviscon formulation C. No subject times were censored for formulation A, while three times and one time were censored for formulations B and C respectively. The negative control group had a median time of 30 minutes and 17 subjects had times censored at 30 minutes. No subject perceived a cooling effect within 5 seconds of dosing with any treatment.

With the subjective assessments, for Gaviscon formulations A, B and C, 60% (lower 95% CL 39.4%), 65% (lower 95% CL 44.2%) and 70% (lower 95% CL 49.2%) of subjects respectively said they would describe any benefits they had felt from the product as "instant", compared to none for the negative control. Similarly in the Gaviscon groups A, B and C, 70%, 60% and 75% said their mouth/throat felt fresher and 80%, 65% and 90% of subjects respectively said they would be willing to use the product again, while none of the negative control group reported their mouth/throat felt fresher and none were willing to use that product again.

SAFETY RESULTS: Six subjects reported a total of 12 treatment emergent adverse events. All events resolved with no sequelae. Nine were mild, two were moderate and one (constipation) was classed as severe. Nine events were categorised by the Investigator as not related or as unlikely to be related to treatment. Three events (constipation, headache and nausea) were classed as possibly related to treatment. There were no serious adverse events and there were no clinically significant changes in vital signs.

CONCLUSION: The negative control performed as expected using the stopwatch methodology. In absolute terms, cooling benefits associated with the three Gaviscon formulations were perceived more quickly than soothing benefits. Using the objective stopwatch methodology, no subject experienced an "instant" sensorial benefit, where "instant" was predefined as being within 5 seconds. Using questioning, more than half of the subjects in each Gaviscon group felt they experienced "instant" benefits when "instant" was left to each subject to define. Future studies need to consider blinding, the real likelihood of any placebo benefit and whether objective or subjective methodology is more likely to provide the required claims support. This study did provide data on which future sample sizes for both approaches can be based. All three Gaviscon liquid formulations were well tolerated.

Date of the report: 11 July 2008

3 TABLE OF CONTENTS

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

3.2 List of Appendices

16 APPENDICES

16.1 STUDY INFORMATION

16.1.1 Protocol and protocol amendments

16.1.2 Sample case report form (unique pages only)

16.1.3 List of IECs or IRBs

16.1.4 List and description of investigators and other important participants in the study

16.1.5 Signature of principal investigator

16.1.6 Listing of subjects receiving test drug(s) from specific batches, where more than one batch was used

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, so this appendix is not present.

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

No subjects discontinued the study, so this appendix is not present.

16.2.2 Protocol Deviations

There were no protocol deviations in this study, so this appendix is not present.

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 Supply Unit
ITT	Intention to Treat
IRB	Institutional Review Board
kg	kilogram
LREC	Local research ethics committee
m	metre
mg	milligram
ml	millilitre
OTC	Over the Counter
PAGB	The Proprietary Association of Great Britain
RB	Reckitt Benckiser
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 20 December 2007.

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 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 P Dewland. 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 monitoring were conducted by Dr K Sarratt, Clinical Project Manager, RB. The writing of the clinical study report was contracted to Insight Clinical Consulting Ltd. 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. A key claim for the brand is based on consumer perception of the product being able to deliver an "instantly soothing" effect. To date, this wording has been supported by market research data. Reckitt Benckiser Healthcare UK wished to strengthen the basis for the "instantly soothing" claim in order to meet the more stringent regulatory requirements for licensed medicinal products. As per the advice of the Proprietary Association of Great Britain (PAGB), "instantly" was defined as within five seconds.

To support this claim, it was considered necessary to assess speed of onset in a prospective, randomised, sensorial based clinical study. Such a design holds scientific and medical credibility by helping to control variation and bias, and generates data of an appropriate standard for claims substantiation. The study was partially blinded as the control and Gaviscon treatments differed in physical form (sublingual tablet and liquid respectively).

A methodology using stopwatches to assess onset of action has been described in migraine and in post operative dental pain.[1,2] The current study adopted this technique to assess the consumer perceived onset of two attributes (soothing and cooling) of Gaviscon. However, as the methodology had not been used in this indication previously, it was considered appropriate to conduct a pilot study to determine if the methodology was likely to be helpful in supporting the required claim and to provide a basis for sample size calculation for future studies.

A control that was not expected to have any effect, (in this case a sublingual tablet) was included in this study on an open label basis to show the validity of the methodology. By using such a control it was planned to show that an oral product that is not swallowed would not produce a soothing or cooling effect. The choice of a sublingual tablet as a control was appropriate for this study because it was envisaged that an oral placebo or any type of oral product of any description that could readily enter the oesophagus through the mouth may have imparted some kind of soothing or cooling effect.

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. The active study treatments were administered by a member of Simbec staff, at a 10ml dose and by an oral route as specified in the product licence, once the subjects had indicated that they were experiencing heartburn of at least moderate severity on a 4 point categorical self-rating scale of none, mild, moderate, or severe. The control treatment was also administered by a member of Simbec staff who provided each subject with one tablet to be placed under the tongue.

8 STUDY OBJECTIVES

The primary objective of this study was to pilot the stopwatch technique for determining the onset of action of products that provide a perceived soothing effect in the throat/oesophagus (foodpipe) during heartburn.

The secondary objectives of this study were to evaluate the time to first perceived cooling effect in the throat/oesophagus (foodpipe); the description of an "instant" benefit from the product; the ability of the product to make the mouth/throat feel fresher; and the subject's willingness to use the product again.

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 pilot study in subjects who displayed symptoms of heartburn following a refluxogenic meal.

The subject population studied were community subjects who experienced post prandial heartburn, but who were otherwise reasonably healthy. Twenty subjects were included in the study. There were two prescreening visits, the second of which took place at least 48 hours after the first and selected out those who did not experience moderate heartburn after a standardised refluxogenic meal containing 60% fat. Those who did experience moderate heartburn were then invited to attend four treatment visits and one post study visit. Each treatment visit required attendance at the Unit at 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 were fasted for at least four hours. They were then provided with a standardised refluxogenic meal containing 60% fat and asked to remain supine. When they experienced heartburn of at least moderate severity on the self-rating scale, they were dosed in a sitting position with their allocated study medication for that 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 in sachets, containing 500mg sodium alginate, 267mg sodium bicarbonate, and 160 mg calcium carbonate per 10ml dose, 10ml suspension in sachet, NL 15334, Batch No. 732491, expiry date 28 February 2009.

Product B: Gaviscon Advance Aniseed Flavour, containing 1000mg sodium alginate and 200mg potassium bicarbonate per 10ml dose, 300 ml suspension in bottle, PL 00063/0097, Batch No. 728581, expiry date 28 February 2009.

Product C: Gaviscon Double Action Liquid, containing 500mg sodium alginate 213mg sodium bicarbonate, and 325mg calcium carbonate per 10ml dose, 300ml suspension in bottle, PL 00063/0156, Batch No. 716481, expiry date 28 February 2009.

Product D: Control, containing 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: 397280, expiry date 28 February 2009.

Subjects who did not experience heartburn of at least moderate severity within 60 minutes of completing their meal were not dosed on that treatment visit. 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.

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. Subjects were asked 5 minutes into the treatment study period if they felt an "instant" benefit from the product. At the end of the treatment study period, subjects were asked whether or not they would be willing to use the

product again, if they experienced any adverse effects, and if their mouth/throat felt fresher after the treatment.

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

This was a pilot study to investigate the use of a stopwatch technique to determine the speed of onset of action of three formulations of Gaviscon in the treatment of moderate, self-rated heartburn. A negative control was chosen which was highly unlikely to have any effect whatsoever on heartburn as it was an inactive, sublingual tablet. Each formulation of Gaviscon was in liquid form, hence complete blinding of the study was not achieved. It could be considered that this might have brought unacceptable bias to the study. However, the objective of determining speed of onset of action was to help support medicinal (marketing) claims. In making such claims about speed, it is the absolute time that a product takes to have a perceptible effect that is important, not a relative time compared to placebo. Hence any bias brought by the open nature of the control was unlikely to be critical in claiming an "instant" effect. It was considered more important in this study to be able to show some discriminatory ability of the stopwatch methodology in this indication.

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.

9.3.1 Inclusion Criteria

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

1) Age: ≥ 18 years ≤ 80 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.
8) Those who had taken proton pump inhibitors within the previous 48 hours prior to screening.
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 or potassium bicarbonate.
11) Those receiving treatment for their upper gastrointestinal problems or gastro-oesophageal reflux disease from their GP.
12) Those unable in the opinion of the Investigator to comply fully with the study requirements.
13) Those who were currently participating in a clinical study or who had participated in any other clinical study within the last 30 days.
14) Those who had previously participated in this randomised study.
15) 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).

16) Those who were on steroids or non-steroidal anti-inflammatory drugs.
17) 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; 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 (°C).
- 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 in sachets, containing 500mg sodium alginate, 267mg sodium bicarbonate, and 160 mg calcium carbonate per 10ml dose, 10ml suspension in sachet, NL 15334, Batch No. 732491, expiry date 28 February 2009.

Product B: Gaviscon Advance Aniseed Flavour, containing 1000mg sodium alginate and 200mg potassium bicarbonate per 10ml dose, 300 ml suspension in bottle, PL 00063/0097, Batch No. 728581, expiry date 28 February 2009.

Product C: Gaviscon Double Action Liquid, containing 500mg sodium alginate 213mg sodium bicarbonate, and 325mg calcium carbonate per 10ml dose, 300ml suspension in bottle, PL 00063/0156, Batch No.716481, expiry date 28 February 2009.

Product D: Control, containing 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: 397280, expiry date 28 February 2009.

A volume of 10ml of products A, B and C was administered orally on a single occasion for each product. 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, PL 00050/5002R, batch no. 074, expiry date 31 October 2009 was supplied by Simbec and a single dose of 10ml administered orally to those subjects who required symptomatic relief after experiencing heartburn during prestudy screening visit 2.

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 Supply Unit (IMSU), Reckitt Benckiser Healthcare UK Ltd, Dansom Lane, Hull HU8 7DS, UK. Market packs of products A, B and C were used. The Gaviscon liquid products were supplied as blinded and the control as open label. They were shipped directly from the IMSU to Simbec Research.

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 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.

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 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.

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, and were labelled only with the blinded treatment codes X, Y and Z. The RB IMSU held the master code for the allocation of codes X, Y and Z to Test products A, B and C. The randomised treatment allocation schedule was an open list and was prepared using the blinded treatment codes X, Y and Z (and D for the control). At each visit the Investigator dispensed the treatment 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 (Physician or appropriately trained staff) administered 10ml of each liquid treatment to the subject using a spoon. Any subjects who did not comply with this form of administration were 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	
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	
Onset of first perceived soothing (by stopwatch)			X	X	X	X	
Onset of first perceived cooling (by stopwatch)			X	X	X	X	
Mouth/throat freshness			X	X	X	X	
Instant Benefit			X	X	X	X	
Willingness to use product again			X	X	X	X	
Adverse Events			X	X	X	X	X

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 prestudy screening visit 1 and the subject's current status as having self rated moderate heartburn confirmed at prestudy screening visit 2. Smoking, alcohol and Drugs of Abuse History and Use were collected at screening as specified in the protocol.

Demographics: Sex, date of birth, race (categorised as Caucasian, Asian, Afro-Caribbean, Other), height (m), weight (kg) and body mass index (kg/m^2) were collected at prestudy 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 prestudy screening visit 1 and at the post-study visit.

Physical Examination: A standard physical examination was conducted at prestudy 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 prestudy 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 prestudy 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), aspartate transaminase (AST, 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 prestudy 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 period.

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.

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 5 minutes after dosing whether they would describe any benefit they had felt from the product as "instant". They were asked if they felt the product had made their mouth/throat feel fresher and whether they would use the product again at 30 minutes after dosing.

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 may experience slight discomfort.
	Moderate	The AE resulted in some limitation of usual activities; the subject may experience significant discomfort.
	Severe	The AE resulted in an inability to carry out usual activities; the subject may experience 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 is 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 pilot study, supportive efficacy questions of subject perception were also asked.

9.5.3 Primary Efficacy Variable(s)

The primary efficacy end-point was the amount of time to first perceived soothing effect in the throat/oesophagus (foodpipe), assessed using a stopwatch. For a subject/visit at which a soothing 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 were 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, sex, initials, subject number)
Smoking and alcohol status
Medical status of subject (clinically significant medical history and other disorders)
ECGs
Laboratory results
AEs
Concomitant medication
Visit dates
GP letter
Date of consent
Demographics (height, weight, race, and BMI)
Vital signs
Physical exam
Subject eligibility (inclusion and exclusion criteria)

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.

The time to first perceived soothing effect was summarised by treatment using the number of subjects assessed, number of subjects with censored and uncensored data, and either the mean, standard deviation, median, minimum, and maximum (where all subjects provided uncensored data) or the median and minimum (where censored data were reported). Where there were no censored observations an upper one-sided 95% confidence limit for the mean time to first perceived soothing effect was computed.

The number and percentage of subjects who had a time to first perceived soothing effect of no more than 5 seconds were summarised by treatment. The lower one-sided 95% confidence limit for the percentage of subjects who had a time to first perceived soothing effect of no more than 5 seconds was also to be computed using exact methods and summarised by treatment. However, no subject in the study reported a time to first perceived soothing effect of 5 seconds or less.

The time to first perceived cooling effect was summarised using the same methods as those for the time to first perceived soothing effect.

The three remaining parameters were summarised by treatment using frequency distributions. The lower one-sided 95% confidence limit for the percentage of subjects who gave a positive response was computed using exact methods and summarised by treatment.

There was no formal statistical comparison of data from the control and Gaviscon groups.

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. 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 in the summary tabulations. 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 via the chi-square test.

9.7.2 Determination of Sample Size

No statistical justification for the sample size in this study was performed because this was a pilot study, intended to provide variance estimates from which sample size estimates for future studies could be derived.

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

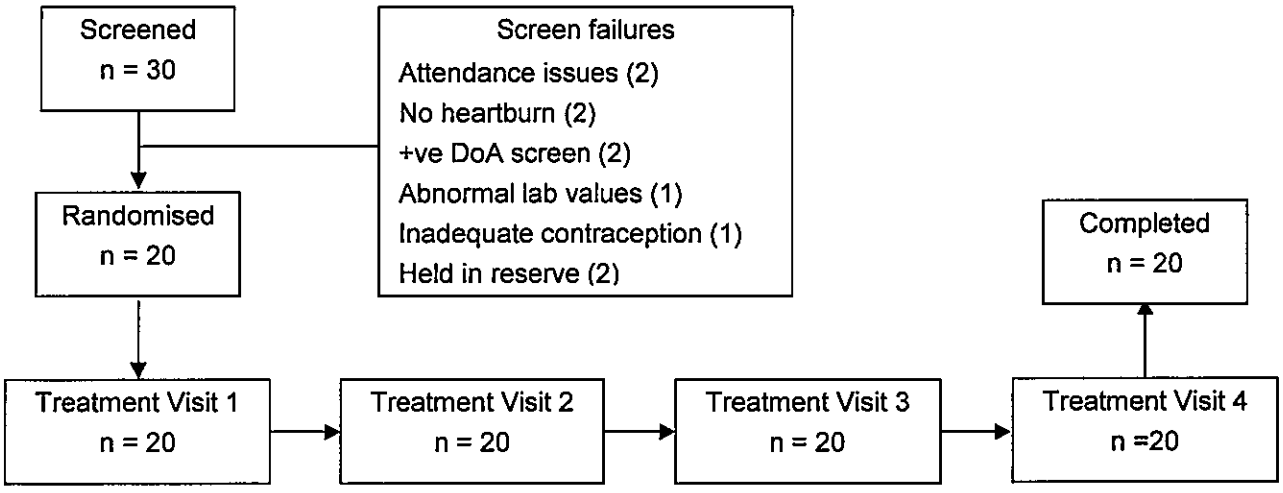
No changes were made in the planned statistical analyses.

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, visits and observations excluded from the efficacy analysis. The reasons for exclusion are presented for the whole treatment group over time.

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 and the blind being broken.

11.2 Demographic and Other Baseline Characteristics

In addition to tables giving group data for baseline variables, relevant individual subject demographic and baseline data, including 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 GA0706

Variable		Male	Female	All
AGE (YRS)	N	4	16	20
	MEAN	40.8	40.1	40.3
	SD	17.2	13.0	13.5
	MIN	28	19	19
	MEDIAN	35	38	38
	MAX	65	64	65
HEIGHT (CM)	N	4	16	20
	MEAN	174.5	161.5	164.1
	SD	1.9	4.8	6.9
	MIN	172	154	154
	MEDIAN	175	161	163
	MAX	176	169	176
WEIGHT (KG)	N	4	16	20
	MEAN	83.6	67.5	70.8
	SD	10.9	16.0	16.3
	MIN	68.5	51.7	51.7
	MEDIAN	86.4	64.5	67.4
	MAX	93.1	112.1	112.1
BMI (KG/M^2)	N	4	16	20
	MEAN	27.4	25.9	26.2
	SD	3.0	5.9	5.4
	MIN	23.2	20.2	20.2
	MEDIAN	28.2	25.2	25.6
	MAX	30.1	40.2	40.2

All subjects 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.

There were no medical history findings or physical examination findings that were considered to breach the eligibility criteria for participation in this study. Subjects 1, 2 and 13 had a gastrointestinal history of heartburn, reflux oesophagitis and occasional indigestion respectively. Subjects 5, 7, 10, 12, 13, 14, 15 and 20 had past histories of musculoskeletal conditions that were not considered to be clinically significant for this study.

Subject 4 had a minor pre and post study ECG abnormality, which the Investigator did not consider clinically significant.

There were no clinically meaningful findings in recordings of pulse, blood pressure and oral temperature. A summary of vital signs pre and post study is provided in Section 14.3.

11.2.3 Concomitant Medications

Eleven of the 16 female subjects were taking contraceptive products. Nine of these were taking oral contraceptive pills and two had implanted subcutaneous products. In addition, two subjects took two concomitant medications (an antibiotic and an analgesic/antipyretic) after their last treatment visit but before their post study assessment visit. Subject 9 took a single dose of Bisacodyl for the treatment of constipation on their last treatment visit but it is not recorded whether this was before or after study medication.

11.3 Measurements of Treatment Compliance

All subjects were administered the study treatments by Simbec staff and were observed during dosing.

11.4 Efficacy Results

11.4.1 Analysis of Efficacy

11.4.1.1 Primary Endpoint (time to first perceived soothing effect)

The time to achieve first perceived soothing effect with each treatment is summarised below in Table 11.4.1.

Table 11.4.1 Time (minutes) to first perceptible soothing effect in study GA0706

Product	N	No. Censored	No. Uncensored	Mean	Upper 95% CL	SD	Minimum	Median	Maximum
Product A	20	0	20	2.14	2.90	1.96	0.17	1.37	7.00
Product B	20	0	20	2.69	3.94	3.24	0.27	1.34	14.60
Product C	20	0	20	1.99	2.76	1.99	0.22	1.17	7.38
Product D	20	16	4	—	—	—	7.48	30.00	—

All three Gaviscon liquid products A, B and C had a median time to first perceptible soothing effect experienced by all subjects within the first one and a half minutes after dosing (1.37 minutes for product A, 1.34 minutes for product B and 1.17 minutes for product C). The negative control product (D) had censored times, i.e. the stopwatch was not stopped within 30 minutes, in 16 of the 20 subjects, resulting in a median time of 30 minutes. No subject experienced a first perception of soothing within five seconds of dosing for any of the test products.

11.4.1.2 Secondary Endpoint (time to first perceived cooling effect)

The time to first perceived cooling effect is summarised in table 11.4.2.

Table 11.4.2 Time (minutes) to first perceptible cooling effect in study GA0706

Product	N	No. Censored	No. Uncensored	Mean (mins)	Upper 95% CL	SD	Minimum	Median	Maximum
Product A	20	0	20	1.31	1.90	1.54	0.20	0.57	6.35
Product B	20	3	17	—	—	—	0.18	1.03	—
Product C	20	1	19	—	—	—	0.23	0.45	—
Product D	20	17	3	—	—	—	5.30	30.00	—

These results mirrored those of time to first perceived soothing effect, with all three liquid Gaviscon formulations having a median time to first perceived cooling effect within the first one and a half minutes of dosing (0.57 minutes for product A, 1.03

minutes for product B and 0.45 minutes for product C). The negative control group had a median time of 30 minutes with 17 subjects having censored times, compared to no subjects with product A, three subjects with product B and one subject with product C having censored times. No subject experienced a first perception of cooling within 5 seconds of dosing for any of the test products.

11.4.1.3 Secondary Endpoints (subjective assessments)

The subjective assessments of whether subjects felt any "instant" benefit from the product or not, whether or not their mouth or throat felt refreshed after product usage and whether or not they would use that product again are summarised in Table 11.4.3.

Table 11.4.3 Subjective assessments in study GA0706

Parameter	Response n (%)	Product A	Product B	Product C	Product D
Instant Benefit	No	8 (40.0)	7 (35.0)	6 (30.0)	20 (100.0)
	Yes	12 (60.0)	13 (65.0)	14 (70.0)	0 (0.0)
	L95% CL for % Yes	39.4	44.2	49.2	0.0
Mouth/Throat Feel Fresher	No	6 (30.0)	8 (40.0)	5 (25.0)	20 (100.0)
	Yes	14 (70.0)	12 (60.0)	15 (75.0)	0 (0.0)
	L95% CL for % Yes	49.2	39.4	54.4	0.0
Willing to Use Again	No	4 (20.0)	7 (35.0)	2 (10.0)	20 (100.0)
	Yes	16 (80.0)	13 (65.0)	18 (90.0)	0 (0.0)
	L95% CL for % Yes	59.9	44.2	71.7	0.0

More than half of the subjects in each Gaviscon product group said that they would describe any benefit they had felt from the product as "instant" (formulation A 60% (lower 95% CL 39.4%); formulation B 65% (lower 95% CL 44.2%); and formulation C 70% (lower 95% CL 49.2%)). No subject agreed with this statement for the negative control sublingual product.

Similarly in the Gaviscon groups A, B, and C, 70% (lower 95% CL 49.2%), 60% (lower 95% CL 39.4%) and 75% (lower 95% CL 54.4%) said their mouth/throat felt fresher; and 80% (lower 95% CL 59.9%), 65% (lower 95% CL 44.2%) and 90% (lower 95% CL 71.7%) said they would be willing to use the product again, respectively; however, no subjects reported that their mouth/throat felt fresher with the negative control and none were willing to use that product again.

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

There are no missing data and no subjects dropped out of the study, therefore this section is not applicable.

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 multiple comparisons were made therefore this section is not applicable.

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 group 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

The negative control group performed as expected, with no subject experiencing onset of action within 30 minutes. Onset times of approximately one minute were found with each of the Gaviscon liquid products. The stopwatch methodology appears to be suitable for assessing onset of action in the indication of heartburn. The result of the negative control may have been influenced by the partial blinding status of the study. In absolute time terms, cooling benefits were perceived more rapidly than soothing benefits. As defined *a priori* in the protocol, no subject perceived an "instant" benefit using the stopwatch method, but 60% or more of the subjects taking each Gaviscon product in this study reported that they would describe any benefits they felt as "instant", on a subjective basis. No subject taking the negative control product reported this effect. Subjective methodology may be an alternative way of achieving claim support for Gaviscon. The study was successful in generating data that will provide the basis for sample size calculations for both objective and subjective approaches for future studies.

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

Twenty subjects received a single dose of each of the study medications.

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 preferred terms according to MedDRA Version 10.0 and the original term used by the investigator.

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. One subject reported one AE before dosing, which is included in the listing in Appendix 16.2.7 but not in the tables here.

12.2.1 Brief Summary of Events

Six subjects reported a total of 12 treatment emergent adverse events. All events resolved with no sequelae. Nine were mild, two were moderate and one (constipation) was classed as severe. There were no serious adverse events. Nine events were categorised by the Investigator as not related or as unlikely to be related to treatment. Three events (constipation, headache and nausea) were classed as possibly related to treatment. No events were classed as probably or 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 and categorization by MedDRA body system and preferred term of the 12 treatment emergent adverse events that occurred in the study 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 GA0706 (safety population)

		Number of Events / Number of Subjects (% brackets)			
MedDRA Primary SOC	MedDRA Preferred Term	A (n=20)	B (n=20)	C (n=20)	D (n=20)
Gastrointestinal disorders	ABDOMINAL PAIN	0 / 0	1 / 1 (5.0)	0 / 0	0 / 0
	CONSTIPATION	1 / 1 (5.0)	0 / 0	0 / 0	0 / 0
	DYSPEPSIA	0 / 0	0 / 0	2 / 2 (10.0)	0 / 0
	GASTROOESOPHAGEAL REFLUX DISEASE	0 / 0	0 / 0	1 / 1 (5.0)	0 / 0
	NAUSEA	2 / 2 (10.0)	0 / 0	0 / 0	2 / 1 (5.0)
	VOMITING	0 / 0	0 / 0	1 / 1 (5.0)	0 / 0
Infections and infestations	NASOPHARYNGITIS	0 / 0	0 / 0	0 / 0	1 / 1 (5.0)
Nervous system disorders	HEADACHE	0 / 0	0 / 0	0 / 0	1 / 1 (5.0)

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 GA0706 (safety population)

			Number of Events		
MedDRA Primary SOC	MedDRA Preferred Term	Product	Mild	Moderate	Severe
Gastrointestinal disorders	ABDOMINAL PAIN (p=1.0000)	B	1	0	0
	CONSTIPATION (p=0.3858)	A	0	0	1
	DYSPEPSIA (p=1.0000)	C	2	0	0
	GASTROOESOPHAGEAL REFLUX DISEASE (p=1.0000)	C	0	1	0
	NAUSEA (p=1.0000)	A	1	1	0
	NAUSEA (p=1.0000)	D	2	0	0
	VOMITING (p=1.0000)	C	1	0	0
Infections and infestations	NASOPHARYNGITIS (p=1.0000)	D	1	0	0
Nervous system disorders	HEADACHE (p=1.0000)	D	1	0	0

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

One subject experienced one severe adverse event of constipation associated with product A (Gaviscon peppermint liquid in sachets). 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 GA0706 (safety population)

			Number of Events				
MedDRA Primary SOC	MedDRA Preferred Term	Product	Definite	Probable	Possible	Unlikely	None
Gastrointestinal disorders	ABDOMINAL PAIN (p=1.0000)	B	0	0	0	1	0
	CONSTIPATION (p=0.3858)	A	0	0	1	0	0
	DYSPEPSIA (p=1.0000)	C	0	0	0	1	1
	GASTROOESOPHAGEAL REFLUX DISEASE (p=1.0000)	C	0	0	0	1	0
	NAUSEA (p=0.3858)	A	0	0	0	2	0
	NAUSEA (p=0.3858)	D	0	0	1	1	0
	VOMITING (p=1.0000)	C	0	0	0	1	0
Infections and infestations	NASOPHARYNGITIS (p=1.0000)	D	0	0	0	0	1
Nervous system disorders	HEADACHE (p=0.3858)	D	0	0	1	0	0

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

Overall three events in two subjects were considered to have a causal (definite, probable or possible) relationship to study medication. Subject 8 experienced headache and nausea, on the same treatment day, both possibly related to treatment with product A (Gaviscon peppermint liquid in sachets). Subject 9 experienced constipation also possibly related to treatment with product A.

No subject was withdrawn due to any adverse event.

12.2.3 Analysis of Adverse Events

Adverse events occurred in all groups and there were no clinically meaningful differences 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 only performed at prestudy screening, not at any other visit. 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. Out of range values for haematology, biochemistry and urinalysis are shown in tables 12.4.1, 12.4.2 and 12.4.3 respectively.

Table 12.4.1 Out of range haematology values at screening in study GA0706 (Safety population)

Subject	Visit	Parameter	Result	Low Range	High Range	Units
11	Pre-Study	Platelets (X10 9.L-1)	364	169	357	10**9/L
12	Pre-Study	Haemoglobin (g.L-1)	154	120	152	G/L
12	Pre-Study	MCHC (g.L-1)	352	320	350	G/L
13	Pre-Study	Haemoglobin (g.L-1)	154	120	152	G/L
14	Pre-Study	MCHC (g.L-1)	363	323	360	G/L
16	Pre-Study	Platelets (X10 9.L-1)	372	169	357	10**9/L
17	Pre-Study	Haematocrit (L.L-1)	0.358	0.362	0.450	L/L
17	Pre-Study	MCH (pg)	25.8	26.5	33.1	PG
17	Pre-Study	MCV (fL)	77.2	78.3	100.1	FL
18	Pre-Study	Platelets (X10 9.L-1)	362	169	357	10**9/L
19	Pre-Study	MCH (pg)	33.7	27.5	33.6	PG

Table 12.4.2 Out of range biochemistry values at screening in study GA0706 (Safety population)

Subject	Visit	Parameter	Result	Low Range	High Range	Units
1	Pre-Study	GGT (IU.L-1)	7.3	7.8	46.8	IU/L
2	Pre-Study	Creatine Kinase (IU.L-1)	228.1	35.1	227.9	IU/L
2	Pre-Study	Sodium (mmol.L-1)	143.3	135.4	142.5	MMOL/L
3	Pre-Study	Albumin (g.L-1)	53.4	42.0	50.5	G/L
3	Pre-Study	Total Protein (g.L-1)	88.7	66.7	80.8	G/L
4	Pre-Study	ALP (IU.L-1)	257.8	84.6	253.4	IU/L
4	Pre-Study	Calcium (mmol.L-1)	2.23	2.24	2.66	MMOL/L
4	Pre-Study	Cholesterol (mmol.L-1)	5.33	0.0	5.2	MMOL/L
5	Pre-Study	ALP (IU.L-1)	76.4	84.6	253.4	IU/L
5	Pre-Study	Cholesterol (mmol.L-1)	6.45	0.0	5.2	MMOL/L
5	Pre-Study	Creatinine (umol.L-1)	53.8	56.0	92.2	UMOL/L
5	Pre-Study	Glucose (mmol.L-1)	5.7	3.8	5.5	MMOL/L
5	Pre-Study Rpt	Cholesterol (mmol.L-1)	6.33	0.0	5.2	MMOL/L
7	Pre-Study	ALT (IU.L-1)	43.3	8.9	32.6	IU/L
7	Pre-Study	Cholesterol (mmol.L-1)	5.67	0.0	5.2	MMOL/L
8	Pre-Study	GGT (IU.L-1)	3.9	7.8	46.8	IU/L
9	Pre-Study	Albumin (g.L-1)	52.0	39.3	48.5	G/L
9	Pre-Study	ALP (IU.L-1)	265.7	84.6	253.4	IU/L
9	Pre-Study	Cholesterol (mmol.L-1)	5.50	0.0	5.2	MMOL/L
9	Pre-Study	Total Protein (g.L-1)	85.8	66.1	81.1	G/L
11	Pre-Study	Cholesterol (mmol.L-1)	7.32	0.0	5.2	MMOL/L
11	Pre-Study	Sodium (mmol.L-1)	142.8	135.4	142.5	MMOL/L
11	Pre-Study	Triglycerides (mmol.L-1)	2.80	0.0	2.3	MMOL/L
11	Pre-Study Rpt	Cholesterol (mmol.L-1)	7.15	0.0	5.2	MMOL/L
11	Pre-Study Rpt	Cholesterol (mmol.L-1)	6.76	0.0	5.2	MMOL/L
13	Pre-Study	Creatine Kinase (IU.L-1)	231.1	35.1	227.9	IU/L
13	Pre-Study	Creatinine (umol.L-1)	47.6	56.0	92.2	UMOL/L
14	Pre-Study	ALP (IU.L-1)	109.5	124.9	294.3	IU/L
14	Pre-Study	ALT (IU.L-1)	74.6	13.0	67.2	IU/L
14	Pre-Study	GGT (IU.L-1)	84.5	10.0	69.7	IU/L
15	Pre-Study	Cholesterol (mmol.L-1)	6.01	0.0	5.2	MMOL/L
16	Pre-Study	GGT (IU.L-1)	7.3	7.8	46.8	IU/L
17	Pre-Study	ALP (IU.L-1)	276.9	84.6	253.4	IU/L

Subject	Visit	Parameter	Result	Low Range	High Range	Units
17	Pre-Study	Total Bilirubin (umol.L-1)	2.9	3.6	22.0	UMOL/L
18	Pre-Study	Sodium (mmol.L-1)	142.8	135.4	142.5	MMOL/L
20	Pre-Study	Calcium (mmol.L-1)	2.23	2.24	2.66	MMOL/L

Table 12.4.3 Out of range urinalysis values at screening in study GA0706 (Safety population)

Subject	Visit	Parameter	Result	Normal Range
2	Pre-Study	Blood	Trace	Negative
7	Pre-Study	Blood	Trace	Negative
8	Pre-Study	pH	8.5	Negative
9	Pre-Study	Blood	Trace	Negative
12	Pre-Study	Blood	+	Negative
13	Pre-Study	Blood	Trace	Negative
18	Pre-Study	pH	8.5	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 14.3.1. All vital signs and ECG parameters were either within normal ranges or were not considered 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 pilot study investigated the possibility that a stopwatch methodology, normally used to assess onset of action of analgesic products, might be appropriate to determine onset of action of products used to relieve heartburn. Laska and his colleagues advocate the use of two stopwatches, one to measure onset of a predefined clinically significant amount of pain relief and the other to measure "offset" i.e. the moment that the clinically significant amount of pain relief is no longer experienced by the subject.[3] Olsen and her colleagues used a single stopwatch to determine onset of "meaningful" relief" in dental pain patients treated with ibuprofen, ketoprofen, paracetamol or placebo.[2] This study GA0706 adapted the technique in two key respects. Firstly, it used two stopwatches to measure two different sensorial benefits in heartburn - soothing and cooling – not analgesic efficacy. Secondly, no predefined size of effect had to be experienced, only a perceived effect had to be felt by the subject before they stopped the clock. These adaptations were considered to be substantial, and hence this study was a pilot study rather than a full investigation using unsubstantiated adaptations. The results suggest the adaptations are feasible in the indication of heartburn. Subjects did not get confused about which stopwatch to press when, supporting the idea that they were capable of distinguishing between two possible benefits of treatment. Additionally, with each of the two Gaviscon formulations that contained peppermint, the median times to onset of cooling were shorter than the median times to onset of soothing. Peppermint is well known to have a cooling effect, particularly in the oral cavity, and associated compounds such as menthol are known to modulate both warm and cold receptor activity.[4] It is interesting that in this small study, subjects could distinguish such activity more quickly than a soothing benefit and this may be worthy of further consideration when deciding on primary and secondary endpoints in future trials.

The absence of a predefined size of effect was not detrimental to this study. In analgesia, criteria for onset are often controversial, since what constitutes a clinically meaningful effect is debatable.[5] The approach by Olsen, allowing patients to decide a "meaningful" benefit for themselves is appropriate in this respect, since at least the person experiencing the pain decides what level of relief means something to them. However the approach still has to allow for considerable variation in response. Requesting that subjects stop the clock whenever they first perceive any effect, (or sensorial benefit, as in this study), rather than a clinically meaningful effect, may reduce the variation somewhat. This then leaves open to debate the issue of whether onset can be claimed, even if the effect size seen at that time is clinically smaller than desirable in an effective product. Given that the placebo "effect" is well documented in many areas of medicine, it is logical that onset can apply to placebo as well as to active ingredients and that the overall size of the effect is not important for determining when that effect starts to be perceived.

Black et al suggested that minimal criteria make it difficult to distinguish between active and placebo.[5] However, in this pilot study, it is very clear that the negative control product can clearly be distinguished from the Gaviscon products. Subjects simply did not stop the clock when they had taken the inactive sublingual tablet and on the vast majority of occasions, onset times with this control were censored at 30 minutes – 16/20 (80%) were censored for soothing and 17/20 (85%) were censored for cooling. These results are comparable to those seen in the placebo group in the dental pain study reported by Olsen and her colleagues, where the majority of the onset times were censored at six hours, only 35.9% of subjects achieving meaningful relief before then, leaving 74.1% who did not.[2]

Another aspect of interpreting these results is the presence of any bias resulting from the partial blinding of the study. It was felt to be important that the negative control was indeed truly negative with no possibility of providing soothing or cooling effects. However, using a liquid formulation as a negative control was thought likely to result in some soothing or cooling. This made blinding problematic. It could be argued that since subjects knew the sublingual tablet was an inactive product, that knowledge brought bias to the study. However, since the study was examining a technique to measure onset, rather than efficacy per se, then it can also be argued that this does not matter, since the results show that when the subject did not perceive a benefit, they did not stop the clock. This suggests the approach is valid. The bias may have affected sensitivity, but assisted in showing the validity of the methodology.

The rationale behind measuring speed of onset was to determine if product support for a claim of "instantly" soothing or cooling sensorial benefit could be supported on the basis of objective methodology. The protocol defined instantly *a priori* as soothing or cooling occurring within five seconds, based on advice from the PAGB. Nothing in the results of this study suggests that any of the treatments resulted in an "instant" sensorial effect based on this definition. However, when the subjects were asked if they would describe any benefits they had felt from the product as "instant", at least 60% stated that they had for each Gaviscon test product. This is a similar situation to that discussed earlier in terms of clinical significance for analgesia. The basis for the PAGB definition of "instant" as five seconds is not known, but clearly when left to decide for themselves, subjects perceive "instant" to be different to that time. It would be possible to substantiate what subjects deem to be instant, by using the group mean time to onset, calculated from only those subjects who stated they would describe a sensorial effect (either soothing or cooling) as instant on a subjective basis. This time could then be used as the basis for the description of "instant" in future trials. Alternatively, a claim of "instant" could be supported subjectively on the basis that if a subject describes a benefit as "instant" for themselves, that is appropriate. This study did not examine the nature of any benefit the subject described as "instant" and that too could be examined in future trials to support more specific benefit claims.

13.2 Conclusion

The negative control performed as expected using the stopwatch methodology. In absolute terms, cooling benefits associated with the three Gaviscon formulations were perceived more quickly than soothing benefits. Using the objective stopwatch methodology, no subject experienced an "instant" sensorial benefit, where "instant" was predefined as being within 5 seconds. Using questioning, more than half of the subjects in each treatment group felt they experienced "instant" benefits when "instant" was left to each subject to define. Future studies need to consider blinding, the real likelihood of any placebo benefit and whether objective or subjective methodology is more likely to provide the required claims support. This study did provide data on which future sample sizes for both approaches can be based. All three Gaviscon liquid formulations were well tolerated.

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 Vital Signs

Pre and post study vital signs are presented in table 14.3.1 below:

Table 14.3.1 Vital signs in study GA0706 (Safety population)

Variable		Pre-Study	Post-Study	Change
SITTING SBP	N	20	20	20
(MMHG)	MEAN	123.6	123.6	0.1
	SD	17.7	15.0	11.4
	MIN	98	94	-16
	MEDIAN	117	125	-3
	MAX	153	146	27
SITTING DBP	N	20	20	20
(MMHG)	MEAN	71.1	70.5	-0.6
	SD	10.1	9.3	6.2
	MIN	54	51	-7
	MEDIAN	72	71	-3
	MAX	87	88	14
SITTING	N	20	20	20
PULSE (BPM)	MEAN	66.7	69.0	2.3
	SD	8.1	8.5	9.6
	MIN	55	54	-19
	MEDIAN	69	70	1
	MAX	84	88	17
TEMP. (C)	N	20	20	20
	MEAN	36.48	36.5	-0.02
	SD	0.52	0.38	0.47
	MIN	35.1	36.0	-1.2
	MEDIAN	36.6	36.5	0.0
	MAX	37.2	37.2	0.9

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) Laska EM, Siegel C. Assessing the onset of relief of a treatment for migraine. Cephalalgia 2000: 20:724-731.
2) Olsen NZ, Otero AM, Marrero I et al. Onset of analgesia for liquigel ibuprofen 400mg, acetaminophen 1000mg, ketoprofen 25mg and placebo in the treatment of postoperative dental pain. J Clin Pharmacol 2001; 41: 1238-1247.
3) Laska EM, Siegel C, Sunshine A. Onset and duration: measurement and analysis. Clin Pharmacol Ther 1991; 49(1): 1-5.
4) Eccles R. Menthol and related cooling compounds. J Pharm Pharmacol 1994; 46: 618-630.
5) Black P, Max MB, Desjardins P, Norwood T, Ardia A, Pallotta T. A randomised, double-blind, placebo-controlled comparison of the analgesic efficacy, onset of action and tolerability of ibuprofen arginate and ibuprofen in post operative dental pain. Clin Ther 2002; 24: 1072-1089.

APPENDIX 16.1 STUDY INFORMATION

This section consists of 12 appendices with their own cover sheets

APPENDIX 16.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

In addition to this cover sheet, this appendix contains:

- Final protocol, dated 13 November 2007 (46 pages)
- Final protocol Approval Signatures (1 page)
- Final protocol Investigator Acceptance Signature (1 page)

Reckitt Benckiser

1 STUDY PROTOCOL TITLE PAGE

EudraCT Number:	2007-005821-31
Study Number:	GA0706
Protocol Title:	A single-centre randomised, partially blind, single dose, crossover pilot study investigating the use of stopwatches to assess the onset of action of soothing and cooling of Gaviscon Peppermint liquid, Double Action Gaviscon liquid, Gaviscon Advance liquid, and a control in subjects with heartburn following a refluxogenic meal.
Short Protocol Title:	Gaviscon Instantly Soothing Pilot Study
Protocol Date:	13th November 2007
Version:	Final
Phase:	IV

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

Telephone No: +44 (0) 1482 326151; Fax No: +44 (0) 1482 582172

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Abbreviation in Full
AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CV	Curriculum Vitae
EC	Ethics Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
RB	Reckitt Benckiser
OTC	Over the Counter
SAE	Serious Adverse Event
SDV	Source Data Verification
kg	kilogram
ml	millilitre
mg	milligram
ANOVA	Analysis of Variance
IMSU	Investigational Material Supply Unit
PAGB	The Proprietary Association of Great Britain
ITT	Intention to Treat

4 INVESTIGATORS AND ADMINISTRATIVE STUCTURE

4.1 Reckitt Benckiser Details

Name	Position	Address & Contact Numbers
Dr K Sarratt	RB Clinical Project Manager	Reckitt Benckiser Healthcare Ltd, Dansom Lane, Hull HU8 7DS. Tel +44 1482 582397
Dr P Berry	RB Study Physician	Reckitt Benckiser Healthcare Ltd, Dansom Lane, Hull HU8 7DS. Tel +44 7734 056121
Mr J Sykes	RB Statistician	Reckitt Benckiser Healthcare Ltd, Dansom Lane, Hull HU8 7DS. Tel +44 1482 582895
	Study Monitor	

The name and address of the study monitor will be provided in the Initiation Visit report.

4.2 Investigational Site

This study will be conducted at Simbec Research Ltd, Merthyr Tydfil, Mid Glamorgan, CF48 4DR. Tel 01443 690977

- Dr P M Dewland will be the Principal Investigator responsible for conducting the study as well as making all trial-site related medical decisions.

4.3 Laboratory

4.3.1 Clinical Laboratories

The Clinical unit of Simbec Research, based at Simbec's premises in Merthyr Tydfil, will conduct the relevant analyses required for this study.

4.3.2 Pharmacokinetic Analysis Laboratory

Pharmacokinetic analyses are not applicable for this study.

5 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) prescribable presentations/formulations to offer consumer choice of flavours and dosing formats. A key claim for the brand is based on consumer perception of the product being able to deliver an "instantly soothing" effect. To date, this wording has been supported by market research data. Reckitt Benckiser Healthcare UK wishes to strengthen the basis for the "instantly soothing" claim in order to meet the more stringent regulatory requirements for licensed medicinal products. As per the advice of the Proprietary Association of Great Britain (PAGB), "instantly" is defined as within five seconds.

To support this claim, it is considered necessary to assess speed of onset in a prospective, randomised, sensorial based clinical study. Such a design holds scientific and medical credibility by helping to control variation and bias, and generates data of an appropriate standard for claims substantiation. The study will be partially blinded as the control and Gaviscon treatments differ in physical form (sublingual tablet vs liquid).

A methodology using stopwatches to assess onset of action has been described in migraine and in post operative dental pain.[1,2] The current study will adopt this technique to assess the consumer perceived onset of two attributes (soothing and cooling) of Gaviscon. However, as the methodology has not been used in this indication previously, it is considered appropriate to conduct a pilot study to determine if the methodology is likely to be helpful in supporting the required claim and to provide a basis for sample size calculation for future studies.

A control, which in this case is a sublingual tablet, has been included in this study on an open label basis to show the validity of the methodology. By using a control that is expected to have no effect, it will demonstrate that an oral product that is not swallowed will not produce a soothing or cooling effect. The choice of a sublingual tablet as a control is appropriate for this study because it is 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.

The population to be studied is a sample of the community based population who has the tendency to suffer from heartburn symptoms following some meals and has access to OTC medications like Gaviscon. In this sensorial based study, the subjects will be provided with a refluxogenic meal to induce the symptoms of heartburn. The Gaviscon liquid products will be spoon administered by a member of Simbec staff, at a 10ml dose and by an oral route as specified in the product licence.

The potential risks to subjects taking part in the present study are considered to be low. The active ingredients and the adverse reactions that occur very rarely as a result of taking Gaviscon liquid products (<1/10,000) are as follows:

1. Sodium alginate – hypersensitivity; subjects sensitive to the ingredient may develop allergic manifestations such as urticaria or bronchospasm, anaphylactic or anaphylactoid reactions

2. Sodium bicarbonate/sodium hydrogen carbonate – hypersensitivity; subjects sensitive to the ingredient may develop allergic manifestations such as urticaria or bronchospasm, anaphylactic or anaphylactoid reactions; increased plasma sodium levels especially for those with renal and cardiovascular conditions on a highly restricted salt diet

3. Potassium hydrogen carbonate – hypersensitivity; subjects sensitive to the ingredient may develop allergic manifestations such as urticaria or bronchospasm, anaphylactic or anaphylactoid reactions; increased plasma potassium levels for those with renal and cardiovascular conditions on a highly restricted salt diet

4. Calcium carbonate – hypersensitivity; subjects sensitive to the ingredient may develop allergic manifestations such as urticaria or bronchospasm, anaphylactic or anaphylactoid reactions; high doses of calcium may cause alkalosis, hypercalcaemia, acid rebound, milk alkali syndrome or constipation

Rarely, more serious reactions have been reported. The potential benefit of the subject taking part in this study is experiencing "instantly soothing" and cooling effects during their heartburn episode when they ingest one of the Gaviscon liquid products. For this reason, the risk benefit balance for the current study is considered to be acceptable.

There are no potential risks to subjects using the control.

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

6 RATIONALE

The study is being conducted to scientifically and medically support the claim of the product(s) being able to deliver "instantly soothing" and cooling effects as well as determine if the use of the stopwatch technique is suitable in assessing the onset of action of products to provide these effects. A control is being included in the study design to show the validity of the model and to enable participants to clearly

distinguish between a soothing, cooling and no sensation feeling in the throat/oesophagus (foodpipe).

7 OBJECTIVES

The primary objective of this study is to pilot the stopwatch technique for determining the onset of action of products that provide a perceived soothing effect in the throat/oesophagus (foodpipe) during heartburn.

The secondary objectives of this study are to evaluate the time to first perceived cooling effect in the throat/oesophagus (foodpipe); the description of an "instant" benefit from the product; the ability of the product to make the mouth/throat feel fresher; and the subject's willingness to use the product again.

8 STUDY DESIGN

8.1 Study Endpoints

8.1.1 Primary Endpoints

The primary efficacy endpoint is the time to first perceived soothing effect in the throat/oesophagus (foodpipe) using a stopwatch.

8.1.2 Secondary Endpoints

The secondary efficacy endpoints are:

- Time to first perceived cooling effect in the throat/oesophagus (foodpipe) using a stopwatch
- Would you describe any benefit you felt from this product as "instant" (yes/no)?
- Did the product make your mouth/throat feel fresher (yes/no)?
- Willingness to use the product to treat heartburn again (yes/no)

8.2 Design Summary

This will be a single-centre, randomised, partially blind, single dose, crossover pilot study in subjects who display symptoms of heartburn following a refluxogenic meal.

8.3 Subject Numbers

This is a pilot study intended to provide sample size information for a future study. It is estimated that 20 subjects will provide sufficient data to predict the sample size for the future study.

8.4 Study Duration

It is estimated that it will take 3 weeks to recruit the required number of subjects. It is anticipated that the clinical phase of this study will commence in January 2008, with completion of the clinical phase by February 2008.

8.5 Subject Commitment to the Study

The duration of each subject's participation in the study will be approximately 6 weeks (from screening visit to post-study visit). The screening visit will be followed by four separate treatment visits, each of which will require the subjects to consume a standardised refluxogenic meal. There will be a 2-7 day(s) washout period between the treatments, in which subjects should avoid food which may cause them to reflux. In addition, subjects, during this time should not take any acid reflux medication. The post-study visit will occur 3-7 day(s) after the final treatment visit.

8.6 End of Study

The end of the study is defined as the last visit of the last subject.

RB will notify the regulatory authority, and Simbec will notify the ethics committee within 90 days of the end of the study (within 15 days if the study is ended prematurely).

9 STUDY POPULATION

9.1 Inclusion Criteria

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

1) Age: ≥18 years ≤80 years
2) Sex: Male and female subjects are eligible for entry.
3) Status: Members of the Simbec Volunteer Panel who state (self-rated) that they have 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 have given written informed consent.

9.2 Exclusion Criteria

Subjects to whom any of the following conditions apply must be excluded:

1) Those who have suffered a recent, significant unexplained weight loss of 6-7kg in the last 6 months.

2) Those who have 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 have 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.
8) Those who have taken proton pump inhibitors within the previous 48 hours prior to screening.
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 or potassium bicarbonate.
11) Those who are receiving treatment for their upper gastrointestinal problems or gastro-oesophageal reflux disease from their GP.
12) Those unable in the opinion of the Investigator to comply fully with the study requirements.
13) Those currently participating in a clinical study or who have participated in any other clinical study within the last 30 days.
14) Those who have previously participated in this randomised study.
15) Woman of childbearing potential, who are 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 [should the subject become sexually active, she must agree to use a double barrier method] or condoms/diaphragm and spermicide). A woman of childbearing potential is defined as any female who is less than 2 years post-menopausal or has not undergone an hysterectomy or surgical sterilisation, e.g. bilateral tubal ligation, bilateral ovariectomy (oophorectomy).
16) Those who are on steroids or non-steroidal anti-inflammatory drugs.
17) Those who are diabetics.

10 STUDY METHODOLOGY

10.1 Recruitment of Study Subjects

Subjects will be recruited from the Simbec database of volunteers who respond to direct advertising for the study. The advertising will make it clear that a response to

the advert is voluntary as is participation in the study. The advert will also specify that subjects should suffer from heartburn following meals.

10.2 Study Visits/Assessments

A subject enters a study when he/she has signed the consent form before the clinical phase of the study begins.

The schedule for assessments for this trial is summarised in the following flowchart:

Flowchart for study GA0706

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 (by stopwatch)			X	X	X	X	
Onset of first perceived cooling (by stopwatch)			X	X	X	X	
Mouth/throat freshness			X	X	X	X	
Instant Benefit			X	X	X	X	
Willingness to use product again			X	X	X	X	
Adverse Events			X	X	X	X	X

10.2.1 Pre-study Screening Visits

10.2.1.1 Pre-study Screening Visit 1

At the first screening visit, potential participants will be asked to provide written consent for the screening against the inclusion and exclusion criteria. Consenting subjects will then be allocated a screening number, in which information on demographics, vital signs (including a 12-lead ECG), and medical history, will be recorded, and laboratory investigations conducted.

Subjects who meet these initial requirements will see a physician who will discuss the purpose and nature of the study with them. The physician must then sign to confirm that the subject has been provided with a copy of the Consent forms and Information Sheets, and that a full explanation of the study had been given. Each subject must sign and date their Consent form before any study specific procedures are conducted (see Section 15.2).

10.2.1.2 Clinical Assessments Performed at Screening Visit 1

The following screening assessments will be conducted/recorded:

Demographic data

- sex
- race (categorised as: Caucasian, Asian, Afro-Caribbean and Other)
- date of birth
- height (cm)
- weight (kg)
- body mass index (kg/m^2)
- smoking/alcohol/drugs of abuse history/use

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 (°C)
- 12-lead ECG

Medical history and current status

- primary diagnosis
- duration of symptoms
- medical history and current status

Medication and therapy history

- current medication usage

- therapy taken in the previous 2 days will be recorded

Physical examination
- a standard physical examination will be conducted

Pregnancy testing
- women of child-bearing potential will undergo serum pregnancy testing

Experience symptoms of heartburn following some meals (self-rated)

Laboratory investigations
- details are provided in section 12.2. Includes haematology, biochemistry, urinalysis, drugs of abuse and pregnancy testing for females

10.2.1.3 Pre-study Screening Visit 2

After at least 48 hours of screening visit 1, eligible potential participants will be invited to attend a second screening visit at which they will be given a refluxogenic meal. Following the meal, subjects will be asked to evaluate the severity of their heartburn symptoms (if any) over a period of 60 minutes. Those who confirm their heartburn symptoms to be of at least moderate severity (self-rated) at any time within the 60 minute period will be invited to progress into the dosing phase of the study on a subsequent visit. At the end of the 60 minute observation period, (or earlier if requested) all subjects will be provided with a 10ml dose of Maalox, if necessary, to relieve their symptoms.

10.2.1.4 Clinical Assessments Performed at Screening Visit 2

- Time of starting refluxogenic meal using the clock
- Time of completing the refluxogenic meal using the clock
- Time start to experience heartburn symptoms of at least moderate severity using the clock
- Severity rating of heartburn after eating a refluxogenic meal
    - Self-rating will be reported as none, mild, moderate or severe

10.2.2 Treatment Visits

10.2.2.1 Treatment Visit 1

There will be at least a 48 hour window between the second screening visit and the subject attending Simbec for the first treatment visit.

On day 1 of treatment visit 1, subjects will report to Simbec Research Centre at approximately 08.00. They will individually affirm that they have taken no prohibited medication (medicines for relief of heartburn) and no alcohol within the previous 48 hours of admission. They will be asked if they have experienced any adverse events since their previous visit to the centre. Subjects will provide a urine sample, which will be analysed for the presence of ethanol and drugs of abuse as well as pregnancy for female subjects. Test results and any adverse events will be entered into each subject's CRF.

At approximately 09.00 subjects will be given a light breakfast and will then be required to fast for at least 4 hours. At around 13.00 subjects will be provided with a standardised refluxogenic meal, containing 60% fat and asked to lie down after consumption. Subjects will be advised to attract the attention of the study nurse when they experience at least moderate symptoms of heartburn (on a self-rated categorical scale of none, mild, moderate, and severe). At this point, the subject will be dosed with the randomised treatment allocated for the visit. However, if the subject does not experience at least moderate heartburn, within 60 minutes of finishing the refluxogenic meal, he/she will not be treated with test medication. Subjects who are not treated with the test medication will be required to stay on site for the following 30 minutes before being able to leave. Subjects who do not achieve moderate heartburn on one or more of the treatment visits will complete the study with the remaining visits (total of 4 treatment visits) for further refluxogenic meal challenges.

If the subject experiences heartburn symptoms of at least moderate severity, they will be spoon treated with either 10ml of the treatment or given the control assigned to them under the randomisation list. Subjects will be dosed in a sitting position. The actual time of dosing will be noted and recorded in the subject's CRF and the stopwatches started. Participants will be provided with two stopwatches, which will be started by the study staff at the time the subject is dosed with the treatment. One of these will be 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 will be instructed (before treatment is administered) to stop the soothing effect stopwatch when they first perceive any soothing effect and to stop the cooling effect stopwatch when they first perceive a cooling effect. The treatment study period will be 30 minutes. Subjects will be asked 5 minutes into the treatment study period if they felt an instant benefit from the product. At the end of the treatment study period, subjects will be asked whether or not they would be willing to use the product again, if they experienced any adverse effects, and if their mouth/throat felt fresher after the treatment.

10.2.2.2 Clinical Assessments at Treatment Visit 1

The following will be recorded at treatment Visit 1:

- Subject's confirmation that they have not taken prohibited medication or alcohol within the previous 48 hours
- Results of pregnancy testing of female subjects
- Results of tests for drugs of abuse and ethanol screen
- Any adverse events that have occurred since the subject's last visit to the centre and any that occur while the subjects are at the centre
- Time of starting refluxogenic meal using the clock
- Time of completing refluxogenic meal using the clock
- Time when subject indicates that experiencing heartburn symptoms of moderate severity, using the clock
- Time of treatment using the clock
- Time to first perceived soothing effect in the throat/oesophagus (foodpipe) post treatment up to 30 minutes using the stopwatch
- Time to first perceived cooling effect in the throat/oesophagus (foodpipe) post treatment up to 30 minutes using the stopwatch
- Answer to the question "Would you describe any benefit you felt from this product as 'instant' (yes/no)?" post treatment at 5 minutes
- Answer to the question "Did the product make your mouth/throat feel fresher (yes/no)?" post treatment at 30 minutes
- Answer to the question "Willingness to use the product to treat heartburn again (yes/no)" post treatment at 30 minutes
- Any adverse events that have occurred post treatment at 30 minutes only

10.2.2.3 Treatment Visits 2, 3, and 4

The clinical and data collection procedures for treatment Visits 2, 3, and 4 will be exactly the same as that described for treatment Visit 1, with the exception that each

subject will receive an alternative treatment according to the randomisation schedule and there will be a 2-7 day(s) washout period between treatments.

10.2.2.4 Clinical Assessments at Treatment Visits 2, 3, and 4

The clinical data gathered for treatment Visit 1 will be exactly the same as that for treatment Visits 2, 3, and 4.

10.2.3 Post Study Follow Up Visit

Subjects will return to Simbec Research Centre for a post study follow-up visit 3-7 days after treatment Visit 4. They will be asked if they have experienced any adverse effects since their last treatment. Subjects' vital signs will be recorded and they will undergo a physical examination.

10.2.3.1 Clinical Assessments at the Post Study Follow Up Visit

The following assessments will be conducted/recorded:

- 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 (°C).
- Physical examination
- Review of concomitant medication
- Review of adverse events

10.3 Efficacy Assessment

Please refer to Sections 10.2.2.1 and 10.2.2.2 for the methods and timing for the assessments.

10.4 Study Specific Supplies

RB will provide the study drug supplies as well as the stopwatches as detailed in Section 11.

10.5 Unscheduled Visits

If unscheduled visits occur, the Investigator must record, in the subject's case report form:

- any adverse events
- concomitant therapy changes
- withdrawal (if deemed appropriate)
- any clinical assessments deemed appropriate for the clinical care of the subject

Unscheduled visits should not alter the timing of the routine study schedule.

10.6 Subject Withdrawal Criteria

The Investigator may withdraw the subject from the study at any time. Reasons for removing a subject from the study include, but are not limited to:

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

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

If a subject is withdrawn prematurely from the study, the following assessments will 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 (°C).
- Physical examination
- Review of concomitant medication
- Review of adverse events

10.6.1 Procedures for Replacing Subjects who are Withdrawn

Withdrawn subjects will not be replaced.

10.7 Additional Care of Study Subjects Following Completion of the Study

Subjects who experience adverse events at the end of the study, or experience the onset of an event after the final visit will be followed up as described in Sections 10.5 and 10.6.

No other additional care of study subjects will take place following completion of the study. The treatment of the patient's condition will follow normal clinical practice.

10.8 Treatment Compliance

Simbec personnel (Physician or appropriately trained staff) will administer 10ml of each liquid treatment to the subject using a spoon. Any subjects who will not comply with this form of administration will be withdrawn from the study.

11 STUDY TREATMENTS

11.1 Identity of Investigational Medicinal Product(s)

The following products will be supplied:

Product A: Gaviscon Peppermint liquid in sachets, contains 500mg sodium alginate, 267mg sodium bicarbonate, and 160 mg calcium carbonate per 10ml dose, 10ml suspension in sachet, NL 15334

Product B: Gaviscon Advance Aniseed Flavour, contains 1000mg sodium alginate and 200mg potassium bicarbonate per 10ml dose, 300 ml suspension in bottle, PL 00063/0097

Product C: 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

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: 397280

All products including the stopwatches will be supplied by Reckitt Benckiser Healthcare UK Ltd, Dansom Lane, Hull HU8 7DS, UK. The Gaviscon products will be used as study drugs along with the control.

All drug supplies will be packed and labelled to GMP standards by the Investigational Material Supply Unit (IMSU), Reckitt Benckiser Healthcare UK Ltd, Dansom Lane, Hull HU8 7DS, UK. Market packs will be used. The Gaviscon

liquid products will be supplied as blinded and the control will be open label. They will be shipped directly from the IMSU to Simbec Research.

11.2 Treatment Allocation

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

In order to maintain the partial blinding of the study, the Gaviscon treatments (Test products A, B and C) will have a blocked-out label, and will be labelled only with the blinded treatment codes X, Y and Z. RB Clinical Trials Supply Unit will hold the master code for the allocation of codes X, Y and Z to Test products A, B and C. The randomised treatment allocation schedule will be an open list and will be prepared using the blinded treatment codes X, Y and Z (and D for the control). At each visit the Investigator will dispense the treatment allocated for the subject/visit by reference to the randomisation list. Since this a partially blinded study and the Gaviscon liquid products are essentially the same in formulation and obviously different from the control, a code break in the event of an emergency is unnecessary. However, in the event of a SAE, the Investigator should withdraw the subject from the study, document the details of the event in the subject's case report form and promptly inform the RB Clinical Project Manager.

RB will break the blinded treatment codes only after all data queries have been answered and the database has been locked.

11.3 Dosage Instructions

Each treatment will be given as a single dose. At each treatment visit, each subject will be administered 10ml of the assigned Gaviscon liquid product orally from a spoon or be given one sublingual tablet from a dosing cup, according to the randomisation list. Each treatment dose will be administered. For the Gaviscon liquid treatments from the bottle, a fresh bottle will be opened at each treatment visit; however, more than one subject will be dosed from the bottle. For the Gaviscon liquid treatment from the sachet, the 10ml from the sachet will be placed on the spoon and then administered. For the control, each group (two groups of 10 subjects) will be dosed from one bottle and told to place the tablet underneath the tongue.

11.4 Packaging

For Gaviscon Peppermint liquid in sachet:

- 10ml
- 48 sachets, each containing 10ml of liquid, will be provided, sufficient to treat 20 subjects in the randomised, partially blind phase.

For Gaviscon Advance liquid and Gaviscon Double Action liquid:

- 300ml
- 20 bottles, each containing 300ml of liquid, will be provided, sufficient to treat 20 subjects in the randomised, partially blind phase.

For the Control:

- 30 tablets
- 4 bottles, each containing 30 tablets, will be provided, sufficient to treat 20 subjects in the randomised, open label phase

11.5 Labelling

11.5.1 Investigational Product(s)

The label on the Study Medication and control will contain the following information:

For clinical trial use only, not for sale

STUDY MEDICATION [10ml, orally] *OR* [1 tablet, sublingually]

Study No.: GA0706

Product: X, Y, Z or D

Expiry date:

Storage: Store at room temperature, not above 30°C. Do not refrigerate.

Batch number:

Keep out of reach and sight of children

Directions for use: Shake well before use. Administer 10ml of liquid using the provided spoon. *OR* Administer one tablet to be placed underneath the tongue.

Investigator: Dr Peter M Dewland, Simbec Research Ltd, Merthyr Tydfil, CF48 4DR, Tel 01443 690977

Each subject will receive an emergency card, which will have the investigator site's name, address & telephone number, and state that the subject is taking part in a clinical study with the study number.

Since this is a partially blind study, each bottle and sachet will have a blocked-out label and the open label control, will contain the product letter. Documentation for the batch number will be kept in the IMSU.

11.5.2 Supplementary Medication

The rescue medication during the second screening visit will be Maalox suspension (PL 00050/5002R), which will be supplied and administered by Simbec.

11.5.3 Outer Container Labels

The label for the box containing all drug supplies for Simbec will be packed in an appropriate container and shipped to the Pharmacy contact at Simbec Research, Dr Christopher Jeans.

- For Clinical Trial Use Only
- Study centre's address
- Sponsor centre's address

11.6 Accountability of Investigational Medicinal Product(s)

The Investigator will keep all study medication in a pharmacy or a secure storage facility, accessible only to those individuals authorised by the Investigator to dispense the medication.

The Investigator or designated individual will maintain an inventory. This will include the description and quantity of study drug received during the course of this study, as well as a record of the materials that are dispensed and returned (how much, to whom, and when). This inventory ("IMP Dispensing Log") will be subject to review by the study monitor during monitoring visits.

The Investigator agrees not to supply study drug to any person except study personnel and subjects in this study.

The study drug and control should be stored at room temperature below 30°C. It should not be refrigerated or frozen. The pharmacy has a fully automated air

conditioning system, which is set to control the temperature between 15 and 25°C, and is monitored by daily readings of maximum/minimum thermometers placed in various locations throughout the pharmacy.

11.7 Disposal of Unused Investigational Medicinal Product(s)

Unused IMP will be returned to the RB IMSU. The Investigator agrees to conduct a drug supply inventory, to record the results of this inventory ("IMP Removal from Site" form) and to return it and all original drug containers, whether empty or containing study medication and supplementary medication, to RB at the end of the study.

RB will arrange for the appropriate and timely destruction of all returned study medication following the end of the study.

11.8 Concomitant Therapies

Concomitant therapies are 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 receives during the course of the study.

The Investigator will record 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 should also be recorded on this form. Any changes in concomitant therapy during the study will be documented, including cessation of therapy, initiation of therapy and dose changes.

11.9 Prohibited Therapies

The use of the following treatments will not be 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 use these therapies during the study will be withdrawn from the study.

No drinking or eating will be allowed other than what is provided by Simbec during the treatment visits. No alcohol will be allowed 48 hours prior to the treatment visits. There will be no smoking allowed during the treatment visits.

12 SAFETY ASSESSMENTS

12.1 Adverse Events

12.1.1 Adverse Event Definitions

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment: an adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

Adverse Reaction to an Investigational Medicinal Product (AR): All untoward and unintended responses to an investigational medicinal product related to any dose administered.

Comment: all adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest causal relationship.

Serious Adverse Event (SAE): Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Comments: Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Examples of such events are:

- intensive treatment in an emergency room or at home for allergic bronchospasm

- blood dyscrasias or convulsions that do not result in hospitalisation
- development of drug dependency or drug abuse

Unexpected Adverse Reaction: An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics (SmPC) for an authorised product).

Comment: When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on patient/event outcome or action criteria.

12.1.2 Information to be Collected on Adverse Events

Each adverse event will be recorded according to the criteria given below "Relationship to study medication" must be determined by the Investigator (if medically qualified) or by a medically qualified Co-investigator.

Variable	Category	Definition
Nature of AE		Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Date AE started		The date on which the AE started. For recurrent AEs, this is the date of onset of the first episode.
Time AE started		The time at which the AE started. For recurrent AEs, this is the time of onset of the first episode.
Date of change in severity of AE		The date on which the AE changed in severity. This date equates to the finish date of the old severity and the onset date of the new severity.
Time of change in severity of AE		The time at which the AE changed in severity. This time equates to the finish time of the old severity and the onset time of the new severity
Severity		Severity will be determined by the Investigator. For symptomatic AEs the following definitions will be applied but medical experience and judgement should also be used in the assessment of severity.
	Mild	The AE does not limit usual activities; the subject may experience slight discomfort.
	Moderate	The AE results in some limitation of usual activities; the subject may experience significant discomfort.
	Severe	The AE results in an inability to carry out usual activities; the subject may experience intolerable discomfort or pain.
Actions taken	None	No action was taken in relation to this AE.
	Study medication dose changed	The dose of study medication [or therapy] was changed due to this AE, i.e. increases, decreases, or temporary discontinuations.
	Study medication permanently discontinued	The study medication [or therapy] was permanently discontinued due to this AE
	Symptomatic therapy	Symptomatic therapy was added or changed due to this AE
	Subject hospitalised or hospitalisation prolonged	The subject was hospitalised or hospitalisation was prolonged due to this AE
	Other action (specify)	Other action was taken due to this AE, e.g. diagnostic tests, laboratories and procedures.

Variable	Category	Definition
Relationship to study medication	Definite	An AE that follows an anticipated response to the study medication; and that is confirmed by both improvement upon stopping the study medication (dechallenge), and reappearance of the reaction on repeated exposure (rechallenge)
	Probable	An AE that follows a reasonable temporal sequence from administration of the study medication, that is an anticipated response to the study medication; and that could not be reasonably explained by the known characteristics of the subject's clinical state or concomitant therapy
	Possible	An AE that follows a reasonable temporal sequence from administration of the study medicines; that may be 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 does not follow an anticipated response to the study medication; which may be attributable to other than the study medication, and that is more likely to have been produced by the subject's clinical state or concomitant therapy.
	None	An AE that is known beyond all reasonable doubt to be caused by the subject's state or concomitant therapy.
Is the AE serious?	Fatal Acute life threatening Required or prolonged hospitalisation Resulted in persistent or significant disability or incapacity resulted in congenital malformation or anomaly	See protocol section 13.1.
Date resolved		The date on which the AE ceased to be present.
Time resolved		The time at which the AE ceased to be present or changed in severity. For recurrent AEs, this is the time that the last occurrence of the AE ended or changed in severity. The time for changes in severity is derived.
Outcome	Ongoing	The AE still persists
	Resolved	The AE is resolved
	Permanent residual effect	The subject is stabilised, but with sequelae from this AE
	Subject died	The subject died whilst this AE was ongoing or as a result of it.

Variable	Category	Definition
Has the subject ever experienced this AE before?	Yes/No	A query confirming whether the subject has a previous medical history of the AE at any time before entering into the study. If the subject has experienced this AE before, brief details should be given under additional information.
Additional information		Additional information regarding the AE

12.1.3 Procedure for Reporting Adverse Events

All adverse events that arise after the subject has received medication will be recorded in the subject's case report form. Adverse events can be reported spontaneously by the subject or in response to questioning or observation by the Investigator or be a significant laboratory abnormality.

The Investigator will ask the subject: "Are you experiencing any symptoms or complaints?" at the baseline visit and "Have you had any symptoms or complaints since the last visit?" during the study. The investigator will also ask at the post-study visit.

Assessments of the relationship of adverse events to study drug must be made by a physician.

12.1.4 Procedure for Reporting Serious Adverse Events

In the event of a serious adverse event, the Investigator should telephone the RB Clinical Project Manager, within 24 hours of knowledge of the event. The name and contact number of the RB Clinical Project Manager will be provided to the Investigator as part of the Clinical Trial Site File.

The Investigator should not break the randomisation code except when it is necessary to do so in order to ensure the subject receives appropriate medical care (see Section 11.2).

The Investigator must inform his/her local ethics committee/institutional review board of all serious adverse events occurring in the study.

12.1.5 Reporting to Regulatory Authorities

Serious and non-serious adverse events will be reported to the appropriate regulatory authorities by RB, in accordance with the authorities' requirements.

12.1.6 Follow-up of Subjects Experiencing Adverse Events upon Completion of / Withdrawal from the Study

All serious adverse events, and those which cause premature withdrawal of the subject from the study, that have not resolved by the end of the study, will be followed up by the Investigator until resolution or until the Investigator believes there will be no further change. This may involve the subject making additional visits to the centre.

All other adverse events (including clinically significant laboratory abnormalities) will be followed up wherever possible to resolution or until the Investigator believes there will be no further change, whichever is the earlier.

The minimum data required are the final outcome and date, which may be obtained by the Investigator in a documented telephone conversation with the subject or subject's GP.

12.1.7 Procedures for Subjects Experiencing Onset of Adverse Events After Completion of the Study

If a subject experiences the onset of a serious adverse event within 24 hours of completion of treatment 4, and, in the opinion of the Investigator, it is associated with the study, it will be followed up and reported as described in section 12.1.4.

12.1.8 Treating Overdose

The dose of Gaviscon to be taken by subjects participating in this study is substantially less than that required to cause overdose. Study drug will be administered to subjects by trained Simbec personnel in strict accordance with the protocol. Subjects will have no access to study drug other than that provided at dosing. Therefore no guidance on the treatment of overdose is provided.

12.1.9 Pregnancy

If a subject is found to be pregnant after being dosed with study medication,

- promptly notify RB Clinical Project Manager
- withdraw subject from study
- perform study completion assessments

Since Gaviscon is permitted for use by pregnant women, a pregnancy follow-up will not be conducted by RB Pharmacovigilance personnel. The data collected from the subject will still be used.

12.2 Clinical Laboratory Investigations

The following investigations will be made:

- Haematology (2.7ml EDTA monovette)
    - Haemoglobin (g/dL)
    - Red cells (10^{12}/L)
    - Haematocrit (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 (9ml serum monovette)
    - 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 (IU/L)
    - Alanine transaminase (IU/L)
    - Gamma glutamyl transferase (IU/L)
    - Alpha hydroxybutyrate dehydrogenase (IU/L)
    - Creatine kinase (IU/L)
    - Total protein (g/L)
    - Albumin (g/L)
    - Cholesterol (mmol/L)
    - Triglycerides (mmol/L)

- Urinalysis
    - pH, protein, glucose, ketones, bilirubin, blood, free haemoglobin, urobilinogen. If abnormal results are found, microscopy and culture will be conducted.

- Viral Serology
    - Hepatitis B surface antigen (positive or negative)
    - Hepatitis C antibody (positive or negative)
    - HIV screening (positive or negative)

- Drugs of abuse (including alcohol) (20ml urine) (+ve or –ve)
    - Opiates, amphetamine, cannabinoids, cocaine, barbiturates, benzodiazepines, methadone, ethanol
- Serum pregnancy test for females (4.5ml serum monovette) (+ve or –ve)
    - hCG

12.2.1 Collection of Laboratory Samples

Blood samples will be collected and labelled in tubes provided by Simbec. Urine samples will be collected and labelled in cups, provided by Simbec, at the screening as well as treatment visits. All samples will be transported immediately in a box to the analytical laboratory and analyzed that day.

12.2.2 Labelling of Laboratory Samples

The unit's standard labels will be used for biological samples. These will be marked with subject number, sampling time, study number and type of sample.

12.2.3 Reference Ranges

Up-to-date reference ranges for the above investigations will be obtained prior to the start of the study and be updated as appropriate during the course of the study.

12.2.4 Laboratory Results Review

The Investigator will review the results and comment, on the laboratory results sheet, upon all abnormal values, identifying those that are clinically significantly abnormal. The Investigator will sign and date the laboratory results sheet, to indicate that the review has taken place.

A copy of these results will be provided to RB.

12.2.5 Good Laboratory Practice (GLP) Compliance

Confirmation of compliance with GLP will be required from the laboratory(ies) involved prior to the start of the study:

- The laboratory(ies) will be requested to provide documented evidence of GLP compliance. This may be a statement of compliance issued by the appropriate national authority, or details of accreditation by a recognised organisation.

An independent inspection of the laboratory(ies) by RB may be conducted.

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

Vital signs will be recorded and physical examinations will be conducted at the pre study as well as at the post study. Subjects will be asked about adverse events at all visits.

13 STATISTICAL CONSIDERATIONS

The statistical analysis will be undertaken by Simbec Research Ltd.

A detailed Statistical Analysis Plan will be finalised before the code for all subjects is broken and prior to analysis of the study being carried out. Any deviations from the analyses described below will be included in the Plan, which will form Appendix 16.1.9 of the clinical study report.

All data recorded in the Case Report Forms (CRF) will be listed in the study appendices and summarised appropriately.

13.1 Sample Size Justification

No statistical justification for the sample size in this study was performed because this is a pilot study, intended to provide variance estimates from which sample size estimates for future studies can be derived.

13.2 Data to be Analysed

Since this is a pilot study the efficacy data from the three Gaviscon groups will be formally analysed and the data from the control summarised.

The following analysis populations will be used for analysis of study data:

Safety population: all subjects who are recruited to the study and receive at least one dose of study medication. This population will be used for summaries of demography and safety.

Intention to treat (ITT) population: all subjects who are recruited to the study, receive at least one dose of study medication and have efficacy data for at least one treatment visit other than that for the control. This population will be used for summaries of efficacy data.

13.3 Demographics

Descriptive summary statistics will be provided for demographic and baseline characteristics for all subjects who received any of the study treatments. For continuous parameters, mean, standard deviation, median, minimum, and maximum will be provided. For categorical parameters, the cell frequencies and percentage of subjects in each demographic category will be provided.

13.4 Efficacy Analyses

13.4.1 Primary Efficacy Analysis End-point

The primary efficacy end-point is the amount of time to first perceived soothing effect in the throat/oesophagus (foodpipe),(assessed using a stopwatch). For a subject/visit at which a soothing effect is not reported within 30 minutes, the result will be reported as censored at 30 minutes.

The time to first perceived soothing effect will be summarised by treatment using the number of subjects assessed, number of subjects with censored and uncensored data, and either the mean, standard deviation, median, minimum, and maximum (if all subjects provide uncensored data) or the median and minimum (when censored data are reported). If there are no censored observations an upper one-sided 95% confidence limit for the mean time to first perceived soothing effect will be computed.

The number and percentage of subjects who have a time to first perceived soothing effect of no more than 5 seconds will be summarised by treatment. The lower one-sided 95% confidence limit for the percentage of subjects who have a time to first perceived soothing effect of no more than 5 seconds will be computed using exact methods and summarised by treatment.

There will be no formal statistical comparison of data from the control and Gaviscon groups.

13.4.2 Secondary Efficacy End-points

The secondary efficacy endpoints are:

- The time to first perceived cooling effect in the throat/oesophagus (foodpipe) (assessed using a stopwatch)

- Would you describe any benefit you felt from this product as "instant" (yes/no)?
- Did the product make your mouth/throat feel fresher (yes/no)?
- Willingness to use the product to treat heartburn again (yes/no)

The time to first perceived cooling effect will be summarised using the same methods as those for the time to first perceived soothing effect (see Section 13.4.1).

The three remaining parameters will be summarised by treatment using frequency distributions. The lower one-sided 95% confidence limit for the percentage of subjects who gave a positive response will be computed using exact methods and summarised by treatment.

There will be no formal statistical comparison of data from the control and Gaviscon groups.

13.4.3 Statistical Methods for Efficacy Analyses

No statistical comparisons between the four treatments are required.

13.5 Safety Analyses

All safety analyses will be presented for the Safety population.

13.5.1 Adverse Events

All treatment emergent adverse events will be 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. reported more than once and which did not cease, will be counted only once; non-continuous adverse events reported several times by the same patient will be counted as multiple events. Events present immediately prior to first dose of study medication that do not worsen in severity, will not be included. Events with start dates during follow-up will not be considered treatment emergent and will be listed separately.

Differences between treatment groups in the proportion of subjects reporting treatment emergent adverse events will be compared via the chi-square test.

13.5.2 Laboratory Data

All laboratory data will be listed in the study appendices. Each pre-study baseline laboratory value will be classified as low, normal, or high based on the reference range and summarised by treatment.

13.5.3 Vital Signs

Vital signs (blood pressure, heart rate and oral temperature) will be summarised by study visit (Screening and Post Study Follow up) using mean, standard deviation, minimum and maximum. Within subject changes in vital signs from Screening to Post Study will also be summarised using the same parameters.

13.5.4 Other Variables Related to Safety

No other safety data will be summarised.

13.5.5 Subjects who are Withdrawn from the Study

All subjects who receive at least one dose of study medication will be included in the analysis of safety. Reasons for, and the time of withdrawal, will be reported.

13.6 Interim Analyses

No interim analysis is planned for this study.

14 Quality Control and Quality Assurance Audit

14.1 Monitoring

The study will be monitored by site visits and meetings with the Investigator and co-workers(s) at intervals agreed with the Investigator. The anticipated monitoring frequency will be stated in the Initiation Visit report. Monitoring will also involve, as appropriate, correspondence and telephone contacts.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during the monitoring visit to review the data and resolve any queries and to allow direct access to the subject's records for source data verification.

At a site visit the case report forms should be made available in order that the accuracy of their completion may be checked. Each completed set of case report forms for each visit must be signed and dated by the Investigator, or a designated member of the Investigator's medical staff, to verify the data and statements submitted. Similarly all alterations must be initialled and dated by the Investigator or a designated person, explained as necessary, with the original mistake left legible

14.2 Source Document Verification

On-site monitoring will also include source document verification (SDV). SDV is the procedure whereby the data contained in the case report forms (CRFs) are compared with the primary source data (e.g. patient notes, original recordings from

automated instruments, X-ray films, ECG tracings, laboratory results) contained in the subject records held at the investigational site, and thereby verified as accurate.

The Investigator must be aware that:

- SDV is a part of the normal monitoring process. It will be carried out by designated study personnel and will be done in such a way as to preserve subject confidentiality, taking into account all ethical and legislative requirements.
- SDV will be carried out by direct comparison of entries made in the CRF with appropriate source data. Direct access to source data requires that the subject gives written, documented consent to this.
- Where source data are in the form of a computer print-out (e.g. medical records, ECG tracings) they will be made available by the Investigator to the monitor. Each will be signed and dated by the Investigator or a designated person, confirming that the print-out is a true and faithful record of the data for that subject. These print-outs will be filed in the CRF.
- The RB Clinical Project Manager/Study Monitor will write an SDV Plan, specifying which data require SDV and what constitutes source data. This plan will also include the identification of any data to be recorded directly on the CRF and therefore considered source data. The Plan will be agreed with the Investigator and documented in the Initiation Visit Report. For all subjects, subject identity (date of birth, sex, initials and subject number), record of entry into the trial and signature of informed must be verified from source documents as a minimum. In addition the following will be verified:
    - The primary efficacy variable or data from which it is derived
    - Diagnosis of the condition under investigation and other selected eligibility criteria
    - Details of serious adverse events

It is important that the subject's notes record important details about their participation in the study. The Investigator or designated person will agree, as a minimum requirement, to record the following information in the subject's notes:

- study number, brief description or title of study
- date that the subject gave written consent
- all visit dates
- all serious adverse events

14.3 Audit

In accordance with the standards defined in ICH GCP, clinical studies sponsored by Reckitt Benckiser may be subject to an independent audit at the study site which will be conducted by personnel from an appropriate Quality Assurance Unit. Full consultation with the Investigator will be made prior to and during such audit, which

will be conducted according to Quality Assurance Unit Standard Operating Procedures.

14.4 RB Policy on Fraud in Clinical Studies

In accordance with Good Clinical Practice, it is RB's policy always to follow up suspected cases of fraud.

15 ETHICS

15.1 Ethics Committee/Institutional Review Board Review

Written approval of the study by an independent and appropriately constituted Ethics Committee or Institutional Review Board must be obtained and a copy provided to RB before any protocol-related procedures, that do not form part of the subject's normal clinical treatment, are performed.

The approval letter must contain:

- name and address of the ethics committee
- date of meeting
- sufficient information to identify the version of both the protocol and subject information/informed consent.
- sufficient information to identify the version of other documents reviewed.

The investigator must also provide RB with a list of Ethics Committee or Institutional Review Board members that includes each member's name, sex and institutional affiliation.

The Investigator must submit all protocol amendments to the Ethics Committee or Institutional Review Board for approval and notify them of any administrative changes.

15.2 Subject Information and Consent

Prior to entering the study, the Investigator or designated assistant will explain to each subject, the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. Subjects will be given information and consent documents and the opportunity to ask questions. They will be informed of their right to withdraw from the study at any time without prejudice. After this explanation and before any study-specific procedures have been performed, the subject, will voluntarily sign and date the informed consent form. The person providing the information to the subject and, if different, the Investigator (if medically qualified) or a medically qualified Co-investigator, will also sign the consent form. Prior to participation in the study, the subject will receive copies of the written information and their signed and dated consent document, plus any other written information provided to them.

15.3 Informing General Practitioners

The Investigator will be responsible for informing the subject's general practitioner of involvement in the study, using the standard Simbec Research template letter.

16 REGULATORY REQUIREMENTS

16.1 Competent Authority Authorisation

This study will be submitted to the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK. The study will only be undertaken when regulatory authorisation has been obtained by RB.

16.2 Curricula Vitae

A current curriculum vitae (CV) will be obtained from all personnel with significant study responsibilities, i.e. the Principal Investigator and those to whom he/she has delegated some of his/her responsibilities as an investigator and whose names appear on the signature and delegation of duties forms (see below).

The CV will contain as a minimum the following information: name, current work address, qualifications, current position and previous positions. It will be signed and dated within 2 years of the start of the study. The CVs will be maintained on file by RB.

Individuals to whom the Principal Investigator has delegated some of his/her responsibilities as an investigator will be asked to provide sample signatures and numbers from 0 to 9. The duties delegated to them will also be recorded on the signature and delegation of duties forms.

17 DATA HANDLING AND RECORD KEEPING

17.1 Case Record Forms

The Investigator is responsible for the quality of the data recorded in the case report form. The data recorded should be a complete and an accurate account of the subject's record collected during the study. The Investigator and study monitor will identify any data that will be recorded directly on the case report form such that the CRF will be considered the source document (i.e. no prior written or electronic record of the data). The study monitor will document this on the Initiation Visit Report.

The Investigator must review all entries for completeness and correctness. When changes or corrections are made on any case report form, the Investigator or authorised persons must draw a single line through the error then initial and date the correction, as well as stating the reason for the error, except when due to a transcription error. The original entry should not be obscured.

The Investigator agrees to complete and sign the case report forms in a timely fashion after completion of each subject and make them available to the study monitor for full inspection. In addition, any data queries prepared after the original case report form has been completed should be answered promptly.

Before acceptance, the study monitor will review the case report forms for completeness and adherence to the protocol. The top copy will be submitted to RB for onward transmission to the organisation responsible for data management and a second copy will be retained by the Investigator in the Trial Site File.

17.2 Retention of Essential Documentation

The Investigator should retain essential documents until at least 5 years after the completion of the study. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with RB. It is the responsibility of RB to inform the Investigator when these documents no longer need to be retained.

Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice. The Investigator must notify RB if his/her institution's policy is to retain documents for a shorter period of time.

Records to be retained by the Investigator include, but are not restricted to the following:

- Signed and dated study protocol and amendments
- Investigator's brochure (or relevant product information, eg Summary of Product Characteristics) current at the end of the study and receipts for any earlier versions.
- Investigator agreement.
- Signed and dated informed consent documents.
- Application(s) to ethics committee/ institutional review board
- Copies of approved advertisements.
- Ethics committee/ institutional review board approval letter(s)
- Ethics committee/ institutional review board composition.
- Regulatory authorisation (if appropriate)
- Curriculum vitae of the Investigator and personnel to whom he/she has delegated some of his/her responsibilities as an Investigator.
- All clinical laboratory normal ranges in place during the study (if appropriate).
- Clinical laboratory accreditation certificate or certification of established QC and/or external QA or other validations (if appropriate).
- Details of study material/supplies shipment dates, batch numbers, method of shipping etc.
- Treatment allocation.
- Study initiation report.

- Monitoring log.
- Case report forms and source data and primary records upon which they are based.
- Serious adverse event reports.
- Notification by RB and/or Investigator to regulatory authorities/ethics committees/ institutional review board of serious adverse events including causality assessments.
- Subject identification log.
- Subject screening/enrolment log.
- Drug accountability logs.
- Signatures and responsibilities of personnel to whom the Investigator has delegated some of his/her responsibilities as an Investigator.
- Records of any retained samples (if appropriate)
- Audit certificate (if appropriate).
- Annual/Final report(s) to the ethics committee/ institutional review board
- Study report synopsis.
- Manuscript/publications of the study (if appropriate)
- Correspondence with RB (and monitoring organisation, if not RB)
- Correspondence with the ethics committee/ institutional review board.

17.3 Protocol Amendments

No change will be made to the agreed protocol without the prior written approval of both the Investigator and the Clinical Project Manager except in circumstances where the immediate safety of the subject is at risk. All protocol amendments require IEC/IRB approval. Additionally the IEC/IRB will be notified of administrative changes.

Protocol amendments will be submitted to the same regulatory authority approval/notification process as the study protocol.

18 FINANCIAL AGREEMENT

Before the study commences, a financial agreement will be signed. This will take the form of a contract between RB and Simbec Research.

19 COMPENSATION AND INDEMNITY

19.1 Compensation

Compensation will be provided for any injury caused by taking part in this study in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI).

Compensation will be paid where the injury probably resulted from:-

- the drug being tested or administered as part of this protocol
- any test or procedure you received as part of the trial

Any payment would be without legal commitment.

Compensation may not be paid where

- The injury resulted from a drug or procedure outside the trial protocol
- The protocol was not followed

In any event, such compensation and treatment shall only be provided by the Sponsor to the extent required by the applicable law.

19.2 Indemnity

RB will provide appropriate indemnity for the Investigator and staff who conduct part or all of this study, upon request. The request must be received before the first subject is recruited.

20 REPORTING, PUBLICATION AND PRESENTATION

A clinical study report will be prepared as part of RB's commitment to Good Clinical Practice. The report will be a record of the total study conduct and will be subject to approval by the Principal Investigator who will sign the final report.

The study data will be owned by Reckitt Benckiser. RB retains the right to publish the data independently of the Investigator. RB agrees that before it publishes the results, it will provide the Investigator with at least 30 days for full review prior to submission of the manuscript to the publisher. The Investigator must submit any proposed manuscript to RB for approval prior to submission for publication.

21 INVESTIGATOR RESPONSIBILITIES

21.1 Pre-Study

Before the start of the study the Investigator must:

i) Sign the final protocol.
ii) Provide a list of appropriately qualified personnel to who he/she has delegated some of his/her responsibilities as an investigator. The list will include specimen signatures, hand-written digits 0-9 and a description of delegated duties. The Investigator will ensure that this list is kept up-to-date

throughout the study and that these personnel are fully informed of the purpose of the study and their obligations.

iii) Provide RB with documentation of ethics committee approval (see Section 16)

iv) Provide RB with an up-to-date curriculum vitae. The Investigator should also provide RB with CVs for all personnel to whom he/she has delegated some of his/her responsibilities as an investigator and whose names appear on the signature and delegation of duties forms.

v) Provide RB with specimen copies of any forms to be used in connection with the study but not provided by RB.

vi) Where applicable, provide RB with reference ranges for laboratory tests performed locally.

21.2 During the Study

The Investigator must:

i) Conduct the study at the study site according to the conditions, instructions and restrictions contained in this study protocol.

ii) Ensure that adequate time and facilities are available for the conduct of the study and that these are maintained throughout the course of the study.

iii) Ensure all materials provided by RB (protocol, drugs, case report forms, investigational brochure etc.) are treated in the strictest confidence. None of this material may be disclosed to any party not involved in the study.

iv) Ensure that all study supplies are appropriated stored.

v) Ensure that written informed consent is obtained from subjects before any study-related procedures are carried out.

vi) Enter all data legibly and sign the case report forms.

vii) Ensure subjects understand how to complete any relevant assessments.

viii) Be able to identify all data pertaining to each subject by means of an unambiguous code kept in the confidential record.

ix) To meet with the study monitor, or other of RB's personnel at a mutually convenient time as frequently as RB deems necessary.

x) Report any serious adverse events to RB immediately by telephone.

xi) Ensure that individual randomisation codes are safely retained and returned to BHI at the end of the study, the treatment codes are only broken in accordance with this protocol, and that the monitor is informed when this is done.

xii) Ensure that he/she is familiar with the system of drug accountability for the study.

xiii) Make no changes to the study without prior agreement of the RB Clinical Project Manager.

xiv) Make all data available to RB/monitor and/or relevant authority where required for verification/audit/inspection purposes.

21.3 After the Study

On completion of the study the Investigator must:

i) Follow-up ongoing serious adverse events as described in Section 12.1.6 and 12.1.7.
ii) Inform the EC/IRB of completion of the study.
iii) Arrange for long-term storage of the study records (see Section 17).

22 REFERENCES

1) Laska EM, Siegel C. Assessing the onset of relief of a treatment for migraine. Cephalalgia 2000: 20:724-731

2) Black P, Max MM, Desjardins P, Norwood T, Ardin A, and Pallotta T. A randomised, double-blind, placebo-controlled comparison of the analgesic efficacy, onset of action and tolerability of ibuprofen arginate and ibuprofen in post operative dental pain. Clin Ther 2002; 24: 1072-1089.

3) France, Lewis and Kay. Statistics in Medicine, 10, 1099-1113, 1991.

Reckitt Benckiser

PROTOCOL APPROVAL

EudraCT Number: 2007-005821-31

Study Number: GA0706

Protocol Title: A single-centre randomised, partially blind, single dose, crossover pilot study investigating the use of stopwatches to assess the onset of action of soothing and cooling of Gaviscon Peppermint liquid, Double Action Gaviscon liquid, Gaviscon Advance liquid, and a control in subjects with heartburn following a refluxogenic meal.

Protocol Date: 13th November 2007

Version: Final

Phase: IV

Reviewed and Agreed by:

Clinical Project Manager:

Dr K Sarratt, PhD — Date: 13/11/07

Statistician:

Mr J Sykes, MSc
Reckitt Benckiser — Date: 12 November 2007.

R & D Manager:

Dr I Jolliffe, B Pharm (Hons), MRPharmS, PhD — Date: 13/11/07

Reviewed and Approved by:

Clinical Project Manager:

Dr S Aspley, PhD — Date: 13/11/07

Global Medical Director:

Dr P Berry MB, ChB, MPH — Date: 13/11/2007

Reckitt Benckiser

PROTOCOL ACCEPTANCE BY THE PRINCIPAL INVESTIGATOR

EudraCT Number:	2007-005821-31
Study Number:	GA0706
Protocol Title:	A single-centre randomised, partially blind, single dose, crossover pilot study investigating the use of stopwatches to assess the onset of action of soothing and cooling of Gaviscon Peppermint liquid, Double Action Gaviscon liquid, Gaviscon Advance liquid, and a control in subjects with heartburn following a refluxogenic meal.
Protocol Date:	13th November 2007
Version:	Final
Phase:	IV

Principal Investigator:

By my signature below, I hereby state that I have read, and agree to abide by the conditions, instructions and restrictions contained in this protocol. I also agree to ensure that all co-workers to whom I delegate any duties have read and are familiar with the requirements of this protocol.

P M Dewland 13 NOV 07

Dr P M Dewland, BSc, MA, MBBS, FFPM, DCPSA — Date

Principal Investigator

Simbec Research Ltd, Merthyr Tydfil, Mid Glamorgan, CF48 4DR

01443 690977

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

Telephone No: +44 (0) 1482 326151; Fax No: +44 (0) 1482 582172

APPENDIX 16.1.2 SAMPLE CASE REPORT FORM (UNIQUE PAGES ONLY).

In addition to this cover sheet, this appendix contains:

- The CRF (final version dated 11 Jan 2008) for study GA0706 (Simbec Study RD266/24573 (43 pages).

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

CASE REPORT FORM

GAVISCON INSTANTLY SOOTHING PILOT STUDY

(RD 266/24573)

A single-centre randomised, partially blind, single dose, crossover pilot study investigating the use of stopwatches to assess the onset of action of soothing and cooling of Gaviscon Peppermint liquid, Double Action Gaviscon liquid, Gaviscon Advance liquid, and a control in subjects with heartburn following a refluxogenic meal.

Chief Investigator : Dr P M Dewland

Subject Number | | | |

Subject Initials | | | |

Subject A. Number | | | | | |

Version Final: 11 Jan 2008

GAVISCON INSTANTLY SOOTHING PILOT STUDY

RD 266/24573

STUDY CONTACT INFORMATION

STUDY SPONSOR:

Reckitt Benckiser Healthcare (UK) Ltd
Dansom Lane
Hull
HU8 7DS
TEL: 01482 326151
FAX: 01482 582172

SPONSOR EMERGENCY CONTACTS:

Dr K Sarratt
RB Clinical Project Manager
TEL: 01482 582397

Dr Phil Berry
RB Study Physician
TEL: 07734 056121

SIMBEC EMERGENCY CONTACTS:

Dr Peter M Dewland
Medical Director

Dr James Mullan
Senior Research Physician

On Call Physician : 07074 800900

Simbec Research : 0800 691995

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

CASE REPORT FORMS

STUDY NAME: Gaviscon Instantly Soothing Pilot Study.

STUDY NUMBER: RD 266/24573

The data in these Case Report Forms are subject to audit by the Simbec Quality Assurance Unit and the sponsor organisation.

Instructions For Completion of Case Report Form.

1. Print all entries with a black indelible/waterproof pen.
2. If an error is made, make a single straight line through the error and print the correct data next to the deleted information. Do not obliterate or white out incorrect data. Each correction must be initialled and dated by the person making the change.
3. No data are to be changed by writing over the incorrect entry. All corrections are to be made as in 2 above.
4. Date is to be recorded as day-month-year; e.g.,

   02/JAN/02

5. Time is to be recorded in a 24 hour format.
   noon=12:00
   midnight=00:00
6. Do not write in any shaded area.
7. Use only the following abbreviations:

   If the answer to a question is unknown, write '**NK**' (Not Known)
   If a question is not applicable, write '**N/A**' (Not Applicable)
   If a requested test has not been done, write '**ND**' (Not Done)
   If data is omitted, i.e. Actual Bleed Times, Staff Initials etc., write '**NR**' (Not Recorded)
   Physicians should note any abnormal findings or out of range parameters as '**CS**' (Clinically Significant) or '**NCS**' (Not Clinically Significant) and normal findings as '**N**' (Normal)

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

STUDY SUBJECT'S BASIC INFORMATION

STUDY NAME: Gaviscon Instantly Soothing Pilot Study

STUDY NO.: RD 266/24573

SUBJECT INITIALS: | | | |

SUBJECT A. NUMBER: | | | | | |

SCREENING NUMBER: | | | |

SUBJECT NO.: | | | |

GROUP NUMBER | |

Information verified against subjects records

Print name in block capitals:_____

Signed:_____ **Date:**_____

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

KEY TO SUBJECT IDENTIFICATION NUMBERS THROUGHOUT

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

'A' number	Is a unique identifier assigned to a volunteer when he/she is recruited onto the volunteer panel. This number allows to reveal the identification of a volunteer.
Screening number	Each volunteer is given a number (in numerical order) as they are screened for a study. This number is used for the volunteer in relation to the specific study, up to dosing when they are given their subject number. Not all volunteers who are screened are dosed, hence the two different numbers.
Subject number	The subject number is the number assigned to a volunteer according to the randomisation code and identifies the subject throughout the study.
'Z' number	Is a unique number assigned to samples, which are normally pre-study screens or unexpected samples generated during a study. Z numbers are not study specific.
'G' number	Is a unique number generated for a study sample, which is study, subject and time point specific.

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

DEMOGRAPHIC DATA

SCREENING - VISIT 1

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

Date : d d m m m y y

Date of subject signature of Informed Consent : d d m m m y y

Version of Informed Consent: _____

Gender: MALE ☐ FEMALE ☐

Race: CAUCASIAN ☐ ASIAN: ☐ AFRO-CARIBBEAN ☐ OTHER ☐

SUBJECT D.O.B.: d d m m m y y

HEIGHT (cm)	WEIGHT (kg)	BODY MASS INDEX (kg/m^2)

Does the subject have a tendency to experience symptoms of heartburn related to reflux, following some meals (self-rated)? : (✓ as applicable)

YES ☐ **NO** ☐ (if "NO" exclude subject)

History of drug, solvent or alcohol abuse? : (✓ as applicable) ☐ **NO** ☐ **YES** (if "yes", exclude subject)

Alcohol User : (✓ as applicable) ☐ **NO** ☐ **YES**

If 'YES' please specify weekly amount _____units / week (1 unit = ½ pint beer, 1 glass wine, 1 measure of spirits)

Tobacco User : (✓ as applicable) ☐ **NO** ☐ **YES**

If 'YES' please specify daily amount _____ / day (e.g. Cigarettes, Cigars, Tobacco etc.)

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

SCREENING – VISIT 1

VITAL SIGNS and 12 LEAD ECG

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

BLOOD PRESSURE (after sitting for 5 mins)	____ / ____ mmHg	**ORAL TEMPERATURE**	___.___(°C)
HEART RATE (radial pulse counted for 30 seconds after resting for 5 mins)	____ (beats/minute)		

Review of Vital Signs	**Staff Signature:**

(✓ as applicable)

Normal ☐ **Abnormal – Not Clinically Significant** ☐ **Abnormal – Clinically Significant** ☐

If 'abnormal-clinically significant' please exclude subject.
If repeat Vital Signs required enter details to Additional Vital Signs (page 8)

Screening 12-Lead ECG

Was the screening 12-lead ECG taken? (✓ as applicable)

YES ☐ **NO** ☐

Review of ECG (✓ as applicable)

Normal ☐ **Abnormal – Not Clinically Significant** ☐ **Abnormal – Clinically Significant** ☐

If "abnormal- clinically significant", please comment and exclude subject:

Repeat ECG required? (✓ as applicable)

NO ☐ **YES** ☐ If 'Yes' please enter details to Additional 12 Lead ECG's (page 8)

FEMALES ONLY

N/A (✓) ☐

Method of Contraception: _____

Print name in block capitals: _____

Signed: _____ **Date:** _____

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

ADDITIONAL VITAL SIGNS & 12 LEAD ECG

SCREENING - VISIT 1

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

N/A (✓) ☐

Repeat Vital Signs

Date: ☐☐ ☐☐ ☐☐☐☐ (d d m m m y y) **Actual Time** ☐☐ : ☐☐

Sitting ☐

Pulse ☐☐☐ bpm **Staff Initials** ☐☐☐

Blood Pressure ☐☐☐ / ☐☐☐ mmHg

Temperature ☐☐ . ☐ °C

Review of Vital Signs | **Staff Signature:**

(✓ as applicable)

Normal ☐ **Abnormal – Not Clinically Significant** ☐ **Abnormal – Clinically Significant** ☐

If 'abnormal-clinically significant' please exclude subject.

N/A (✓) ☐

Repeat 12-Lead ECG

☐☐ ☐☐ ☐☐☐☐ (d d m m m y y)

Was the additional 12-lead ECG taken? (✓ as applicable)

YES ☐ **NO** ☐

Review of ECG (✓ as applicable) :

Normal ☐ **Abnormal** – Not Clinically Significant ☐ **Abnormal** – Clinically Significant ☐

If "abnormal- clinically significant", please comment and exclude subject:

SCREENING – VISIT 1

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

RELEVANT MEDICAL HISTORY AND CURRENT DISORDERS

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

Has the subject experienced a Condition/Illness in 14 Days prior to study entry?
(✓ as applicable) ☐ YES ☐ NO If 'YES' please complete details on page 10

Is the subject currently taking medication, or have they taken any therapy in the 48 hours prior to study entry?
(✓ as applicable) ☐ YES ☐ NO If 'YES' please complete details on page 11

Does the subject have any relevant medical history?
(✓ as applicable) ☐ YES ☐ NO If 'YES' please complete details below

SYSTEM	DETAILS	DATES *where available or Not Known (NK)*			*CLINICALLY SIGNIFICANT*	
		Start Date	End Date	Ongoing(✓)	YES (✓)	NO (✓)
E.N.T.						
OPHTHALMOLOGICAL						
DERMATOLOGICAL						
CARDIOVASCULAR						
RESPIRATORY						
GASTRO-INTESTINAL						
GENITO-URINARY						
NEUROLOGICAL						
PSYCHIATRIC						
MUSCULOSKELETAL						
ENDOCRINOLOGICAL						
ALLERGIES						

** If 'Clinically Significant' exclude from study.*

Print name in block capitals: _____

Signed: _____ **Date:** _____

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

SCREENING CONDITIONS/ILLNESSES

SCREENING – VISIT 1

Study Name: Gaviscon Instantly Soothing Pilot Study

Study No: RD 266/ 24573

Subject Initials				A Number						Subject Number			

Has the subject experienced any conditions/illnesses in 14 days prior to study entry? (✓ as applicable): **NO** ☐ **YES** ☐ (If 'Yes' please complete details below)

Event	Condition/Illness	Date of Onset	Time of Onset (24 HR Clock)	Sign	Date of Resolution	Time of Resolution (24 HR Clock)	Sign	Severity (Enter code from list below)	Action (Enter code from list below)	Outcome of Condition/ Illness (Enter code from list below)	Sign
a											
b											
c											
d											
e											

Codes

Severity	Action Taken	Outcome of Condition/Illness
1 = Mild 2 = Moderate 3 = Severe	1 = No Action 2 = Specific Concomitant Drug Therapy (Complete Concomitant Medication Form) 4 = Other Action (Complete Additional Medical Notes Form)	1 = Completely Recovered 2 = Recovered with Sequelae 3 = Condition Improving 4 = Condition Still Present & Unchanged 5 = Condition Deteriorated 6 = Death

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

SCREENING MEDICAL AND THERAPY HISTORY

SCREENING = VISIT 1

Study Name: Gaviscon Instantly Soothing Pilot Study

Study No: RD 266/ 24573

Subject Initials				A Number						Subject Number			

Is the subject currently taking medication and has the subject taken any therapy in the 48 hours prior to study entry?

(✓ as applicable): **NO** ☐ **YES** ☐ (If 'Yes' please complete details below)

EVENT CODE:	MEDICATION / THERAPY	DOSE	ROUTE	DATE	TIME	SIGNATURE

Route Codes			
PO = Oral IV = Intravenous IM = Intramuscular	Inh = Inhalation SL = Sublingual SC = Subcutaneous	PR = Rectal PV = Vaginal	T = Topical O = Optical N = Nasal A = Aural

SCREENING – VISIT 1

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

PHYSICAL EXAMINATION

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

PHYSICAL EXAMINATION						
	(✓) AS APPROPRIATE			ADDITIONAL DETAILS	'Clinically Significant' (✓)	
	NORMAL	ABNORMAL	NOT DONE		YES	NO
E.N.T.						
OPHTHALMOLOGICAL						
DERMATOLOGICAL						
CARDIOVASCULAR						
RESPIRATORY						
GASTRO-INTESTINAL						
C.N.S.						
LYMPH NODES						
MUSCULO-SKELETAL						
OTHER						

Print name in block capitals:_____

Signed:_____ **Date:**_____

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

SCREENING – VISIT 1

VIROLOGY

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

Date : d d m m m y y

Hepatitis Screen: (✓ as applicable)

Hepatitis B Surface Antigen (HBsAg)	**Negative**	☐	**Positive**	☐
Hepatitis C antibody	**Negative**	☐	**Positive**	☐

If 'Positive' exclude from the study

HIV Screen: (✓ as applicable)

HIV	**Negative**	☐	**Positive**	☐

If 'Positive' exclude from the study

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

LABORATORY RESULTS

SCREENING – VISIT 1

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

Laboratory Evaluation

Screening:
(Biochemistry, Haematology and Urinalysis)

Date:

d d m m m y y

Please enter Z Number below:

Were the screening blood and urinalysis samples taken?
(✓as applicable)

YES ☐ **Staff Initials** ☐

Review of blood and urinalysis results (✓ as applicable):

Normal ☐ **Abnormal** Not Clinically Significant ☐ **Abnormal** Clinically Significant ☐

Did any of the results need repeating (✓as applicable)

YES ☐ **NO** ☐

If 'Yes' please enter details below.

Repeat Laboratory Evaluation

Date:

d d m m m y y

Please enter Z Number below:

Were additional blood and/or urinalysis samples taken?
(✓as applicable)

YES ☐ **Staff Initials** ☐

Review of blood and/or urinalysis results (✓ as applicable):

Normal ☐ **Abnormal** Not Clinically Significant ☐ **Abnormal** Clinically Significant ☐

Did any of the results need repeating (✓as applicable)

YES ☐ **NO** ☐

If 'Yes' please enter details to Additional Laboratory Samples Page 39.

Result of Drugs of Abuse screen taken during Screening: (✓ as applicable):

☐ **NEGATIVE** ☐ **POSITIVE** A positive result will exclude the subject from the study

Result of Pregnancy Test taken during screening: (✓ as applicable):

☐ **NEGATIVE** ☐ **POSITIVE** ☐ **N/A** A positive result will exclude the subject from the study

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

STUDY INCLUSION CRITERIA

SCREENING VISIT 1

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

Date : d d m m m y y

Please answer *all* questions by ticking the appropriate box.

		TICK BOX YES	NO
1	Age: ≥ 18 years ≤ 80 years		
2	Status: Members of the Simbec Volunteer Panel who state (self-rated) that they have a tendency to experience symptoms of heartburn related to reflux, following some meals.		
3	Primary diagnosis: Those with self-rated at least moderate heartburn within 60 minutes following ingestion of a standardised refluxogenic meal at the screening visit.		
4	Subjects who have given written informed consent.		

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

STUDY EXCLUSION CRITERIA

SCREENING – VISIT 1

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Volunteer Initials				A Number						Subject Number			

Please answer *all* questions by ticking the appropriate box.

		TICK BOX YES	NO
1.	Those who have suffered a recent, significant unexplained weight loss of 6-7kg in the last 6 months.		
2.	Those who have 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 have 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.		
8.	Those who have taken proton pump inhibitors within the previous 48 hours prior to screening.		
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 or potassium bicarbonate.		
11.	Those who are receiving treatment for their upper gastrointestinal problems or gastro-oesophageal reflux disease from their GP.		
12.	Those unable in the opinion of the Investigator to comply fully with the study requirements.		
13.	Those currently participating in a clinical study or who have participated in any other clinical study within the last 30 days.		
14.	Those who have previously participated in this randomised study.		

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

STUDY EXCLUSION CRITERIA CONTINUED

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Volunteer Initials				A Number						Subject Number			

Please answer *all* questions by ticking the appropriate box.

15.	**Woman of childbearing potential, who are 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 [should the subject become sexually active, she must agree to use a double barrier method] or condoms/diaphragm and spermicide). A woman of childbearing potential is defined as any female who is less than 2 years post-menopausal or has not undergone an hysterectomy or surgical sterilisation, e.g. bilateral tubal ligation, bilateral ovariectomy (oophorectomy).**		
16.	**Those who are on steroids or non-steroidal anti-inflammatory drugs.**		
17.	**Those who are diabetics.**		

Is the subject eligible to attend the second Screening visit? (✓as applicable) **YES** ☐ **NO** ☐ If 'NO' please complete Study Termination page.

Physician's Signature:_____ **Date:**_____

SCREENING – VISIT 2

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

REFLUXOGENIC MEAL and HEARTBURN

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Volunteer Initials				A Number						Subject Number			

Has at least 48 hrs passed since Screening Visit 1?

(✓as applicable) YES ☐ NO ☐

Date : d d m m m y y

Refluxogenic meal start time: ☐☐:☐☐ (24 hour clock)

Refluxogenic meal finish time: ☐☐:☐☐

Onset of heartburn time:
(Must be within 60 mins of finishing meal) ☐☐:☐☐

Degree of heartburn experienced by the subject (Self-rated): (✓ as applicable)

NONE (Exclude subject) ☐ **MILD** (Exclude subject) ☐ **MODERATE** ☐ **SEVERE** ☐

* AT END OF 60 MIN OBSERVATION PERIOD (OR EARLIER IF REQUESTED) ALL SUBJECTS WILL BE PROVIDED WITH 10ML OF MAALOX, IF NECESSARY, TO RELIEVE THEIR SYMPTOMS.

ENROLMENT STATUS

Did subject satisfy all of the Inclusion and Exclusion Criteria? (✓as applicable)	**YES** ☐	**NO** ☐	If 'NO' please comment below.
Is the subject suitable for enrolment onto the study? (✓as applicable)	**YES** ☐	**NO** ☐	If 'NO' please complete Study Termination page 42.

Physician's Signature:_____ **Date:**_____

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

SCREENING COMPLETION

SCREENING

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

OUTCOME OF SCREENING:-

		TICK BOX
1	Entered Study	
2	Not Eligible (Please specify below.)	
3	Withdrew Consent	
4	Other (Please specify below)	

Date screening completed: d d m m m y y

Comments:_____

_____

_____

_____

_____

Signed:_____ **Date:**_____
(Research Physician/Principal Investigator)

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

QUALITY CONTROL FORM (SCREENING)

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

DATE	CRF PAGE No.	QUESTION	QC'ed BY	QUERY TO:- (STAFF MEMBER)	RESOLVED BY	
					INITIALS	DATE

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

SCHEDULE OF EVENTS FOR TREATMENTS 1, 2, 3 AND 4

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No: RD 266/ 24573**

08.00 (approx):

* Subject will report to Simbec Research Centre.
* Confirm no prohibited medication (medicines to relieve heartburn) and no alcohol has been consumed within the previous 48 hours.
* Check any Adverse events since previous visit.
* Urine sample (DOA x 8 and for females, pregnancy test).

09.00 (approx):

* Subject provided with light breakfast.
* Fast for at least 4 hours.

13.00 (approx):

* Subject provided with a standardised refluxogenic meal (60% fat) and must lie down after consumption.
* Subect must experience AT LEAST MODERATE symptoms of heartburn within 60 minutes of finishing meal. If no heartburn is experienced within this time, the subject is allowed to leave (but is required to stay on site for 30 minutes beforehand).
* Subject must attract the attention of the study nurse AS SOON as they experience at least moderate symptoms of heartburn.
* DOSE and start SOOTHING and COOLING Stopwatches immediately.
* Subjects to stop soothing and cooling stopwatches when the corresponding effects of the medication are felt (i.e. AS SOON as cooling sensation is experienced, subject is to press STOP on the COOLING STOPWATCH).
* After 5 minutes, ask the subject if they felt any instant benefit from the product.
* The treatment study period will be for 30 minutes after dose.
* At the end of this study period, subject will be asked whether or not they would be willing to use the product again, if they experienced any adverse effects, and if their mouth/throat felt fresher after treatment.

The clinical and data collection procedures for all 4 treatment visits will be exactly the same BUT each subject will receive an alternative treatment according to the randomisation schedule and there will be 2-7 day(s) washout period between treatments.

TREATMENT VISIT 1

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

DOSE ADMINISTRATION RECORD

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

Has at least 48 hrs passed since Screening Visit 2?

(✓as applicable) YES ☐ NO ☐

Date : d d m m m y y

Has photographic ID been confirmed? (✓as applicable):

☐ **YES** ☐ **NO** Staff initials.:_____

If NO please comment on additional notes page 41.

Result of Drugs of Abuse & Ethanol screen taken on Treatment Visit 1 (✓ as applicable):

☐ **NEGATIVE** ☐ **POSITIVE** A positive result will exclude the subject from the study

Result of Pregnancy Test taken on Treatment Visit 1: (✓ as applicable):

☐ **NEGATIVE** ☐ **POSITIVE** (exclude from study) ☐ **N/A**

Is the subject experiencing any symptoms or complaints? (✓as applicable):

☐ **YES** ☐ **NO** If 'yes' please complete adverse events page 33.

Has there been any changes in the Subject's medical history since the previous visit? (✓as applicable):

☐ **NO** ☐ **YES** If 'YES' please complete Screening Conditions/Illnesses and Concomitant Medication pages 11 and 12.

Is Subject eligible for dosing? (✓ as applicable):

☐ **YES** ☐ **NO** If 'NO' please complete Study Termination page 42.

STUDY DRUG ADMINISTRATION: TREATMENT VISIT 1

Date	Time	Administered By	Checked By	Treatment assigned (i.e. X, Y, Z or D)
d d m m m y y	(24 hour clock)			

TREATMENT VISIT 1

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

STUDY MONITORING SHEET

Study Name: Gaviscon Instantly Soothing Pilot Study

Study No: RD 266/ 24573

Subject Initials				A Number						Subject Number			

EVENT	TIME		ACTION
LIGHT BREAKFAST	:		
START FAST			
60% FAT MEAL (To be consumed in approx. 15-20 mins)	START : MUST BE AT LEAST 4 HOURS AFTER BREAKFAST	FINISH :	SUBJECT TO LIE DOWN ON COMPLETION OF MEAL
MODERATE HEART BURN?	**NO**		SUBJECT TO REMAIN IN UNIT FOR 30 MINS THEN ALLOWED TO LEAVE.
	YES :		DOSE AND START SOOTHING AND COOLING STOPWATCHES.
	MUST BE WITHIN 60 MINUTES OF MEAL FINISH TIME		
DOSE AND START SOOTHING AND COOLING STOPWATCHES	:		* **AFTER 5 MINS ASK :** WOULD YOU DESCRIBE ANY BENEFIT YOU FELT FROM THIS PRODUCT AS 'INSTANT'? (✓ as applicable): ☐ YES ☐ NO
STOP STOPWATCH WHEN FIRST SOOTHING AND COOLING IS PERCEIVED (record on additional notes page 41 if effects not perceived)	SOOTHING EFFECT : WITHIN 30 MINS OF DOSE	COOLING EFFECT :	

*** AT 30 MINS ASK:**

- DID THE PRODUCT MAKE YOUR MOUTH/THROAT FEEL FRESHER? ☐ YES ☐ NO
- WILLINGNESS TO USE THE PRODUCT TO TREAT HEARTBURN AGAIN? ☐ YES ☐ NO
- DID THE SUBJECT EXPERIENCE ANY ADVERSE EVENTS? ☐ YES ☐ NO (If 'YES' please complete adverse events page 33)

TREATMENT VISIT 2

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

DOSE ADMINISTRATION RECORD

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

Has there been a 2-7 day washout period since the previous treatment visit? (✓as applicable) YES ☐ NO ☐ **Date :** d d m m m y y

Has photographic ID been confirmed? (✓as applicable):

☐ **YES** ☐ **NO** Staff initials.:_____
If NO please comment on additional notes page 41.

Result of Drugs of Abuse & Ethanol screen taken on Treatment Visit 2 (✓ as applicable):

☐ **NEGATIVE** ☐ **POSITIVE** A positive result will exclude the subject from the study

Result of Pregnancy Test taken on Treatment Visit 2: (✓ as applicable):

☐ **NEGATIVE** ☐ **POSITIVE** (exclude from study) ☐ **N/A**

Has the subject had any symptoms or complaints since the last time they were asked? (✓ as applicable):

☐ **YES** ☐ **NO** If 'yes' please complete adverse events page 33.

Has there been any changes in the Subject's medical history since the previous visit? (✓as applicable):

☐ **NO** ☐ **YES** If 'YES' please complete adverse events (page 33) and Concomitant Medication (page 36).

Is Subject eligible for dosing? (✓ as applicable):

☐ **YES** ☐ **NO** If 'NO' please complete Study Termination page 42.

STUDY DRUG ADMINISTRATION: TREATMENT VISIT 2

Date	Time	Administered By	Checked By	Treatment assigned (i.e X, Y, Z or D)
d d m m m y y	(24 hour clock)			

TREATMENT VISIT 2

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

STUDY MONITORING SHEET

Study Name: Gaviscon Instantly Soothing Pilot Study

Study No: RD 266/ 24573

Subject Initials				A Number						Subject Number			

EVENT	TIME		ACTION
LIGHT BREAKFAST	:		
START FAST			
60% FAT MEAL (To be consumed in approx. 15-20 mins)	START : MUST BE AT LEAST 4 HOURS AFTER BREAKFAST	FINISH :	SUBJECT TO LIE DOWN ON COMPLETION OF MEAL
MODERATE HEART BURN?	**NO**		SUBJECT TO REMAIN IN UNIT FOR 30 MINS THEN ALLOWED TO LEAVE.
	YES :		DOSE AND START SOOTHING AND COOLING STOPWATCHES.
	MUST BE WITHIN 60 MINUTES OF MEAL FINISH TIME		
DOSE AND START SOOTHING AND COOLING STOPWATCHES	:		* **AFTER 5 MINS ASK :** WOULD YOU DESCRIBE ANY BENEFIT YOU FELT FROM THIS PRODUCT AS 'INSTANT'? (✓ as applicable): ☐ YES ☐ NO
STOP STOPWATCH WHEN FIRST SOOTHING AND COOLING IS PERCEIVED (record on additional notes page 41 if effects not perceived)	SOOTHING EFFECT :	COOLING EFFECT :	
	WITHIN 30 MINS OF DOSE		

*** AT 30 MINS ASK:** - DID THE PRODUCT MAKE YOUR MOUTH/THROAT FEEL FRESHER? ☐ YES ☐ NO

- WILLINGNESS TO USE THE PRODUCT TO TREAT HEARTBURN AGAIN? ☐ YES ☐ NO

- DID THE SUBJECT EXPERIENCE ANY ADVERSE EVENTS? ☐ YES ☐ NO

(If 'YES' please complete adverse events page 33)

TREATMENT VISIT 3

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

DOSE ADMINISTRATION RECORD

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials:				A Number						Subject Number			

Has there been a 2-7 day washout period since the previous treatment visit? (✓as applicable) YES ☐ NO ☐

Date : d d m m m y y

Has photographic ID been confirmed? (✓as applicable):

☐ **YES** ☐ **NO** Staff initials.:_____

If NO please comment on additional notes page 41.

Result of Drugs of Abuse & Ethanol screen taken on Treatment Visit 3 (✓ as applicable):

☐ **NEGATIVE** ☐ **POSITIVE** A positive result will exclude the subject from the study

Result of Pregnancy Test taken on Treatment Visit 3: (✓ as applicable):

☐ **NEGATIVE** ☐ **POSITIVE** (exclude from study) ☐ **N/A**

Has the subject had any symptoms or complaints since the last time they were asked? (✓ as applicable):

☐ **YES** ☐ **NO** If 'yes' please complete adverse events page 33

Has there been any changes in the Subject's medical history since the previous visit? (✓as applicable):

☐ **NO** ☐ **YES** If 'YES' please complete adverse events (page 33) and Concomitant Medication (page 36).

Is Subject eligible for dosing? (✓ as applicable):

☐ **YES** ☐ **NO** If 'NO' please complete Study Termination page 42.

STUDY DRUG ADMINISTRATION: TREATMENT VISIT 3

Date	Time	Administered By	Checked By	Treatment assigned (i.e. X, Y, Z or D)
d d m m m y y	(24 hour clock)			

TREATMENT VISIT 3

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

STUDY MONITORING SHEET

Study Name: Gaviscon Instantly Soothing Pilot Study

Study No: RD 266/ 24573

Subject Initials				A Number						Subject Number			

EVENT	TIME		ACTION
LIGHT BREAKFAST	:		
START FAST			
60% FAT MEAL (To be consumed in approx. 15-20 mins)	START : MUST BE AT LEAST 4 HOURS AFTER BREAKFAST	FINISH :	SUBJECT TO LIE DOWN ON COMPLETION OF MEAL
MODERATE HEART BURN?	**NO**		SUBJECT TO REMAIN IN UNIT FOR 30 MINS THEN ALLOWED TO LEAVE.
	YES :		DOSE AND START SOOTHING AND COOLING STOPWATCHES.
	MUST BE WITHIN 60 MINUTES OF MEAL FINISH TIME		
DOSE AND START SOOTHING AND COOLING STOPWATCHES	:		* **AFTER 5 MINS ASK :** WOULD YOU DESCRIBE ANY BENEFIT YOU FELT FROM THIS PRODUCT AS 'INSTANT'? (✓ as applicable): ☐ YES ☐ NO
STOP STOPWATCH WHEN FIRST SOOTHING AND COOLING IS PERCEIVED (record on additional notes page 41 if effects not perceived)	SOOTHING EFFECT :	COOLING EFFECT :	
	WITHIN 30 MINS OF DOSE		

*** AT 30 MINS ASK:** - DID THE PRODUCT MAKE YOUR MOUTH/THROAT FEEL FRESHER? ☐ YES ☐ NO

- WILLINGNESS TO USE THE PRODUCT TO TREAT HEARTBURN AGAIN? ☐ YES ☐ NO

- DID THE SUBJECT EXPERIENCE ANY ADVERSE EVENTS? ☐ YES ☐ NO (If 'YES' please complete adverse events page 33)

TREATMENT VISIT 4

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

DOSE ADMINISTRATION RECORD

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

Has there been a 2-7 day washout period since the previous treatment visit? (✓as applicable)

YES ☐ NO ☐ **Date :** ☐☐ ☐☐☐ ☐☐ (d d m m m y y)

Has photographic ID been confirmed? (✓as applicable):

☐ **YES** ☐ **NO** Staff initials.:_____

If NO please comment on additional notes page 41.

Result of Drugs of Abuse & Ethanol screen taken on Treatment Visit 4 (✓ as applicable):

☐ **NEGATIVE** ☐ **POSITIVE** A positive result will exclude the subject from the study

Result of Pregnancy Test taken on Treatment Visit 4: (✓ as applicable):

☐ **NEGATIVE** ☐ **POSITIVE** (exclude from study) ☐ **N/A**

Has the subject had any symptoms or complaints since the last time they were asked? (✓ as applicable):

☐ **YES** ☐ **NO** If 'yes' please complete adverse events page 33

Has there been any changes in the Subject's medical history since the previous visit? (✓as applicable):

☐ **NO** ☐ **YES** If 'YES' please complete adverse events (page 33) and Concomitant Medication (page 36).

Is Subject eligible for dosing? (✓ as applicable):

☐ **YES** ☐ **NO** If 'NO' please complete Study Termination page 42.

STUDY DRUG ADMINISTRATION: TREATMENT VISIT 4

Date	Time	Administered By	Checked By	Treatment assigned (i.e. X, Y, Z and D)
d d m m m y y	(24 hour clock)			

TREATMENT VISIT 4

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

STUDY MONITORING SHEET

Study Name: Gaviscon Instantly Soothing Pilot Study

Study No: RD 266/ 24573

Subject Initials				A Number						Subject Number			

EVENT	TIME		ACTION
LIGHT BREAKFAST	:		
START FAST			
60% FAT MEAL (To be consumed in approx. 15-20 mins)	START : MUST BE AT LEAST 4 HOURS AFTER BREAKFAST	FINISH :	SUBJECT TO LIE DOWN ON COMPLETION OF MEAL
MODERATE HEART BURN?	**NO**		SUBJECT TO REMAIN IN UNIT FOR 30 MINS THEN ALLOWED TO LEAVE.
	YES :		DOSE AND START SOOTHING AND COOLING STOPWATCHES.
	MUST BE WITHIN 60 MINUTES OF MEAL FINISH TIME		
DOSE AND START SOOTHING AND COOLING STOPWATCHES	:		* **AFTER 5 MINS ASK :** WOULD YOU DESCRIBE ANY BENEFIT YOU FELT FROM THIS PRODUCT AS 'INSTANT'? (✓ as applicable): ☐ YES ☐ NO
STOP STOPWATCH WHEN FIRST SOOTHING AND COOLING IS PERCEIVED (record on additional notes page 41 if effects not perceived)	SOOTHING EFFECT : WITHIN 30 MINS OF DOSE	COOLING EFFECT :	

*** AT 30 MINS ASK:** - DID THE PRODUCT MAKE YOUR MOUTH/THROAT FEEL FRESHER? ☐ YES ☐ NO

- WILLINGNESS TO USE THE PRODUCT TO TREAT HEARTBURN AGAIN? ☐ YES ☐ NO

- DID THE SUBJECT EXPERIENCE ANY ADVERSE EVENTS? ☐ YES ☐ NO (If 'YES' please complete adverse events page 33)

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

DEMOGRAPHIC and SAFETY DATA

POST-STUDY

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

BLOOD PRESSURE (after sitting for 5 mins)	____ / ____ mmHg	**ORAL TEMPERATURE**	___.___ (°C)
HEART RATE (radial pulse counted for 30 seconds after resting for 5 mins)	____ (beats/minute)		

Review of Vital Signs | **Staff signature:**

(✓ as applicable)

Normal ☐ **Abnormal – Not Clinically Significant** ☐ **Abnormal – Clinically Significant** ☐

If 'abnormal-clinically significant' please complete Adverse Event page 33.
If repeat Vital Signs required enter details to Additional Vital Signs page 37

Laboratory Evaluation

Post Study
(Biochemistry, Haematology and Urinalysis)

Date: ☐☐ ☐☐ ☐☐
d d m m m y y

Please enter G Number below:

Were the post blood and urinalysis samples taken? (✓as applicable)

YES ☐ **Staff Initials** ☐

Review of blood and urinalysis results (✓ as applicable):

Normal ☐ **Abnormal** Not Clinically Significant ☐ **Abnormal** Clinically Significant ☐

Did any of the results need repeating (✓as applicable)

YES ☐ **NO** ☐

If 'Yes' please enter details to Additional Laboratory Samples page 39

12-Lead ECG

Was the Post Study 12-lead ECG taken? (✓ as applicable)

YES ☐ **NO** ☐

Review of ECG (✓ as applicable) :

Normal ☐ **Abnormal** – Not Clinically Significant ☐ **Abnormal** – Clinically Significant ☐

If "abnormal clinically significant", please specify below and complete Adverse Event page 33:

Repeat ECG required? (✓ as applicable)

NO ☐ **YES** ☐ If 'Yes' please enter details to Additional 12 Lead ECG's page 38

POST STUDY

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

PHYSICAL EXAMINATION

Study Name: Gaviscon Instantly Soothing Pilot Study

Study No: RD 266/ 24573

Subject Initials				A Number						Subject Number			

Are there any changes in physical examination since the pre-study assessment?: ☐ YES ☐ NO If 'YES' please complete details below
(✓ as applicable)

PHYSICAL EXAMINATION						
	(✓) AS APPROPRIATE			ADDITIONAL DETAILS	'Clinically Significant' (✓)	
	NORMAL	ABNORMAL	NOT DONE		YES	NO
E.N.T.						
OPHTHALMOLOGICAL						
DERMATOLOGICAL						
CARDIOVASCULAR						
RESPIRATORY						
GASTRO-INTESTINAL						
C.N.S.						
LYMPH NODES						
MUSCULO-SKELETAL						
OTHER						

Print name in block capitals:_____ **Signed:**_____ **Date:**_____

POST STUDY

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

ADVERSE EVENTS

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No: RD 266/ 24573**

Subject Initials				A Number						Subject Number			

Instructions and definitions — Adverse Events

Any serious AE or AE that gives rise to significant cause for concern must be reported to the study director within 24 hours of knowledge of the event.

Use one AE form to record the details of one Adverse Event and its course during the trial.

- Complete the first panel as soon as you become aware of the AE.
- Complete the third panel **only** when the outcome of the event is known. Do not tick the "ongoing" box unless the AE is still ongoing at the end of the study
- Complete the second panel only if the AE changes in severity.

Notes:

Ⓐ **Important Medical Events** that may not be immediately life-threatening or result in death or hospitalisation but which may jeopardise the subject or require intervention to prevent one of the other outcomes listed in the seriousness criteria above should also usually be considered as serious adverse events. However, clinical and scientific judgement should be used in the interpretation of the underlying circumstances.

Ⓑ **Severity** will be determined by the investigator. For symptomatic AEs the following definitions will be applied:

- **Mild** - The AE does not limit usual activities; the subject may experience slight discomfort.
- **Moderate** - The AE results in some limitation of usual activities; the subject may experience significant discomfort.
- **Severe** - The AE results in an inability to carry out usual activities; the subject may experience intolerable discomfort or pain. Medical experience and judgement should also be used in the assessment of severity.

Ⓒ Report as for serious AE and contact the Study Director. Please give details in "Additional Information" section in the third panel.

Ⓓ Complete "Final Evaluation" form.

Ⓔ **Has the subject ever experienced this AE before?** A query confirming whether the subject has experienced this AE before, brief details should be given under "Additional information".

Ⓕ Relationship to study drug must be determined by a physician. The following guidance should be used:

- **Definite** - an AE that follows an anticipated response to the study medication; and that is confirmed by both improvement upon stopping the study medication (dechallenge), and reappearance of the reaction on repeated exposure (rechallenge).
- **Probable** - an AE that follows a reasonable temporal sequence from administration of the study medication, that is an anticipated response to the study medication; and that could not be reasonably explained by the known characteristics of the subject's clinical state or concomitant therapy.
- **Possible** - an AE that follows a reasonable temporal sequence from administration of the study medicines; that may be an anticipated response to the study medication; but that could have been produce by the subject's clinical state or concomitant therapy.
- **Unlikely** - an AE that does not follow an anticipated response to the study medication; which may be attributable to other than the study medication, and that is more likely to have been produced by the subject's clinical state or concomitant therapy.
- **None** - an AE that is known beyond all reasonable doubt to be caused by the subject's clinical state or concomitant therapy.

POST STUDY

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

ADVERSE EVENTS

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No: RD 266/ 24573**

Subject Initials				A Number						Subject Number			

Nature of AE [01]

Is this a serious adverse event? yes [02] no

- 03 ☐ fatal
- 04 ☐ acute life threatening
- 05 ☐ required or prolonged hospitalisation
- 06 ☐ resulted in persistent or significant disability or incapacity
- 07 ☐ resulted in congenital malformation/anomaly
- 08 ☐ important medical event ●

Date AE started [09] day / month / year

Time AE started [10] (24 hour clock)

Severity ●
- ☐ mild
- ☐ moderate
- ☐ severe [11]

Action taken *(more than one box may be ticked)*
- 12 ☐ none
- 13 ☐ hospitalised or hospitalisation prolonged ●
- 14 ☐ symptomatic therapy *(complete concomitant medications page)*
- 15 ☐ study medication dose changed
- 16 ☐ study medication permanently discontinued ●
- 17 ☐ other action

Has the subject ever experienced this AE before? ● yes [18] no → **Complete additional information box below**

Date & time of change in severity of AE

Date severity changed [19] day / month / year

Time severity changed [20] (24 hour clock)

Severity ●
- ☐ mild
- ☐ moderate
- ☐ severe [21]

Action taken *(more than one box may be ticked)*
- 22 ☐ none
- 23 ☐ hospitalised or hospitalisation prolonged ●
- 24 ☐ symptomatic therapy *(complete concomitant medications page)*
- 25 ☐ study medication dose changed
- 26 ☐ study medication permanently discontinued ●
- 27 ☐ other action

Date severity changed [28] day / month / year

Time severity changed [29] (24 hour clock)

Severity ●
- ☐ mild
- ☐ moderate
- ☐ severe [30]

Action taken *(more than one box may be ticked)*
- 31 ☐ none
- 32 ☐ hospitalised or hospitalisation prolonged ●
- 33 ☐ symptomatic therapy *(complete concomitant medications page)*
- 34 ☐ study medication dose changed
- 35 ☐ study medication permanently discontinued ●
- 36 ☐ other action

Please complete the rest of this page when final outcome of AE is known

Outcome of AE *tick one box only*
- 37 ☐ Resolved - *give date of resolution, and time if known*
- ☐ Permanent residual effect - *give date when diagnosed as permanent*
- ☐ Ongoing
- ☐ Subject died - *give date of death, and time if known*

[38] day / month / year

[39] (24 hour clock)

Relationship to study drug ● *tick one box only*
- 40 ☐ definite
- ☐ probable
- ☐ possible
- ☐ unlikely
- ☐ none

Additional Information [41]

Date of signature [42] day / month / year

Physician signature [43]

POST STUDY

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

ADVERSE EVENTS

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

Nature of AE [01]

Is this a serious adverse event ? yes [02] no

- 03 ☐ fatal
- 04 ☐ acute life threatening
- 05 ☐ required or prolonged hospitalisation
- 06 ☐ resulted in persistent or significant disability or incapacity
- 07 ☐ resulted in congenital malformation/anomaly
- 08 ☐ important medical event ❶

Date AE started [09] day month year

(24 hour clock)

Time AE started [10]

Severity ❶
- ☐ mild
- ☐ moderate
- ☐ severe [11]

Action taken *(more than one box may be ticked)*
- 12 ☐ none
- 13 ☐ hospitalised or hospitalisation prolonged ❷
- 14 ☐ symptomatic therapy *(complete concomitant medications page)*
- 15 ☐ study medication dose changed
- 16 ☐ study medication permanently discontinued ❸
- 17 ☐ other action

Has the subject ever experienced this AE before? ❹ yes [18] no → **Complete additional information box below**

Date & time of change in severity of AE

Date severity changed [19] day month year

(24 hour clock)

Time severity changed [20]

Severity ❶
- ☐ mild
- ☐ moderate
- ☐ severe [21]

Action taken *(more than one box may be ticked)*
- 22 ☐ none
- 23 ☐ hospitalised or hospitalisation prolonged ❷
- 24 ☐ symptomatic therapy *(complete concomitant medications page)*
- 25 ☐ study medication dose changed
- 26 ☐ study medication permanently discontinued ❸
- 27 ☐ other action

Date severity changed [28] day month year

(24 hour clock)

Time severity changed [29]

Severity ❶
- ☐ mild
- ☐ moderate
- ☐ severe [30]

Action taken *(more than one box may be ticked)*
- 31 ☐ none
- 32 ☐ hospitalised or hospitalisation prolonged ❷
- 33 ☐ symptomatic therapy *(complete concomitant medications page)*
- 34 ☐ study medication dose changed
- 35 ☐ study medication permanently discontinued ❸
- 36 ☐ other action

Please complete the rest of this page when final outcome of AE is known

Outcome of AE *tick one box only*
- 37 ☐ Resolved - *give date of resolution, and time if known*
- ☐ Ongoing
- ☐ Permanent residual effect - *give date when diagnosed as permanent*
- ☐ Subject died - *give date of death, and time if known*

day [38] month year

(24 hour clock) [39]

Relationship to study drug ❶ *tick one box only*
- 40 ☐ definite
- ☐ probable
- ☐ possible
- ☐ unlikely
- ☐ none

Additional Information [41]

Date of signature [42] day month year

Physician signature [43]

POST STUDY

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

CONCOMITANT MEDICATION RECORD

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

Instructions — Concomitant Medication

Notes:

Product name: Enter either brand or generic name. If a combination product is being taken, enter the brand name.

Dose: Enter the dosage regimen of the medication, not the total daily dose. If a combination product is being given, enter the number of tablets, volume of liquid, etc.

Units: For medications containing a single active moiety, enter the unit (eg mg, mcg, ml). If a combination product is being given, enter the dosage form, eg. tablet, teaspoon.

Frequency: Use the following abbreviations:

od - once daily
bd - twice daily
tds - three times daily
qds - four times daily
prn - as required
nocte - at night

Route: Use the following abbreviations:

po - oral
top - topical
inh - inhaled
buc - buccal/sublingual
rec - rectal

Stop date: If medication will continue beyond the end of the subject's participation in the study, draw a horizontal line through the boxes.

POST STUDY

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

CONCOMITANT MEDICATION RECORD

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No: RD 266/ 24573**

Subject Initials				A Number						Subject Number			

Please complete a panel for each medication taken by the subject in the 14 days prior to study entry. Also record all changes in medication use during the study period.

Product name 01 | Dose 02 | Unit 03 | Frequency 04 | Route 05

Reason taken 06

Start date 07: day month year | Stop date 08: day month year

Reason medication was stopped 09

Product name 01 | Dose 02 | Unit 03 | Frequency 04 | Route 05

Reason taken 06

Start date 07: day month year | Stop date 08: day month year

Reason medication was stopped 09

Product name 01 | Dose 02 | Unit 03 | Frequency 04 | Route 05

Reason taken 06

Start date 07: day month year | Stop date 08: day month year

Reason medication was stopped 09

Product name 01 | Dose 02 | Unit 03 | Frequency 04 | Route 05

Reason taken 06

Start date 07: day month year | Stop date 08: day month year

Reason medication was stopped 09

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

ADDITIONAL VITAL SIGNS

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

Were any additional vital signs recorded? *(✓ as applicable)*

☐ NO ☐ YES If 'YES' please complete details below

Repeat Vital Signs

Date: d d m m m y y **Actual Time** : **Period** ☐ **Day** ☐ **Time-Point** ☐ (Hour/Min)

Supine ☐ **Sitting** ☐ **Standing** ☐ Please indicate position vital sign was taken

Pulse ☐☐☐ bpm **Staff Initials** ☐

Blood Pressure ☐☐☐ / ☐☐☐ mmHg

Temperature ☐☐.☐ °C **Resps** ☐☐ Breaths per min

Review of Vital Signs | **Staff signature:**

Normal ☐ **Abnormal – Not Clinically Significant** ☐ **Abnormal – Clinically Significant** ☐

If 'abnormal-clinically significant' please add to Adverse Events page 33.

Repeat Vital Signs

Date: d d m m m y y **Actual Time** : **Period** ☐ **Day** ☐ **Time-Point** ☐ (Hour/Min)

Supine ☐ **Sitting** ☐ **Standing** ☐ Please indicate position vital sign was taken

Pulse ☐☐☐ bpm **Staff Initials** ☐

Blood Pressure ☐☐☐ / ☐☐☐ mmHg

Temperature ☐☐.☐ °C **Resps** ☐☐ Breaths per min

Review of Vital Signs | **Staff signature:**

Normal ☐ **Abnormal – Not Clinically Significant** ☐ **Abnormal – Clinically Significant** ☐

If 'abnormal-clinically significant' please add to Adverse Events page 33.

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

ADDITIONAL 12 LEAD ECG's

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

Were any additional 12-Lead ECG's recorded? *(✓ as applicable)*

☐ **NO** ☐ **YES** If 'YES' please complete details below

12-Lead ECG

Date: d d m m m y y **Actual Time** : (Hour/Min) **Phase** ☐ **Day** ☐ **Time-point** ☐

Was the additional 12-lead ECG taken? (✓ as applicable)

YES ☐ **NO** ☐

Review of ECG (✓ as applicable) **:**

Normal ☐ **Abnormal** – Not Clinically Significant ☐ **Abnormal** – Clinically Significant ☐

If "abnormal- clinically significant", please comment and add to Adverse Events page 33:

12-Lead ECG

Date: d d m m m y y **Actual Time** : (Hour/Min) **Phase** ☐ **Day** ☐ **Time-point** ☐

Was the additional 12-lead ECG taken? (✓ as applicable)

YES ☐ **NO** ☐

Review of ECG (✓ as applicable) **:**

Normal ☐ **Abnormal** – Not Clinically Significant ☐ **Abnormal** – Clinically Significant ☐

If "abnormal- clinically significant", please comment and add to Adverse Events page 33:

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

ADDITIONAL LABORATORY SAMPLES

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

Were any additional blood/urine samples taken? *(✓ as applicable)*

☐ NO ☐ YES If 'YES' please complete details below

Laboratory Evaluation

Date:

d d m m m y y

Time-point (Phase, Day, Hour/Min):

Phase: ☐ **Day:** ☐

Time Point: ☐

Please enter Z Number below:

Additional blood/urine samples taken? (✓as applicable)

YES ☐ **Staff Initials** ☐

Review of blood results (✓ as applicable):

Normal ☐ **Abnormal** Not Clinically Significant ☐ **Abnormal** Clinically Significant ☐

Did any of the results need repeating (✓as applicable)

YES ☐ **NO** ☐

If Yes please record below

Laboratory Evaluation

Date:

d d m m m y y

Time-point (Phase, Day, Hour/Min):

Phase: ☐ **Day:** ☐

Time Point: ☐

Please enter Z Number below:

Additional blood/urine samples taken? (✓as applicable)

YES ☐ **Staff Initials** ☐

Review of blood results (✓ as applicable):

Normal ☐ **Abnormal** Not Clinically Significant ☐ **Abnormal** Clinically Significant ☐

Did any of the results need repeating (✓as applicable)

YES ☐ **NO** ☐

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

PROTOCOL DEVIATION COMMENTS

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

Are there any protocol deviations? *(✓ as applicable)*

☐ NO ☐ YES If 'YES' please complete details below

PAGE	DATE	PROTOCOL DEVIATION	INITIALS/DATE

Signed:_____ **Date:**_____
(Research Physician/Chief Investigator)

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

ADDITIONAL NOTES

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

Are there any additional notes? *(✓ as applicable)*

☐ NO ☐ YES If 'YES' please complete details below

PAGE	DATE	ADDITIONAL NOTES	INITIALS/DATE

Signed:_____ **Date:**_____
(Research Physician/Chief Investigator)

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

STUDY TERMINATION

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

To be completed when all data is available:

REASON FOR STUDY TERMINATION:-

		TICK BOX
1	Study Completed	

Date Subject completed the study : d d m m m y y

Withdrawn due to :-

2	Protocol Deviation (Please specify below.)	
3	Adverse Event	
4	Personal Reasons	
5	Lost to Follow Up	
6	Ineligible for entry on Day 1	
7	Other (Please specify below)	

Date Subject withdrew from study : d d m m m y y

Comments:_____

_____

_____

Print name in block capitals:_____

Signed:_____ **Date:**_____
(Study Officer)

Print name in block capitals:_____

Signed:_____ **Date:**_____
(Research Physician/Chief Investigator)

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

QUALITY CONTROL FORM

Study Name: Gaviscon Instantly Soothing Pilot Study **Study No:** RD 266/ 24573

Subject Initials				A Number						Subject Number			

DATE	CRF PAGE No.	QUESTION	QC'ed BY	QUERY TO:- (STAFF MEMBER)	RESOLVED BY	
					INITIALS	DATE

APPENDIX 16.1.3 LIST OF IECs OR IRBs

In addition to this cover sheet, this appendix contains:

- The Ethics Committee approval letter (4 pages)
- The combined Subject Information Sheet and Consent Form (16 pages)

Canolfan Gwasanaethau Busnes
Business Services Centre

South East Wales Research Ethics Committee - Panel D

Telephone: 02920 376823
Facsimile: 02920 376835
Email: Carl.phillips@bsc.wales.nhs.uk

Dr Peter Dewland
Medical Director
Simbec Research Limited
Merthyr Tydfil
Mid Glamorgan
CF48 4DR

20 December 2007

Dear Dr Dewland

Full title of study:	**A single-centre randomised, partially blind, single dose, crossover pilot study investigating the use of stopwatches to assess the onset of action of soothing and cooling of Gaviscon Peppermint liquid, Double Action Gaviscon liquid, Gaviscon Advance liquid, and a control in subjects with heartburn following a refluxogenic meal.**
REC reference number:	**07/WSE04/130**
Protocol number:	**Final**
EudraCT number:	**2007-005821-31**

Thank you for your letter of 17 December 2007, responding to the Committee's request for further information on the above research, and for submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation [as revised].

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application	5.5	13 November 2007
Investigator CV	Dr P Dewland	25 September 2007
Protocol	Final	13 November 2007
Compensation Arrangements	Allianz Certificate of Insurance	13 November 2007
Letter of invitation to participant	1	13 November 2007
GP/Consultant Information Sheets	1	13 November 2007
Participant Information Sheet	2	13 December 2007
Participant Consent Form: HIV Antibody Testing	2	13 December 2007
Participant Consent Form: Volunteer	2	13 December 2007
Response to Request for Further Information	K Owen	17 December 2007
Study Schedule	1	13 November 2007
Summary of Product Characteristics	Gaviscon Double Action Liquid	
Summary of Product Characteristics	Gaviscon Advanced Oral Suspension	
Summary of Product Characteristics	Gaviscon oral suspension in sachets	
MHRA Request Form		13 November 2007

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from http://www.rdforum.nhs.uk/rdform.htm.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

Here you will find links to the following

a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service on the application procedure. If you wish to make your views known please use the feedback form available on the website.
b) Progress Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
c) Safety Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
d) Amendments. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
e) End of Study/Project. Please refer to the attached Standard conditions of approval by Research Ethics Committees.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nationalres.org.uk .

07/WSE04/130	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Carl Phillips
Executive Officer
South East Wales Research Ethics Committees

Enclosures: Standard approval conditions SL-AC2

Site approval form

Copy to: Mr Kevin Owen, Simbec Research Ltd

Clinical Trials Unit, MHRA

South East Wales Research Ethics Committee - Panel D

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	07/WSE04/130	**Issue number:**	0	**Date of issue:**	20 December 2007
Chief Investigator:	Dr Peter Dewland				
Full title of study:	A single-centre randomised, partially blind, single dose, crossover pilot study investigating the use of stopwatches to assess the onset of action of soothing and cooling of Gaviscon Peppermint liquid, Double Action Gaviscon liquid, Gaviscon Advance liquid, and a control in subjects with heartburn following a refluxogenic meal.			

This study was given a favourable ethical opinion by South East Wales Research Ethics Committee - Panel D on 20 December 2007. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes* (1)
Dr Peter Dewland	Medical Director	Simbec Research Ltd	South East Wales REC - Panel D	20/12/2007	

Approved by the Chair on behalf of the REC:

..... (Signature of Chair/Co-ordinator)

(delete as applicable)

..... (Name)

(1) *The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.*

SUBJECT INFORMATION SHEET

PART 1

1. STUDY TITLE

Study Title	A single-centre randomised, partially blind, single dose, crossover pilot study investigating the use of stopwatches to assess the onset of action of soothing and cooling of Gaviscon Peppermint liquid, Double Action Gaviscon liquid, Gaviscon Advance liquid, and a control in subjects with heartburn following a refluxogenic meal.
Simplified Title	Pilot study using stopwatches to assess the onset of soothing and cooling of Gaviscon Peppermint, Double Action Gaviscon, Gaviscon Advance and a control in subjects with heartburn.
Study Number	Simbec Study Code: RD266/24573 Sponsor Study Code: GA0706

2. INVITATION PARAGRAPH

You are being asked to take part in a research study. Before you decide, it is important that you understand why the research is being done and what it will involve. Please take time to read this information carefully and discuss it with your friends and relatives. Take time to decide whether or not you want to take part.

- Part 1 tells you the purpose of this study and what will happen to you if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you want to take part. Volunteers are able to gain independent advice regarding clinical trials from UK Clinical Research Collaboration (UKCRC) at www.ukcrc.org.

You will be asked to sign a form to confirm your consent to take part and that you understand the information provided to you.

Thank you for reading this.

3. WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to assess the stopwatch technique in measuring the onset of actions of medications that provide a soothing and cooling effect in the throat/oesophagus during heartburn. In this study the stopwatch technique is being used to measure the speed of onset of 3 different types of Gaviscon (a widely used and well known treatment for symptoms such as heartburn and indigestion) and a control, which is a sublingual (under the tongue) tablet with no active ingredients, when used to treat the heartburn/indigestion discomfort caused by eating a meal that would cause this discomfort to occur.

4. WHY HAVE I BEEN CHOSEN?

A total of 20 subjects are needed for this study, who are males or females between 18 and 80 years (inclusive) of age. All subjects must comply with the study entry and exclusion criteria. The most important entry criteria are:

- Subjects must not be taking any medication
- Subjects must not have experienced any bleeding from the stomach or bowel
- Subjects must have a tendency of experiencing heartburn symptoms following some meals

Simbec considers that you may be eligible to enter the study and has therefore asked if you wish to participate.

5. DO I HAVE TO TAKE PART?

No. It is up to you to decide to take part. If you do, you will be given this information sheet to keep and asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

You can withdraw from treatment but keep in contact with us to let us know your progress. Information collected may still be used. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish.

6. WHAT WILL HAPPEN TO ME IF I TAKE PART?

If you enter the study you will receive a single dose of each of the 4 following treatments, one each on 4 separate occasions:

- Gaviscon Peppermint Liquid (10ml)
- Gaviscon Advance Liquid (10ml)
- Gaviscon Double Action Liquid (10ml)
- Control (a sublingual tablet placed under the tongue)

The trial is a crossover design, which means that all the subjects have all the 4 different treatments in turn. The order in which the treatments are given is picked at random by a computer.

There is a break between each of the treatments and the next.
The trial will last about weeks

Screening Visit 1

If you decide to take part in the study, screening tests will be performed to decide if you are eligible. These tests will include:

- Blood and urine samples for laboratory safety tests
- A brief medical examination, including an ECG (electrocardiogram) to monitor your heart function.
- Questions about your medical history.
- A record of your age, weight, height, blood pressure, pulse and oral temperature .

You will also be asked about your ethnic origin as it is known that different racial groups can react to or handle different drugs in different ways.

Screening Visit 2

If the results obtained show that you are considered to be eligible for the study you will be requested to attend Simbec (at least 48 hors after Screening Visit 1) to eat what is known as a refluxogenic meal. This is a normal meal, but one that is considered to be likely to cause heartburn symptoms i.e. it is a high fat meal and we will ask you to lie flat on your back after eating the food to increase the likelihood of symptoms occurring.
If you do experience heartburn symptoms following the meal you will be eligible to continue with the study. If you require it we will then give you a regular remedy to treat the heartburn known as Maalox.

Study Visits

The first part of the study treatment can commence at least 48 hours following Screening Visit 2 and will involve you attending Simbec at about 8:00am on the day of the dosing. The study doctor will then see you to check if you have been well and if you have taken any medications since you were last seen. You will also be required to give a urine sample to test for alcohol and other drugs. Females will also have their sample tested to check for pregnancy.
We would require you not to eat anything on the morning you attend Simbec but we will provide you with a light breakfast (cereal or toast) at about 9:00am. Following the breakfast you will be required to not eat or drink anything until about 1:00pm when you will be given the refluxogenic meal and then asked to lie down after eating it.
When you feel that your heartburn symptoms are at a moderate level you will be asked to immediately report this to the clinic staff. You will then be given the study treatment allocated for you for that visit.
As soon as you are administered the study treatment 2 stopwatches will be started. You will then be required to stop 1 of the stopwatches when you first feel the **soothing** effect of the medication and stop the second stopwatch when you first feel a **cooling** effect of the medication.
At set times following administration of the study medication you will be asked set questions regarding the benefit that you felt from taking the study medication.
You will then be allowed to leave the Simbec clinical unit approximately 1 hour following the dose of the study medication.

Treatment Visits 2, 3 and 4 will follow the same pattern as Treatment Visit 1, there being a period of 2 to 7 days between each visit.

Post Study Visit

You will be asked to attend the trial centre 3 to 7 days after administration of the last (4^{th}) dose for a post study visit. If you are withdrawn from the study you will still be asked to attend for a post-study assessment.

The following procedures will be performed prior to discharge from the trial :

- Blood samples will be taken for laboratory safety tests.
- A physical examination will be performed.
- Your demographic data (weight, age, blood pressure, and pulse etc.) will be recorded.

You may be asked to return again if we need to follow you up.

You will receive a maximum payment of £650.00 for the inconvenience of participating in and satisfactorily completing the trial. Payment will be made in full if you are withdrawn from the study for any medical reason. Payment will usually be made on a

pro-rata basis if you choose to withdraw, or are withdrawn for any non-medical reasons, including non-compliance with any of the study procedures and conditions outlined in the study protocol and this information sheet.

Simbec will provide transport related to this study. In exceptional circumstances travelling expenses may be reimbursed. Prior arrangement with Simbec will be required. The normal reimbursement rate if travelling by car is £0.10 per mile.

7. WHAT DO I HAVE TO DO?

During the study you will be asked to comply with the following:

- You must not have taken part in a Phase I study at Simbec **or elsewhere** during the previous 12 weeks.
- Whilst at Simbec you must eat and drink only what is provided.
- You must not take any drugs or medicine whether prescribed or bought 'over the counter' during two weeks prior to the study or throughout the whole study.
- You will have to avoid coffee, tea, drinking chocolate and other caffeine-containing drinks (includes many soft drinks) and foods (such as chocolate or coffee flavoured cakes, yogurts and ice-cream), throughout the study. You will fast overnight prior to dosing and for 4 hours afterwards when you will receive the refluxogenic meal. During fasts only water will be allowed.
- Alcohol intake must be restricted to two units per day from 7 days prior to the study and alcohol is to be avoided from 48 hours before dosing and throughout the whole study. One unit of alcohol is equivalent to half a pint of beer/lager, 1 glass of wine or a single measure of spirits.
- You must not undertake any exercise more strenuous than normal walking throughout the whole study period.
- You must not give a blood donation for at least one month after the study ends.
- You will not be permitted to use the Volunteer Recreation Room until at least 8 hours after each dose.

8. WHAT IS THE DRUG THAT IS BEING TESTED?

Three of the treatments contain variations of Gaviscon, which is a widely used treatment for heartburn.
The fourth treatment in the study is a control, which in this case is a sublingual tablet with no active ingredients.

9. WHAT ARE THE ALTERNATIVES FOR TREATMENT?

This is a study in healthy volunteers and therefore alternative treatment is not applicable.

10. WHAT ARE THE SIDE EFFECTS OF ANY TREATMENT RECEIVED WHEN TAKING PART?

You may experience some adverse effects of the drug.

The side-effects of taking Gaviscon are very rare but the appearance of rashes could occur.

The control (a sublingual i.e. under the tongue, tablet) is not considered likely to cause you any ill effects.

In any clinical study reactions to the study medications can occur, but it is felt that the risks with the medications used in this study i.e. forms of Gaviscon and the placebo will be very low. If any reaction does happen to occur eg rashes,etc, however unlikely, then Simbec will ensure that the reaction is treated appropriately.

You should report any side effects to the clinical staff at Simbec Research.

11. WHAT ARE THE OTHER POSSIBLE DISADVANTAGES AND RISKS OF TAKING PART?

A total of approximately 12 ml blood if you are male and 17ml if you are female (approximately 1 tablespoon) will be taken from you during this study. This is far less than that removed during a normal blood donation. It is possible that you may feel some

discomfort when the blood samples are being taken. You may also experience bruising and / or bleeding at or around the area of needle / cannula insertion site.

If you have private medical insurance you should let your insurers know that you intend to take part in a research project. They will be able to tell you if this will affect your insurance - we will give you an explanatory letter for them if you so wish.

There is a possibility that the tests performed during the study will find a medical condition which you did not know about. If this happens your research doctor will arrange appropriate treatment and/or, with your permission, will refer you to your GP.

12. WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?

Taking part in this study is not expected to be of any medical benefit to you.

13. WHAT HAPPENS WHEN THE RESEARCH STUDY STOPS?

Following your post study visit, if the results are acceptable to the doctor, you will be discharged from the study. There are no planned procedures for follow-up after the end of the trial other than those for your post-study assessment detailed in Section 6. If you have any side-effects that have not yet resolved you will be required to attend the unit for follow-up procedures.

If any new, analyses on any of your samples or data is planned in the future, then you will be told of this before the analyses is performed and you will be asked to give your consent for the additional analyses. You will retain the right to refuse further analyses.

Blood and urine samples for laboratory testing will be measured on site at Simbec Research and will be kept for approximately 3 months, after which they will be destroyed.

All other data collected will be stored for up to 15 years by Simbec Research. Copies of these data will also be provided to the Sponsor (Reckitt Benckiser Healthcare (UK) Ltd). Details of who may have access to this data and what might happen to this data during this time are provided in Part 2.

14. WHAT IF THERE IS A PROBLEM?

Any complaint about the way you have been dealt with during the study or any possible harm you suffer will be addressed. The detailed information on this is given in Part 2.

15. WILL MY TAKING PART IN THE STUDY BE KEPT CONFIDENTIAL?

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

16. CONTACT DETAILS?

The following persons may be contacted for further information regarding this study:

Chief Investigator: **Dr Peter Dewland**

Simbec Co-Investigators: **Dr James Mullan, Dr Rahul Dimber and Dr Disala Fernando**

Study Manager: **Mr Kevin Owen**

Simbec Freephone Number: 0800 691995
Simbec Emergency Contact Number: 07074 800 900

If you decide to take part in the study you will be provided with a contact card with the telephone number of Simbec Research

If you decide to take part in the study you will be given a copy of your signed consent form and this information sheet to keep.

This completes Part 1 of the Information Sheet. If the information in Part 1 has interested you and you are considering taking part, please continue to read the additional information in Part 2 before making any decision.

PART 2

17. WHAT IF RELEVANT NEW INFORMATION BECOMES AVAILABLE?

Sometimes during a research project, new information becomes available about the medicine that is being studied. If this happens your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

On receiving new information your research doctor may consider it to be in your best interests to stop the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

18. WHAT WILL HAPPEN IF I DON'T WANT TO CARRY ON WITH THE STUDY?

If you withdraw from the study, you are advised that any data up to the point at which you withdraw will be analysed, reported and provided to the Sponsor unless you request otherwise. No further information will be collected from the point of your withdrawal. You may ask that all previously retained samples be destroyed.

In the event that you are withdrawn from the study by the Chief Investigator your data will still be analysed, reported and provided to the Sponsor.

19. WHAT IF THERE IS A PROBLEM?

Compensation for any injury caused by taking part in this study will be in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI). These guidelines recommend that 'the sponsor' without legal commitment, should compensate you without your having to prove that it is at fault. This applies in cases where it is likely that such injury results from giving any new drug or any other procedure carried out in accordance with the protocol for this study. In the event of your suffering injury or ill health as a result of participation in the study you should contact one of the persons listed in section 16 of the information sheet on freephone telephone

number 0800 691995. Your right at law to claim compensation for injury where you can prove negligence is not affected. Copies of these guidelines are available on request.

20. WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

If you agree to take part in the research some parts of your medical records and the data collected for the study may be seen by the company sponsoring (and/or the company organising) the research for purposes of analysing the results. They may also be looked at by people from the company and by representatives of regulatory authorities to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site. Your GP will be informed if you decide to take part in this study.

We may be required by law to disclose the results of the study and the data generated from the study may be submitted to the Medicines Regulating Bodies of one or several countries. You will not be referred to by name in any of these reports and your medical confidentiality will be respected. If you agree to take part in the study, then your information may be passed on to researchers or regulatory authorities in countries that do not provide the same data protection as the UK. Simbec Research will take all reasonable steps to protect your privacy.

All information collected about you during the course of the study will be kept strictly confidential. Any information about you that leaves the Unit will have your full name and address removed so that you cannot be recognised.

In order to maintain the confidentiality of the study for the Sponsor you will agree to keep all information relating to the conduct of the study confidential.

This study is undertaken according to the ethical guidelines of the Declaration of Helsinki (South Africa, 1996) and complies with the recommendations of the Royal College of Physicians on Healthy Volunteers (1986) and also complies with local laws, recommendations and guidelines at present in force in the United Kingdom for the investigation of new therapeutic agents.

All data collected will be stored for up to 15 years by Simbec Research. Copies of these data will also be provided to the Sponsor (Reckitt Benckiser Healthcare (UK) Ltd).

21. WHAT WILL HAPPEN TO ANY SAMPLES I GIVE?

Your name will not be included on any of your samples and your medical confidentiality will be respected.

22. WILL ANY GENETIC TESTS BE DONE?

No genetic tests will be performed during this study.

23. WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

If you agree to take part in the research, your medical records may be inspected by Reckitt Benckiser Healthcare (UK) Ltd for purposes of analysing the results. They may also be looked at by people from Reckitt Benckiser Healthcare (UK) Ltd or by regulatory authorities to check that the study is being carried out correctly. Your data will be analysed by Reckitt Benckiser Healthcare (UK) Ltd or other companies acting on behalf of Reckitt Benckiser Healthcare (UK) Ltd to see how the drug has worked in you and the other people in the study. Your data may be analysed in any country world-wide. Certain statistical tests will be carried out on your data, along with that collected from the other volunteers who entered the study. Reckitt Benckiser Healthcare (UK) Ltd may forward the results of the study to health authorities world-wide, and the results may also be used in reports of the study or scientific presentations or publications.

If you do withdraw from the study, you are advised that any data obtained from you up to the point at which you withdraw will be analysed, reported and provided to the Sponsor unless you ask otherwise. No further information will be added to the database from the point of your withdrawal from the study. You may request that all previously retained samples be destroyed to prevent further analysis.

In the event that you are withdrawn from the study by the Chief Investigator your data will still be analysed, reported and provided to the Sponsor.

Should you decide to withdraw from the study at any time, information collected on you up until that point will still be provided to Reckitt Benckiser Healthcare (UK) Ltd.

24. WHO IS ORGANISING AND FUNDING THE RESEARCH?

The Chief Investigator for this study is:
Dr Peter Dewland
Simbec Research Limited
Merthyr Tydfil
South Wales

The Co-Investigators for this study are:
Dr James Mullan, Dr Rahul Dimber & Dr Disala Fernando
Simbec Research Limited
Merthyr Tydfil
South Wales

The study is sponsored by: Reckitt Benckiser Healthcare (UK) Ltd

Simbec Research Limited is a commercial organization and will be receiving payment for this study.

25. WHO HAS REVIEWED THE STUDY?

This study has been reviewed by South East Wales Research Ethics Committee who raised no objections on ethical grounds.

If you decide to take part in the study you will be given a copy of your signed consent form and this information sheet to keep.

For most studies we need to recruit extra subjects (reserves) in case another subject drops out at the last minute because of illness, problems with tests or other issues. We cannot always say who will be the reserves prior to the study day itself. We cannot guarantee that you will participate in this study and therefore receive full payment.

If we are unable to include you in this study you will receive a payment which will reflect the inconvenience of the study procedures in which you have been involved.

CONSENT FORM

STUDY TITLE: A single-centre randomised, partially blind, single dose, crossover pilot study investigating the use of stopwatches to assess the onset of action of soothing and cooling of Gaviscon Peppermint liquid, Double Action Gaviscon liquid, Gaviscon Advance liquid, and a control in subjects with heartburn following a refluxogenic meal.

STUDY NO: RD266/24573 (GA0706)

A Number :	A
Subject Initials:	
Date of Birth:	

Name of Chief Investigator: Dr Peter Dewland

The following consent form will be signed by the subject to confirm consent

Please initial box

1. I confirm that I have read and understood the information sheet dated 13 December 2007 (Issue: Version 2) for this study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I am willing to allow my GP to be informed of my participation in the study. ☐

4. I understand that sections of any of my medical notes may be looked at by responsible individuals from Simbec Research, the study sponsor or from regulatory authorities where it is relevant to my taking part in research. I give permission for those individuals to have access to my records. I agree that data about me relating to this study may be sent to countries that do not have data protection laws similar to those in the UK. ☐

5. I agree to take part in the above study. ☐

1. Consent for Screening Procedures

Name of Subject	Signature	Date
Name of Person taking consent for screening procedures (if different from investigator)	Signature	Date

2. Consent for Study Participation

Name of Subject	Signature	Date
Investigator	Signature	Date

Two copies: 1 for subject, 1 for Volunteer Master File

I confirm that I have received a copy of this Consent Form and Information Sheet

Subject Initials

INFORMED CONSENT FOR HIV ANTIBODY TESTING

STUDY TITLE: A single-centre randomised, partially blind, single dose, crossover pilot study investigating the use of stopwatches to assess the onset of action of soothing and cooling of Gaviscon Peppermint liquid, Double Action Gaviscon liquid, Gaviscon Advance liquid, and a control in subjects with heartburn following a refluxogenic meal.

STUDY NUMBER: RD266/24573 (GA0706)

1. **INTRODUCTION: HIV ANTIBODY TEST:** is a test currently being used to determine if someone may have been infected by HIV . The test does not tell if you have HIV or if you will get HIV. It takes 4 to 6 weeks or longer from exposure to HIV to positive results in the blood. A positive test result should be confirmed by further testing.

   The sponsor of this study requests that this test will be run on all subjects wishing to participate in the study, and Simbec Research is required to perform this test.

   You will receive counselling by a physician before you take the test. The physician will explain to you the possible consequences of taking the test and prepare you for the results of the test. The test will be explained to you in the context of this research study.

2. **PROCEDURE:** If your test result to the HIV antibody test is negative and all other laboratory test requirements are within the range as required by the protocol, you will qualify for entry into the study. The test results will become part of your case report form.

If your test result to the HIV antibody is positive, you will not be allowed to enter the study.

If your result to the HIV antibody test at Simbec Research is positive, a blood sample will be sent to an independent laboratory in order to confirm the result. At this stage, only if your result is confirmed as being positive will you be called to the clinical pharmacology unit (CPU), at Simbec Research and informed of a positive result. If your test result to the HIV antibody is confirmed as positive, your laboratory results will be given to you or

destroyed. You are advised that if your result is confirmed as positive your GP will be informed and by signing the consent form you agree to this. Other than this, your results will remain confidential. If your result is confirmed as positive, Simbec Research will also refer you, with your permission, to the Department of Genito-Urinary Medicine for further investigations and treatment as necessary. This clinic operates on a code which assures your confidentiality. Simbec Research Limited cannot be held responsible for any further testing or treatment.

Taking the HIV test will not in any way affect your ability to obtain insurance and / or a mortgage or other services. However, It must be emphasised that, while you are waiting for the results of an HIV test, or if you have a positive HIV test result, your ability to obtain life insurance, health insurance, a mortgage, employment and other services, could be adversely affected.

You have read and fully understand the information stated above and you willingly sign this consent form, a copy of which will be given to you. You understand that you have not waived any of your legal rights by signing this document.

VOLUNTEER'S SIGNATURE _____ DATE _____

A Number:	A					

SIGNATURE OF PERSON TAKING CONSENT FOR STUDY PARTICIPATION _____ DATE _____

APPENDIX 16.1.4 LIST AND DESCRIPTION OF INVESTIGATORS AND OTHER IMPORTANT PARTICIPANTS IN THE STUDY

In addition to this cover sheet, this appendix contains:

- The CV of Dr P Dewland (5 pages)
- Table listing the names and affiliations of the individuals whose participation materially affected the conduct of the study, together with their role (1 page).

CURRICULUM VITAE

Peter Maurice Dewland
GMC No: 1526185

Business Address:

Simbec Research Ltd
Merthyr Tydfil Ind Park
Cardiff Road
Merthyr Tydfil
Mid Glamorgan
CF48 4DR

Date of Birth: 13 August 1947

Education:

St. Thomas' Hospital Medical School London	1968 BSc Biochemistry 2.1
St Thomas' Hospital Medical School London	1968-1971 MB BS
Diploma in Pharmaceutical Medicine Royal College of Physicians	1984 Dip Pharm Med
Founder Member of Faculty of Pharmaceutical Medicine	1989 MFPM
Faculty of Pharmaceutical Medicine Royal College of Physicians Elected to Fellowship	1993 FFPM
Awarded Masters in Philosophy and Healthcare (Medical Ethics) University of Wales Dissertation entitled "Research Ethics Committees"	1991 MA
Diploma in Clinical Pharmacology Society of Apothecaries	DCPSA 1997

Pat Dewland
25 Sep 07

Positions:	**House Surgeon, Woolwich**	**1971**
	House Physician, Croydon	**1971-1972**
	Senior House Physician Mayday Hospital, Croydon Emergency Medicine, Paediatrics, Obstetrics & Gynaecology, Orthopaedics	**1972-1974**
	General Medical Practice Banstead, Surrey	**1974-1979**
	Metropolitan Police Surgeon	**1974-1979**
	Simbec Research Limited Research Physician and Head, Clinical Studies Department	**1979-1985**
	Medical Director Simbec Research Limited	**1985-1997**
	Senior Medical Director International Division & Head UK Office, Omnicare Clinical Research, Chippenham, Wilts	**1997-2004**
	Medical Director Simbec Research Limited	**Sept 2004- to date**

Dr Dewland has been Principal Investigator for over 100 FIM trials, supervising the administration of NCEs, biotechnology products, vaccines, medical devices etc

Professional Affiliations:

Trainer and Tutor for Diploma in Clinical Pharmacology (DCPSA) Society of Apothecaries

Fellow of the Royal Society of Medicine

**Accredited Educational Supervisor
Royal College of Physicians**

**Supervisor of Physician Trainees in
Pharmaceutical Medicine**

**Lecturer and Tutor MSc in Clinical Science,
University of Cardiff**

Founder of Cambridge Ethics Committee Training Workshops

Committee Member AHPPI

Training: **Member of Faculty of Pharmaceutical Medicine CPD Scheme**

GCP Training Omnicare 2004 and regular annual updates. His activities as Trainer and Tutor involve regular teaching sessions in GCP.

Publications:

1. **Long-term monitoring of the effects of thymoxamine hydrochloride tablets in the management of patients with Raynaud's Disease**

   Curr-Med-Res-Opin 1982, VOL:8 (3), P:158-70,
   Aylward, Dewland P et al

2. **Urinary recovery and tolerability of FCE 22101 following single intravenous administration under restricted and high fluid intake**

   J-Antimicrob-Chemother 1989 Mar, VOL: 23 Suppl C, P197-203
   Sassella, Dewland et al

3. **Mefanamic acid and diclofenac sodium in osteoarthritis of the weight bearing joints: a double blind comparison**

   Br-J-Clin_Pract 1985 Apr, VOL: 39 (4), P:135-9,
   Aylward, Dewland et al

4. **Clinical evaluation of Acetylcysteine in the treatment of patients with chronic obstructive bronchitis. A balanced double-blind trial with placebo control (1980).**

   Eur. J. Respir. Dis., 61, Suppl. 111, 81-89
   Dewland, P et al

5. **Bioverfuegbatkeit von Nitroglycerin-Sprays als voraussetzung fuer die aequivalente dosierung beim kardialen notfall.**

   Herz and Gefasse, 7, 10/1986, 536-544
   Dewland, P et al

6. **The effects of Cicletanine, a new anti-hypertensive compound, on the flare and weal response to histamine.**

   Drugs Exptl, Clin. Res. 1988. 14(2-3) 225-230
   Dewland , P; Wright, T

7. **Pharmokinetics of Cilazapril during repeated oral dosing in health young volunteers**

European Journal of Drug Metabolism and Pharmacokinetics 1990. VOL: 15, NO.1, 63-67
Williams, Dewland, P et al

8. **AICA-Riboside: Safety, tolerance, and pharmacokinetics of a novel Adenosine-regulating agent**

J. Clin Pharmacol. 1991: 31(4) 342-347
Dixon, Dewland, P et al

9. **Single dose pharmacokinetic and tolerance of Pancopride in healthy volunteers**

Arzneimettel, Forshnung. 1995, 45(2), 177-183
Dewland , P et al

10. **Absence of a Sertraline mediated effect of Digoxin pharmacokinetics and electrocardiograph findings**

J. Clin. Psychiatry 1996; 57 Suppl. 1: 16-9
Rapeport, Dewland P, et al

11. **Absence of a Sertraline mediated effect on the pharmacokinetics and pharmacodynamics of Carbamazepine**

J. Clin. Psychiatry 1996; 57 Suppl. 1: 20-3
Rapeport, Dewland, P et al

12. **Effect of Tenidap Sodium on Digoxin pharmacokinetics in health young men**

Br J Clin Pharmac 1995: 39: 43S-46S
Dewland, P et al

13. **At the coalface, but on the receiving end**

J Med Ethics 1999, 25(6), 541-546
Dewland P, Dewland J

Presentations:

1. **The experience of anxiety in Phase I trials**

   Journal of Psychopharmacology 10,3, (1996): Supplement A42:168
   Dewland, P: Wright, L: Howell, AJ

2. **Dose Linearity of Inhaled Fentanyl, (FT) with Comparative Pharmacokinetics to Transmucosal Fentanyl, (A)**

   Jekunen A, Dewland P M, et al
   ASCO 2006, Abstract No 8629

3. **Migration Properties of Two Different Botulinum Toxin Type A Formulations in the Forehead**

   Dewland P, et al

4. **Migration Properties of Two Different Botulinum Toxin Type A Formulations in the Lower Middle Back**

   Dewland P, et al

Names and Affiliations of Key Individuals in the Study

Title and Name	Qualifications	Job Title	Work Address	Study Role
Dr P Dewland	BSc., MA, MBBS, FFPM, DCPSA	Medical Director	Simbec Research, Merthyr Tydfil, Mid Glamorgan, CF48 4DR	Principal Investigator
Mr K Owen	BSc, RGN	Project Manager	Simbec Research, Merthyr Tydfil, Mid Glamorgan, CF48 4DR	Simbec Project Manager
Dr K Sarratt	BSE, PhD	Clinical Project Manager	Reckitt Benckiser Healthcare, Dansom Lane, Hull HU8 7DS	Study Monitor

APPENDIX 16.1.5 SIGNATURE OF PRINCIPAL INVESTIGATOR

In addition to this cover sheet, this appendix contains:

- The Investigator signature page, completed by the Principal Investigator (1 page)

Reckitt Benckiser

PRINCIPAL INVESTIGATOR'S SIGNATURE

Study Number: GA0706

Report Title: A single-centre randomised, partially blind, single dose, crossover pilot study investigating the use of stopwatches to assess the onset of action of soothing and cooling of Gaviscon Peppermint liquid, Double Action Gaviscon liquid, Gaviscon Advance liquid, and a control in subjects with heartburn following a refluxogenic meal.

Phase: IV

Principal Investigator:

By my signature below, I hereby state that I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study. I agree its conclusions and do not wish to make an additional statement regarding the safety of the product under test.

24 July 2008

Dr Peter Dewland BSc, MA, MBBS, FFPM, DCPSA

Medical Director

Simbec Research Limited
Merthyr Tydfil,
Mid Glamorgan
CF48 4DR
Wales, UK

Tel: 01443 690977

Date

APPENDIX 16.1.6 LISTING OF SUBJECTS RECEIVING TEST DRUG(S) FROM SPECIFIC BATCHES WHERE MORE THAN ONE BATCH WAS USED

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

APPENDIX 16.1.7 RANDOMISATION SCHEME AND CODES

In addition to this cover sheet, this appendix contains:

- The randomisation code for study GA0706 (1 page)
- Details of generation of randomisation code for study GA0706 (1 page)

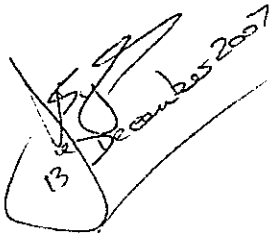
Description of randomisation for GA0706

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.

Project Viva

RANDOMISATION LIST

Volunteer Number	Period 1	Period 2	Period 3	Period 4
01	Treatment Y	Treatment D	Treatment X	Treatment Z
02	Treatment D	Treatment Z	Treatment Y	Treatment X
03	Treatment Z	Treatment X	Treatment D	Treatment Y
04	Treatment X	Treatment Y	Treatment Z	Treatment D
05	Treatment Z	Treatment X	Treatment D	Treatment Y
06	Treatment X	Treatment Y	Treatment Z	Treatment D
07	Treatment Y	Treatment D	Treatment X	Treatment Z
08	Treatment D	Treatment Z	Treatment Y	Treatment X
09	Treatment Z	Treatment X	Treatment D	Treatment Y
10	Treatment Y	Treatment D	Treatment X	Treatment Z
11	Treatment D	Treatment Z	Treatment Y	Treatment X
12	Treatment X	Treatment Y	Treatment Z	Treatment D
13	Treatment X	Treatment Y	Treatment Z	Treatment D
14	Treatment Y	Treatment D	Treatment X	Treatment Z
15	Treatment D	Treatment Z	Treatment Y	Treatment X
16	Treatment Z	Treatment X	Treatment D	Treatment Y
17	Treatment Z	Treatment X	Treatment D	Treatment Y
18	Treatment Y	Treatment D	Treatment X	Treatment Z
19	Treatment D	Treatment Z	Treatment Y	Treatment X
20	Treatment X	Treatment Y	Treatment Z	Treatment D



APPENDIX 16.1.8 AUDIT CERTIFICATES

In addition to this cover sheet, this appendix contains:

- Audit certificate for study GA0706 (1 page)

SIMBEC
CLINICAL RESEARCH AND DEVELOPMENT

QUALITY ASSURANCE AUDIT CERTIFICATE

STUDY TITLE: **A single-centre randomised, partially blind, single dose crossover pilot study investigating the use of stopwatches to assess the onset of action of soothing and cooling of Gaviscon Peppermint liquid, Double Action Gaviscon liquid, Gaviscon Advance liquid and a control in subjects with heartburn following a refluxogenic meal.**

STUDY NUMBER: RD 266/24573 (GA0706)

The data contained in this report have been verified as an accurate presentation of the raw data obtained.

This was confirmed during the audits summarised below:

	Audit / Review Conducted	Audit Report Issued
CRF Audit	11th & 14th January 08	14th January 08
Database Audit	11th April 08 25th April 08 (screening failures only)	16th April 08 25th April 08 (screening failures only)
Clinical Report Audit	15th-17th July 08	17th July 08

SIGNED: L Harries DATE: 25th July 08.

Lisa Harries
QUALITY ASSURANCE UNIT

APPENDIX 16.1.9 DOCUMENTATION OF STATISTICAL METHODS

In addition to this cover sheet, this appendix contains:

- The final Statistical Analysis Plan (18 pages)
- Signature page for final SAP (1 page)

Statistical Analysis Plan

A single-centre, randomized, partially blind, single dose, crossover pilot study investigating the use of stopwatches to assess the onset of action of soothing and cooling of Gaviscon Peppermint liquid, Double Action Gaviscon liquid, Gaviscon Advance liquid, and a control in subjects with heartburn following a refluxogenic meal.

Clinical Phase IV

Sponsor Protocol Identification: GA0706

Simbec Protocol Identification: RD 266/24573

Version: Final, 18th April 2008

Prepared by:

Darren Hughes 18 Apr 2008.

Darren Hughes, Simbec Senior Statistician **Date**

Reviewed by:

Kendra Sarratt 21 Apr 2008

Kendra Sarratt, Reckitt Benckiser Project Manager **Date**

L. Owen 18/APR/2008.

Kevin Owen, Simbec Project Manager **Date**

Approved by:

John Sykes 18 April 2008

John Sykes, Reckitt Benckiser Senior Statistician **Date**

Statistical Analysis Plan

A single-centre, randomized, partially blind, single dose, crossover pilot study investigating the use of stopwatches to assess the onset of action of soothing and cooling of Gaviscon Peppermint liquid, Double Action Gaviscon liquid, Gaviscon Advance liquid, and a control in subjects with heartburn following a refluxogenic meal.

Clinical Phase IV

Sponsor Protocol Identification: GA0706

Simbec Protocol Identification: RD 266/24573

Version: Final, 18th April 2008

Prepared by:

....
Darren Hughes, Simbec Senior Statistician **Date**

Reviewed by:

....
Kendra Sarratt, Reckitt Benckiser Project Manager **Date**

....
Kevin Owen, Simbec Project Manager **Date**

Approved by:

....
John Sykes, Reckitt Benckiser Senior Statistician **Date**

1. Protocol

This statistical analysis plan is written based on the clinical trial protocol produced by Reckitt Benckiser Healthcare (UK) Ltd. of the 13th November 2007.

2. Purpose

The primary objective of this study was to pilot the stopwatch technique for determining the onset of action of products that provide a perceived soothing effect in the throat/oesophagus (foodpipe) during heartburn.

The secondary objectives of this study were to evaluate the time to first perceived cooling effect in the throat/oesophagus (foodpipe); the description of an "instant" benefit from the product; the ability of the product to make the mouth/throat feel fresher; and the subject's willingness to use the product again.

3. Study Design

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

4. Treatment Description

Subjects were treated with a single dose of each of the following treatments, according to a pre-defined randomisation schedule.

Product A: Gaviscon Peppermint liquid in sachets, contains 500mg sodium alginate, 267mg sodium bicarbonate, and 160mg calcium carbonate per 10ml dose, 10ml suspension in sachet, NL15334.

Product B: Gaviscon Advance Aniseed Flavour, contains 1000mg sodium alginate and 200mg potassium bicarbonate per 10ml dose, 300ml suspension in bottle, PL00063/0097.

Product C: Gaviscon Double Action Liquid, contains 500mg sodium alginate 213mg sodium bicarbonate, and 325mg calcium carbonate per 10ml dose, 300ml suspension in bottle, PL00063/0156.

Product D: Control, contains 50.10mg lactose, 30.00mg mannitol, 15.00mg maize starch, 2.00mg povidine K30, 1.48mg citric acid anhydrous granular, 0.75mg magnesium stearate, and 0.67mg sodium citrate per 100mg tablet, Batch No: 397280.

5. Sample Size

No statistical justification for the sample size in this study was performed because this is a pilot study intended to provide variance estimates from which sample size estimates for future studies can be derived.

6. Populations

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

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

7. Study End-Points

The primary study end-point is:

- time to first perceived soothing effect in the throat/oesophagus (foodpipe) using a stopwatch

The secondary study end-points are:

- time to first perceived cooling effect in the throat/oesophagus (foodpipe) using a stopwatch
- 'instant' benefit (yes/no)
- mouth/throat freshness (yes/no)
- willingness to use product to treat heartburn again (yes/no)

The safety end-points for this study are:

- vital signs
- adverse events
- laboratory data

8. Pharmacokinetic Analysis

Not applicable

9. Statistical Analysis

The primary endpoint is the amount of time to first perceived soothing effect in the throat/oesophagus (assessed using a stopwatch). When a soothing effect is not reported within 30 minutes the results will be reported as censored at 30 minutes.

The time to first perceived soothing effect will be summarised by treatment using the number of subjects assessed, the number of subjects with censored and uncensored data and either the mean standard deviation, minimum, median and maximum (if all subjects provide uncensored data) or the median and minimum (when censored data are reported). If there are no censored observations an upper one-sided 95% confidence limit for the mean time to first perceived soothing effect will be computed.

The number and percentage of subjects who have a time to first perceived soothing effect of no more than 5 seconds will be summarised by treatment. The lower one-sided 95% confidence limit for the percentage of subjects who have a time to first perceived soothing effect of no more than 5 seconds will be computed using exact methods and summarised by treatment

The secondary endpoint amount of time to first perceived cooling effect in the throat/oesophagus (assessed using a stopwatch) will be summarised using the same methods as for time to perceived soothing effect.

The three remaining parameters 1) 'instant' benefit 2) mouth/throat freshness and 3) willingness to use product to treat heartburn again will be summarised by treatment using a frequency distribution. For each parameter the lower one-sided 95% confidence limit for the percentage of subjects who gave a positive response will be computed using exact methods and summarized by treatment.

There will be no formal statistical comparison of data from the control and Gaviscon groups.

SAS for Windows 9.1.3 statistical software will be employed for all statistical calculations.

No study-specific validation of SAS programs will be undertaken. Instead all output regarding summary information and statistical analysis will be quality controlled. An independent statistician will perform the same analysis to ensure the information contained in the clinical report is correct.

10. Safety Analysis

10.1 Vital Signs

Descriptive statistics (n, mean, standard deviation, minimum, median and maximum) will be calculated for vital signs parameters at pre-study and post-study. These descriptive statistics will also be presented for the change from pre-study in vital signs parameters.

10.2 Adverse Events

All adverse events will be coded using the MedDRA version 10.0 dictionary. Only treatment emergent adverse events that occur post dosing will be included in the summary tables. Incidence of the number of subjects reporting adverse events by MedDRA preferred term, severity and relationship will be tabulated by treatment.

Additionally, the incidence of treatment emergent adverse events will be 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.

10.3 Laboratory Data (Biochemistry and Haematology)

Descriptive statistics (n, mean, standard deviation, minimum, median and maximum) of absolute values at pre-study will be calculated for all laboratory parameters.

11. Other Analyses

11.1 Demographics

Descriptive statistics (n, mean, standard deviation, minimum, median and maximum) will be calculated for the continuous variables age, height, weight and BMI by gender and overall.

12. Release of Data

After database lock the Simbec study Statistician will list and tabulate all the safety data, additionally they will perform the statistical analyses on the efficacy data. The Simbec study statistician will then send a zipped file to Reckitt Benckiser of all the safety listings, tables and statistical analyses, which will also include a list of the study populations.

List of Listings (Study Population)

- Screening Failures (All Subjects)
- Subject Populations (All Subjects)
- Visit Dates (All Subjects)
- Demographic Data (All Subjects)
- Vital Signs Data (All Subjects)
- General History (All Subjects)
- Medical History (All Subjects)
- Concurrent Conditions (All Subjects)
- Physical Examination (All Subjects)
- Previous Medication (All Subjects)
- Inclusion/Exclusion Criteria (All Subjects)
- Drugs of Abuse and Pregnancy Results (All Subjects)
- Virology Results (All Subjects)
- Refluxogenic Meal Data (All Subjects)
- Dose Administration (All Subjects)
- ECG Data (All Subjects)
- Soothing and Cooling Effect Data (All Subjects)
- Adverse Events (All Subjects)
- Concomitant Medications (All Subjects)
- Protocol Deviations (All Subjects)
- Additional Medical Notes (All Subjects)
- Final Evaluation (All Subjects)
- Biochemistry Data (All Subjects)
- Haematology Data (All Subjects)
- Urinalysis Data (All Subjects)
- Microscopy Results (All Subjects)
- Biochemistry Out of Ranges (All Subjects)
- Haematology Out of Ranges (All Subjects)
- Urinalysis Out of Ranges (All Subjects)

List of Summary Tables (Study Population)

- Demography (Safety Population)
- Vital Signs (Safety Population)
- Adverse Events by Organ System and Preferred Term (Safety Population)
- Adverse Events by Severity (Safety Population)
- Adverse Events by Relationship (Safety Population)
- Biochemistry Data (Safety Population)
- Haematology Data (Safety Population)
- Time to First Perceived Soothing Effect (ITT Population)
- Frequency of Subjects with Time to First Perceived Soothing Effect of No More than 5 Seconds (ITT Population)
- Time to First Perceived Cooling Effect (ITT Population)
- Subjective Assessments (ITT Population)

TABLE SHELLS

Demography (Safety Population)

Variable		Male	Female	All
AGE (YRS)	N	15	5	20
	MEAN	27.1	27.3	27.2
	SD	8.7	7.5	8.2
	MIN	18	18	18
	MEDIAN	24	24	24
	MAX	45	36	45
HEIGHT (M)	N	15	5	20
	MEAN	1.81	1.63	1.75
	SD	0.07	0.08	0.11
	MIN	1.70	1.52	1.52
	MEDIAN	1.81	1.61	1.79
	MAX	1.96	1.73	1.96
WEIGHT (KG)	N	15	5	20
	MEAN	79.0	63.8	74.2
	SD	6.2	8.0	9.8
	MIN	68.4	53.6	53.6
	MEDIAN	78.3	63.3	76.7
	MAX	91.8	74.1	91.8
BMI (KG/M^2)	N	15	5	20
	MEAN	24.2	24.0	24.1
	SD	1.9	1.7	1.8
	MIN	20.6	21.9	20.6
	MEDIAN	25.1	23.2	24.4
	MAX	26.6	26.2	26.6

Vital Signs (Safety Population)

Variable		Pre-Study	Post-Study	Change
SITTING SBP	N	20	20	20
(MMHG)	MEAN	137.5	144.2	6.7
	SD	5.5	8.3	8.3
	MIN	131	136	-1
	MEDIAN	137	143	4.5
	MAX	147	159	21
SITTING DBP	N	20	20	20
(MMHG)	MEAN	75.1	76.8	1.6
	SD	13.6	15.8	8.0
	MIN	59	55	-4
	MEDIAN	74	81.5	-3
	MAX	96	94	12
SITTING	N	20	20	20
PULSE (BPM)	MEAN	65.0	63.3	-1.1
	SD	10.9	10.9	5.7
	MIN	50	51	-7
	MEDIAN	65	64.5	-1.5
	MAX	79	82	7
TEMP. (C)	N	20	20	20
	MEAN	36.77	36.4	-0.35
	SD	0.47	0.22	0.41
	MIN	35.9	36.2	-0.9
	MEDIAN	36.9	36.4	-0.45
	MAX	37.2	36.8	-0.3

Adverse Events by Preferred Term (Safety Population)

		Number of Reports / Number of Subjects (% brackets)			
MedDRA Primary SOC	MedDRA Preferred Term	A (n=20)	B (n=20)	C (n=20)	D (n=20)
General Disorders and Administration Site Conditions	THIRST	1 / 1 (4.2)	2 / 2 (8.3)	2 / 2 (8.3)	0
Nervous System Disorders	DIZZINESS	2 / 1 (4.2)	1 / 1 (4.2)	1 / 1 (4.2)	0
	HEADACHE	0	0	0	1 / 1 (4.2)

Product A: Gaviscon Peppermint liquid in sachets, contains 500mg sodium alginate, 267mg sodium bicarbonate, and 160mg calcium carbonate per 10ml dose, 10ml suspension in sachet, NL15334.

Product B: Gaviscon Advance Aniseed Flavour, contains 1000mg sodium alginate and 200mg potassium bicarbonate per 10ml dose, 300ml suspension in bottle, PL00063/0097.

Product C: Gaviscon Double Action Liquid, contains 500mg sodium alginate 213mg sodium bicarbonate, and 325mg calcium carbonate per 10ml dose, 300ml suspension in bottle, PL00063/0156.

Product D: Control, contains 50.10mg lactose, 30.00mg mannitol, 15.00mg maize starch, 2.00mg povidine K30, 1.48mg citric acid anhydrous granular, 0.75mg magnesium stearate, and 0.67mg sodium citrate per 100mg tablet, Batch No: 397280.

Adverse Events by Severity (Safety Population)

Product A

MedDRA Primary SOC	MedDRA Preferred Term	Mild	Moderate	Severe
General Disorders and Administration Site Conditions	THIRST (p=1.0000)	1	0	0
Nervous System Disorders	DIZZINESS (p=0.6345)	0	1	0
	HEADACHE (p=1.0000)	1	1	0

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

Adverse Events by Relationship (Safety Population)

Product A

MedDRA Primary SOC	MedDRA Preferred Term	Definite	Probable	Possible	Unlikely	None
General Disorders and Administration Site Conditions	THIRST (p=1.0000)	0	0	1	0	0
Nervous System Disorders	DIZZINESS (p=1.0000)	1	0	0	0	0
	HEADACHE (p=0.4512)	0	0	1	1	0

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

Biochemistry Data (Safety Population)

Phase	Parameter	N	Mean	SD	Minimum	Median	Maximum
Pre-Study	ALP (IU.L-1)	24	156.31	35.83	96.1	196.25	229.3
Pre-Study	ALT (IU.L-1)	24	20.09	7.22	8.5	20.20	37.4
Pre-Study	AST (IU.L-1)	24	21.84	4.77	16.6	22.3	36.3
Pre-Study	Albumin (g.L-1)	24	45.10	2.94	39.3	44.15	52.7
Pre-Study	Calcium (mmol.L-1)	24	2.57	0.1	2.37	2.37	2.74
Pre-Study	Cholesterol (mmol.L-1)	24	4.69	0.75	3.3	4.45	5.8
Pre-Study	Creatine Kinase (IU.L-1)	24	121.86	78.89	25.0	138.45	396.7
Pre-Study	Creatinine (umol.L-1)	24	79.80	13.43	57.8	76.8	110.6
Pre-Study	GGT (IU.L-1)	24	16.00	5.25	7.6	16.1	27.1
Pre-Study	Glucose (mmol.L-1)	24	4.72	0.58	3.5	4.7	6.3
Pre-Study	HBD (IU.L-1)	24	128.94	20.9	102.7	116.4	188.2
Pre-Study	Phosphorus (mmol.L-1)	24	1.12	0.15	0.76	1.05	1.35
Pre-Study	Potassium (mmol.L-1)	24	4.48	0.29	4.02	4.46	5.06
Pre-Study	Sodium (mmol.L-1)	24	140.04	1.58	136.7	139	142.9
Pre-Study	Total Bilirubin (umol.L-1)	24	10.50	4.66	5.8	11.65	24.5
Pre-Study	Total Protein (g.L-1)	24	73.54	3.88	63.3	72.05	79.5
Pre-Study	Triglycerides (mmol.L-1)	24	1.19	0.79	0.45	1.18	3.46
Pre-Study	Urea (mmol.L-1)	24	4.58	1.31	2.2	4.0	6.9
Pre-Study	Uric Acid (mmol.L-1)	24	0.3	0.08	0.13	0.33	0.42

Haematology Data (Safety Population)

Phase	Parameter	N	Mean	SD	Minimum	Median	Maximum
Pre-Study	Basophils (X10 9.L-1)	24	0	0	0	0	0
Pre-Study	Eosinophils (X10 9.L-1)	24	0.146	0.078	0.1	0.0	0.4
Pre-Study	Haematocrit (L.L-1)	24	0.417	0.030	0.345	0.447	0.458
Pre-Study	Haemoglobin (g.L-1)	24	14.417	0.987	12.3	15.15	15.8
Pre-Study	Lymphocytes (X10 9.L-1)	24	1.550	0.344	0.9	1.65	2.1
Pre-Study	MCH (pg)	24	30.921	1.375	28.7	28.15	34.7
Pre-Study	MCHC (g.L-1)	24	34.608	0.882	33.4	34	37.1
Pre-Study	MCV (fL)	24	89.354	3.547	83.1	84.15	97.3
Pre-Study	Monocytes (X10 9.L-1)	24	0.371	0.112	0.2	0.4	0.6
Pre-Study	Neutrophils (X10 9.L-1)	24	3.104	0.984	1.9	3.6	5.5
Pre-Study	Platelets (X10 9.L-1)	24	24.438	3.466	19.9	263.5	31.5
Pre-Study	RBC (X10 12.L-1)	24	4.674	0.409	3.68	5.35	5.2
Pre-Study	WBC (X10 9.L-1)	24	5.313	1.118	3.7	5.7	8.0

Time to First Perceived Soothing Effect (ITT Population)

Product	N	No. Censored	No. Uncensored	Mean	Upper 95% CI	SD	Minimum	Median	Maximum
Product A	20	0	20	2.69	4.20	3.24	0.27	1.34	14.60
Product B	20	0	20	1.99	2.92	1.99	0.22	1.17	7.38
Product C	20	0	20	2.14	3.05	1.96	0.17	1.37	7.00
Product D	20	16	4	---	---	---	7.48	30.00	---

A similar table will be presented for Time to First Perceived Cooling Effect

Frequency of Subjects with Time to First Perceived Soothing Effect of No More than 5 Seconds (ITT Population)

Product	N	Time < 5 Seconds N (%))
Product A	20	0 (0.0)
Product B	20	0 (0.0)
Product C	20	0 (0.0)
Product D	20	0 (0.0)

Subjective Assessments (ITT Population)

	Response n (%)	Product A	Product B	Product C	Product D
Parameter					
Instant Benefit	No	20 (100.0)	7 (35.0)	6 (30.0)	8 (40.0)
	Yes	0 (0.0)	13 (65.0)	14 (70.0)	14 (60.0)
	L95% CL for % Yes	0	10.0	12.5	20.0
Mouth/Throat Feel Fresher	No	20 (100.0)	8 (40.0)	5 (25.0)	6 (30.0)
	Yes	0 (0.0)	12 (60.0)	15 (75.0)	14 (70.0)
	L95% CI for % Yes	0	17.5	22.5	25.0
Willing to Use Again	No	20 (100.0)	7 (35.0)	2 (10.0)	4 (20.0)
	Yes	0 (0.0)	13 (65.0)	18 (90.0)	16 (80.0)
	L95% CI for % Yes	0	15.0	45.0	35.0

APPENDIX 16.1.10 DOCUMENTATION OF INTER-LABORATORY STANDARDISATION METHODS AND QUALITY ASSURANCE PROCEDURES

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

APPENDIX 16.1.11 PUBLICATIONS BASED ON THE STUDY

- None of the data from this study has been published so this appendix is not present

APPENDIX 16.1.12 IMPORTANT PUBLICATIONS REFERENCED IN THE REPORT

- None of the publications referenced in the report is appended

APPENDIX 16.2 SUBJECT DATA LISTINGS

This section consists of 8 appendices with their own cover sheets

APPENDIX 16.2.1 DISCONTINUED SUBJECTS

No subjects discontinued the study. This appendix contains:

- The study termination listing (1 page)

RD 266/24573 (GA0706)

Study Termination

Subject Number	Completed Study	Date Completed
1	YES	12FEB2008
2	YES	13FEB2008
3	YES	13FEB2008
4	YES	14FEB2008
5	YES	13FEB2008
6	YES	13FEB2008
7	YES	13FEB2008
8	YES	13FEB2008
9	YES	13FEB2008
10	YES	14FEB2008
11	YES	13FEB2008
12	YES	19FEB2008
13	YES	19FEB2008
14	YES	21FEB2008
15	YES	19FEB2008
16	YES	20FEB2008
17	YES	19FEB2008
18	YES	20FEB2008
19	YES	19FEB2008
20	YES	19FEB2008

Output File: term, 28APR2008 8:22, Final

APPENDIX 16.2.2 PROTOCOL DEVIATIONS

There were no protocol deviations so this appendix is not present.

APPENDIX 16.2.3 SUBJECTS EXCLUDED FROM THE ANALYSES

In addition to this cover sheet, this appendix contains:

- The screen failures listing (1 page)
- The study population data listing (1 page)

RD 266/24573 (GA0761)

Screening Failures

Screening Number	Subject Init.	Date of Consent	Eligible to Attend 2nd Screening	Passed all Inclusion /Exclusion Criteria	Suitable for Enrolment	Completed Study	Date Withdrew	Reason for Termination
7	JMP	24JAN2008	YES	NO	NO	NO	24JAN2008	DID NOT ATTEND FOR THE SCREENING VISIT 2
9	DRP	24JAN2008	YES	YES	YES	NO	28JAN2008	UNABLE TO GET TIME OFF WORK
12	P-L	24JAN2008	YES	NO	NO	NO	28JAN2008	NO HEARTBURN AT SCREENING VISIT 2
13	AME	24JAN2008	YES	NO	NO	NO	28JAN2008	NO HEARTBURN AT SCREENING VISIT 2
20	J C	28JAN2008	YES	YES	NO	NO	31JAN2008	CHOLESTEROL TOO HIGH
24	LAH	28JAN2008	YES	YES	YES	NO	05JAN2008	SUBJECT POSITIVE COCAINE ON TREATMENT VISIT 1 (05 FEB 08). BANNED
25	N-F	30JAN2008	NO	NO	NO	NO	30JAN2008	NOT BEEN TAKING CONTRACEPTION FOR LONG ENOUGH
26	LTC	30JAN2008	NO	NO	NO	NO	30JAN2008	CANNABINOID POSITIVE RESULT
28	SAD	31JAN2008	YES	YES	YES	NO	04FEB2008	SUBJECT WAS A RESERVE
29	MLR	31JAN2008	YES	YES	YES	NO	04FEB2008	SUBJECT WAS A RESERVE

Output File: scr_fail, 28APR2008 9:13, Final

RD 266/24573 (GA0706)

Subject Populations

Subject Number	Safety Population	ITT Population
1	Yes	Yes
2	Yes	Yes
3	Yes	Yes
4	Yes	Yes
5	Yes	Yes
6	Yes	Yes
7	Yes	Yes
8	Yes	Yes
9	Yes	Yes
10	Yes	Yes
11	Yes	Yes
12	Yes	Yes
13	Yes	Yes
14	Yes	Yes
15	Yes	Yes
16	Yes	Yes
17	Yes	Yes
18	Yes	Yes
19	Yes	Yes
20	Yes	Yes

Output File: pops, 28APR2008 11:22, Final

APPENDIX 16.2.4 DEMOGRAPHIC DATA

In addition to this cover sheet, this appendix contains:

- Concomitant Medications listing (1 page)
- Concurrent Conditions listing (2 pages)
- Demographic Data listing (1 page)
- ECG Results listing (2 pages)
- Abnormal Physical Examination listing (1 page)
- General History listing (e.g. heartburn, smoking and alcohol history) (1 page)
- Medical History listing (4 pages)
- Inclusion/Exclusion criteria listing (1 page)
- Additional Medical Notes listing (2 pages)
- Previous Medications and Contraceptive Use listing (1 page)
- Vital Signs listing (2 pages)
- Refluxogenic meal listing (1 page)

RD 266/24573 (GA0706)

Listing of Concomitant Medication

Subject	Concomitant Medication	Dose	Unit	Frequency	Route	Reason Taken	Start Date	Stop Date	Reason Stopped
Gaviscon Advance Aniseed Flavour									
15	CLARITHROMYCIN	500	MG	TDS	PO	UPPER RESPIRATORY TRACT INFECTION	15FEB2008	21FEB2008	COURSE OF ANTIBIOTICS COMPLETED
Gaviscon Double Action Liquid									
9	BISACODYL	10	MG	OD	PO	CONSTIPATION	08FEB2008	08FEB2008	SINGLE DOSE
Control									
12	COCODOMOL	2 TABLETS	GRM	BD	PO	FOR COMMON COLD	17FEB2008	18FEB2008	FELT BETTER

Output File: cmed, 29APR2008 9:40, Final

RD 266/24573 (GA0706)

Concurrent Conditions

Subject	System	Details	Start Date	Clinically Significant
1	GASTRO-INTESTINAL	OCCASIONAL HEARTBURN	2000	NO
2	GASTRO-INTESTINAL	REFLUX OESOPHAGITIS	DEC2005	NO
5	OPHTHALMOLOGICAL	GLASSES FOR DRIVING	NK	NO
5	GENITO-URINARY	IUCD	2005	NO
5	MUSCULOSKELETAL	OSTEOARTHRITIS RIGHT MTP JOINT	2006	NO
6	CARDIOVASCULAR	PALPITATIONS IN PAST	NK	NO
6	GASTRO-INTESTINAL	MILD GASTRITIS ON OGD	NK	NO
7	MUSCULOSKELETAL	PATELLO-FEMORAL DISORDER (BILATERAL)	1998	NO
8	ALLERGIES	HAYFEVER	2003	NO
9	CARDIOVASCULAR	MURMUR IN PREGNANCY ECHO NORMAL	1994	NO
10	MUSCULOSKELETAL	BACK PAIN	1991	NO

RD 266/24573 (GA0706)

Concurrent Conditions

Subject	System	Details	Start Date	Clinically Significant
11	DERMATOLOGICAL	ECZEMA	2003	NO
12	GASTRO-INTESTINAL	CONSTIPATION (INTERMITTENT)	1992	NO
12	MUSCULOSKELETAL	LOW BACK PAIN	FEB1998	NO
13	DERMATOLOGICAL	BREAST IMPLANT	1972	NO
13	DERMATOLOGICAL	ROSACEA	NK	NO
13	CARDIOVASCULAR	OCCASIONAL PALPITATION	NK	NO
13	GASTRO-INTESTINAL	OCCASIONAL INDIGESTION	NK	NO
13	MUSCULOSKELETAL	SCIATICA	2003	NO
14	MUSCULOSKELETAL	SUBLUXATION RIGHT SHOULDER	2007	NO
15	MUSCULOSKELETAL	SHOULDER ARTHRITIS	NK	NO
16	RESPIRATORY	ASTHMA - INFREQUENT USE OF MEDICATION	2002	NO
20	MUSCULOSKELETAL	LOW BACK PAIN	2001	NO

Output File: cond, 28APR2008 9:52, Final

RD 266/24573 (GA0706)

Demographic Data

Subject Number	Subject Init.	Date of Consent	Sex	Race	Age (yrs)	Height (cm)	Pre-Study Weight (kg)	BMI
1	LJO	24JAN2008	FEMALE	CAUCASIAN	19	162	56.1	21.4
2	SLT	22JAN2008	FEMALE	CAUCASIAN	49	161	56.9	22.0
3	LBB	22JAN2008	MALE	CAUCASIAN	29	172	68.5	23.2
4	NJF	25JAN2008	FEMALE	CAUCASIAN	37	155	93.6	39.0
5	B-D	25JAN2008	FEMALE	CAUCASIAN	56	160	63.8	24.9
6	S-D	23JAN2008	FEMALE	CAUCASIAN	58	154	61.7	26.0
7	KEH	25JAN2008	FEMALE	CAUCASIAN	36	164	68.5	25.5
8	MLD	25JAN2008	FEMALE	CAUCASIAN	33	160	57.0	22.3
9	S-R	25JAN2008	FEMALE	CAUCASIAN	38	155	51.9	21.6
10	BAP	24JAN2008	FEMALE	CAUCASIAN	29	167	74.3	26.6
11	R-M	23JAN2008	FEMALE	CAUCASIAN	50	158	51.7	20.7
12	AJB	21JAN2008	FEMALE	CAUCASIAN	36	161	74.1	28.6
13	TMH	25JAN2008	FEMALE	CAUCASIAN	64	158	66.2	26.5
14	D-P	24JAN2008	MALE	CAUCASIAN	41	176	93.1	30.1
15	WGM	24JAN2008	MALE	CAUCASIAN	65	174	83.0	27.4
16	HLD	28JAN2008	FEMALE	CAUCASIAN	25	168	72.5	25.7
17	S-P	28JAN2008	FEMALE	CAUCASIAN	45	167	112.1	40.2
18	L-H	28JAN2008	FEMALE	CAUCASIAN	23	165	55.1	20.2
19	C-W	30JAN2008	MALE	CAUCASIAN	28	176	89.8	29.0
20	N-T	31JAN2008	FEMALE	CAUCASIAN	44	169	65.2	22.8

Output File: dmog, 20MAY2008 12:08, Final

RD 266/24573 (GA0706)

ECG Results

Subject	Visit	Heart Rate (bpm)	PR Interval (mSec)	QRS Width (mSec)	QT Interval (mSec)	QTC Interval (mSec)	Review
1	Pre-Study	73	178	76	359	395	NORMAL
1	Post-Study	59	143	80	389	385	NORMAL
2	Pre-Study	74	138	91	379	420	NORMAL
2	Post-Study	72	140	72	371	406	NORMAL
3	Pre-Study	55	169	106	406	388	NORMAL
3	Post-Study	65	171	98	383	398	NORMAL
4	Pre-Study	64	119L	78	381	393	ABNORMAL - NCS
4	Post-Study	72	105L	80	363	397	ABNORMAL - NCS
5	Pre-Study	60	183	83	404	404	NORMAL
5	Post-Study	52	177	75	409	380	NORMAL
6	Pre-Study	51	171	71	418	385	NORMAL
6	Post-Study	49	173	72	420	379	NORMAL
7	Pre-Study	63	157	83	368	377	NORMAL
7	Post-Study	63	171	83	374	383	NORMAL
8	Pre-Study	69	169	77	365	391	NORMAL
8	Post-Study	57	171	82	402	391	NORMAL
9	Pre-Study	62	151	88	362	367	NORMAL
9	Post-Study	64	161	81	350	361	NORMAL
10	Pre-Study	50	153	76	406	370	NORMAL
10	Post-Study	66	153	74	374	392	NORMAL

Output File: ecg, 28APR2008 9:38, Final

H = Above Normal Range
L = Below Normal Range
RD 266/24573 (GA0706)

ECG Results

Subject	Visit	Heart Rate (bpm)	PR Interval (mSec)	QRS Width (mSec)	QT Interval (mSec)	QTC Interval (mSec)	Review
11	Pre-Study	65	172	80	369	384	ABNORMAL - NCS
11	Pre-Study Rpt	61	186	75	368	371	ABNORMAL - NCS
11	Post-Study	63	178	77	370	379	NORMAL
12	Pre-Study	66	185	85	363	380	NORMAL
12	Post-Study	71	177	92	342	372	NORMAL
13	Pre-Study	65	132	84	367	381	NORMAL
13	Post-Study	67	132	86	363	383	NORMAL
14	Pre-Study	72	157	87	376	411	NORMAL
14	Post-Study	64	163	85	371	383	NORMAL
15	Pre-Study	60	161	70	406	406	NORMAL
15	Post-Study	67	160	71	373	394	NORMAL
16	Pre-Study	59	162	80	416	412	NORMAL
16	Post-Study	61	155	75	409	412	NORMAL
17	Pre-Study	88	138	85	339	410	NORMAL
17	Post-Study	88	140	85	336	406	NORMAL
18	Pre-Study	57	144	80	409	398	NORMAL
18	Post-Study	71	146	86	373	405	NORMAL
19	Pre-Study	58	158	88	346	340L	ABNORMAL - NCS
19	Pre-Study Rpt	61	153	88	345	347L	ABNORMAL - NCS
19	Post-Study	59	154	83	355	352	NORMAL
20	Pre-Study	53	145	76	415	390	NORMAL
20	Post-Study	55	145	75	403	385	NORMAL

Output File: ecg, 28APR2008 9:38, Final

H = Above Normal Range
L = Below Normal Range

RD 266/24573 (GA0706)

Abnormal Physical Examination at Screening

Subject	System	Details
2	DERMATOLOGICAL	TATTOO LEFT SHOULDER
3	DERMATOLOGICAL	TATTOOS ON RIGHT + LEFT HANDS
6	GASTRO-INTESTINAL	HYSTERECTOMY SCAR
7	DERMATOLOGICAL	TATTOO ON THE BACK
8	DERMATOLOGICAL	TATTOO LEFT SHOULDER
9	DERMATOLOGICAL	SCAR (POST OP KIDNEY SURGERY) RIGHT/FLANK
10	DERMATOLOGICAL	TATTOO ON THE BACK
11	DERMATOLOGICAL	PATCH OF ECZEMA ON LEFT LOWER LEG
12	DERMATOLOGICAL	TATTOOS BACK, RIGHT ARM
13	OPHTHALMOLOGICAL	BILATERAL INTRAOCULAR LENS
13	DERMATOLOGICAL	BILATERAL BREAST IMPLANT
17	DERMATOLOGICAL	TATTOO LEFT BREAST,
17	GASTRO-INTESTINAL	ABDOMINOPLASTY SCAR, CAESAREAN SECTION SCAR
18	DERMATOLOGICAL	TATTOOS IN LIF (LEFT ILLIAC FOSSA), RIGHT SHOULDER BLADE, BASE + MIDDLE SPINE
20	DERMATOLOGICAL	LASERATION SCAR ON THE RIGHT FOREARM

RD 266/24573 (GA0706)

General History

Subject	History of Heartburn Related to Reflux	History of Drug, Solvent or Alcohol Abuse	Alcohol User	Alcohol Consumption (u/week)	Tobacco User	Tobacco Amount per Day
1	YES	NO	YES	2	NO	
2	YES	NO	YES	4	NO	
3	YES	NO	YES	2	NO	
4	YES	NO	YES	10	NO	
5	YES	NO	YES	10	NO	
6	YES	NO	YES	1	NO	
7	YES	NO	YES	4	NO	
8	YES	NO	NO		YES	10
9	YES	NO	YES	6	YES	5
10	YES	NO	NO		YES	8
11	YES	NO	NO		NO	
12	YES	NO	YES	10	YES	5
13	YES	NO	YES	8	NO	
14	YES	NO	NO		NO	
15	YES	NO	YES	6	NO	
16	YES	NO	YES	10	NO	
17	YES	NO	YES	10	NO	
18	YES	NO	YES	4	NO	
19	YES	NO	YES	12	NO	
20	YES	NO	YES	2	YES	10

Medical History

Subject	System	Details	Start Date	Stop Date	Clinically Significant
1	DERMATOLOGICAL	ACNE	2005	2006	NO
1	RESPIRATORY	ASTHMA	1994	1999	NO
1	NEUROLOGICAL	MENINGITIS	1995	1995	NO
3	OPHTHALMOLOGICAL	RETINAL DETACHMENT	FEB2003	2003	NO
3	GENITO-URINARY	ENURESIS + ENCOPORESIS	1987	1987	NO
3	PSYCHIATRIC	CONSULTATION REGARDING ENURESIS + ENCOPORESIS	1987	1987	NO
4	DERMATOLOGICAL	ATOPIC DERMATITIS HANDS	1994	1994	NO
4	MUSCULOSKELETAL	ARTHROSCOPY LEFT KNEE	25MAR1999	25MAR1999	NO
5	ENT	TONSILLECTOMY	1958	1958	NO
5	GENITO-URINARY	BREAST LUMP	2004	2004	NO
5	NEUROLOGICAL	VASO VAGAL ATTACKS	1997	1997	NO
6	GENITO-URINARY	HYSTERECTOMY + OOPHORECTOMY	08JAN2001	08JAN2001	NO
7	GASTRO-INTESTINAL	GASTRO OESOPHAGEAL REFLUX OGD NORMAL, NOT ON TREATMENT	2002	2002	NO
7	GENITO-URINARY	CIN III LLETZ	2002	2002	NO
7	GENITO-URINARY	DRAINAGE OF BREAST ABSCESS	1989	1989	NO
7	PSYCHIATRIC	DEPRESSION	1994	1994	NO

Output File: hist, 29APR2008 9:03, Final

Subject	System	Details	Start Date	Stop Date	Clinically Significant
8	GENITO-URINARY	CIN CERVIX	2002	2002	NO
8	GENITO-URINARY	LARGE LOOP EXCISION OF TRANSITIONAL ZONE OF CERVIX	2002	2002	NO
9	GENITO-URINARY	DUPLEX RT KIDNEY	1975	1975	NO
9	GENITO-URINARY	TOP - TERMINATION OF PREGNANCY	2001	2001	NO
9	PSYCHIATRIC	PERIOD OF LOW MOOD + ANXIETY	2006	2006	NO
10	GENITO-URINARY	LAPAROSCOPY + DYE TEST	1996	1996	NO
10	GENITO-URINARY	1 TOP/MISCARRIAGE	2007	2007	NO
11	GASTRO-INTESTINAL	IRRITABLE BOWEL SYNDROME	1995	1995	NO
11	GENITO-URINARY	ECTOPIC PREGNANCY	1982	1982	NO
11	PSYCHIATRIC	REACTIVE DEPRESSION	2005	2005	NO
12	GASTRO-INTESTINAL	GASTRITIS	FEB2003	MAR2003	NO
12	GASTRO-INTESTINAL	BILIARY COLIC	07SEP2006	SEP2006	NO
13	OPHTHALMOLOGICAL	CATARACT EXTRACTION	2004	2004	NO
13	GENITO-URINARY	DILATION AND CURETTAGE	1970	1970	NO

Subject	System	Details	Start Date	Stop Date	Clinically Significant
14	GASTRO-INTESTINAL	HAEMORRHOIDS	1998	1998	NO
14	GENITO-URINARY	VASECTOMY	2003	2003	NO
14	PSYCHIATRIC	MILD DEPRESSION	1996	1996	NO
14	MUSCULOSKELETAL	SURGERY ON LEFT PATTELO-FEMORAL JOINT	1992	1992	NO
15	MUSCULOSKELETAL	RIGHT KNEE ARTHROSCOPY	FEB2007	2007	NO
16	ENT	TONSILLECTOMY	1999	1999	NO
17	GASTRO-INTESTINAL	ABDOMINOPLASTY	JAN2001	JAN2001	NO
17	PSYCHIATRIC	POST NATAL DEPRESSION	MAR1990	1990	NO
18	GASTRO-INTESTINAL	ANAL STENOSIS AS BABY	1984	1984	NO
18	PSYCHIATRIC	PARACETAMOL OD	2001	2001	NO
18	ALLERGIES	URTICARIA	2001	2001	NO
19	RESPIRATORY	CHILDHOOD ASTHMA	1987	1994	NO
19	MUSCULOSKELETAL	INJURY TO RIGHT WRIST (FRACTURE SCAPHUS BONE)	2001	2001	NO

Subject	System	Details	Start Date	Stop Date	Clinically Significant
20	ENT	TONSILLAR CYST (BENIGN)	1997	1997	NO
20	DERMATOLOGICAL	URTICARIAL RASH	NK	NK	NO
20	CARDIOVASCULAR	PALPITATIONS - ANXIETY RELATED	2000	2000	NO
20	GENITO-URINARY	STERILIZATION (LAPAROSCOPIC) 1992	1992	1992	NO
20	GENITO-URINARY	D&C DILATION & CURRETAGE 1999	1999	1999	NO
20	PSYCHIATRIC	POST NATAL DEPRESSION	1984	1984	NO
20	PSYCHIATRIC	ANXIETY PANIC ATTACK	2000	2000	NO
20	MUSCULOSKELETAL	WHIPLASH CERVICAL INJURY	NOV2001	2001	NO

RD 266/24573 (GA0706)

Inclusion/Exclusion Criteria

Subject Number	Incl. 1	Incl. 2	Incl. 3	Incl. 4	Excl. 1	Excl. 2	Excl. 3	Excl. 4	Excl. 5	Excl. 6	Excl. 7	Excl. 8	Excl. 9	Excl. 10	Excl. 11	Excl. 12	Excl. 13	Excl. 14	Excl. 15	Excl. 16	Excl. 17	Passed All	Suitable for Enrolment
1	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
2	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
3	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	N/A	NO	NO	YES	YES
4	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
5	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
6	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
7	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
8	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
9	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
10	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
11	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
12	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
13	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
14	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	N/A	NO	NO	YES	YES
15	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	N/A	NO	NO	YES	YES
16	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
17	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
18	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
19	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	N/A	NO	NO	YES	YES
20	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES

Output File: inex, 28APR2008 15:15, Final

RD 266/245732 (GA0706)

Additional Medical Notes

Subject	Date	Additional Notes
3	06FEB08	COOLING STOPWATCH STOPPED INAPPROPRIATELY, NO COOLING EFFECT FELT BY SUBJECT
4	08FEB08	NO COOLING OR SOOTHING EFFECT FELT BY SUBJECT
5	06FEB08	SUBJECT DID NOT PERCEIVE SOOTHING OR COOLING WITH TREATMENT D
6	08FEB08	NO COOLING OR SOOTHING EFFECT FELT BY SUBJECT
7	04FEB08	VOLUNTEER NOT PERCEIVED SOOTHING OR COOLING EFFECTS FOLLOWING DOSE D
8	01FEB08	NO COOLING/SOOTHING EFFECT FROM TREATMENT D
9	06FEB08	SUBJECT DID NOT PERCEIVE SOOTHING OR COOLING EFFECT FOLLOWING TREATMENT D
10	04FEB08	NO BENEFIT (SOOTHING OR COOLING) PERCEIVED

Output File: note, 28APR2008 8:33, Final

RD 266/245732 (GA0706)

Additional Medical Notes

Subject	Date	Additional Notes
11	01FEB08	NO RELIEF FROM SYMPTOMS WITH TREATMENT D
12	13FEB08	NO COOLING OR SOOTHING EFFECT FELT BY SUBJECT
13	13FEB08	DOA FOR DAY 4 WAS POSITIVE FOR OPIATES DUE TO POPPY SEEDS. DISCUSSED WITH DR. P. BERRY SPONSOR STUDY PHYSICIAN. SUBJECT WAS ALLOWED TO CONTINUE
13	13FEB08	SUBJECT DID NOT PERCEIVE COOLING OR SOOTHING EFFECT FOLLOWING TREATMENT D
14	07FEB08	NO SOOTHING OR COOLING EFFECTS FELT BY SUBJECT, STOP WATCHES NOT STOPPED
16	11FEB08	SUBJECT DID NOT PERCEIVE COOLING OR SOOTHING FOLLOWING TREATMENT D
17	07FEB08	NO COOLING EFFECT FELT BY SUBJECT
17	11FEB08	NO COOLING OR SOOTHING EFFECT FELT BY SUBJECT
18	07FEB08	NO COOLING OR SOOTHING EFFECT FELT BY SUBJECT
18	11FEB08	SUBJECT DID NOT PERCEIVE A COOLING EFFECT FOLLOWING TREATMENT X
19	07FEB08	NO COOLING OR SOOTHING FELT BY SUBJECT
19	15FEB08	NO COOLING EFFECT PERCEIVED BY SUBJECT FOLLOWING TREATMENT X
20	11FEB08	NO COOLING EFFECT FELT BY SUBJECT
20	15FEB08	NO COOLING OR SOOTHING EFFECT FELT BY SUBJECT

Output File: note, 28APR2008 8:33, Final

RD 266/24573 (GA0706)

Listing of Previous Medications and Contraceptive Use

Subject	Previous Medication	Dose	Route	Date	Time
1	CILEST	ONE TAB	PO	DEC 07	N/A
2	MARVELON	ONE TAB	PO	2007	N/A
4	FEMODENE	ONE TAB	PO	NK/1986	N/A
7	FEMODENE	ONE TAB	PO	NK/1993	N/A
8	IMPLANON	1 ROD	S/C	EVERY 3 YEARS	N/A
9	MICROGYNON	1 TAB	PO	NK	NK
10	MICROGYNON	1 TABLET	PO	NK	NK
12	MARVELON	ONE TAB	PO	N/K (ONGOING)	N/A
13	LIVIAL (HRT)	1 TAB	PO	SINCE 1997	07:15
16	MICROGYNON	ONE TAB	PO	1999	N/A
18	IMPLANON	N/A	S/C	NOV 07	N/A

Output File: pmed, 28APR2008 8:41, Final

RD 266/24573 (GA0706)

Vital Signs Data

Subject Number	Visit	Sitting Systolic Blood Pressure (mmHg)	Sitting Diastolic Blood Pressure (mmHg)	Sitting Pulse Rate (bpm)	Temperature (C)
1	Pre-Study	107	63	73	36.9
1	Post-Study	112	57	54	36.3
2	Pre-Study	134	64	70	36.7
2	Post-Study	127	58	75	36.7
3	Pre-Study	134	72	55	36.5
3	Post-Study	123	71	72	36.8
4	Pre-Study	112	74	77	37.0
4	Post-Study	121	71	83	36.5
5	Pre-Study	152H	76	62	36.0
5	Pre-Study Rpt	146H	74		
5	Post-Study	136	75	58	36.2
6	Pre-Study	114	67	55	36.1
6	Post-Study	111	62	55	36.5
7	Pre-Study	114	72	71	36.6
7	Post-Study	107	78	70	36.0
8	Pre-Study	116	62	68	36.8
8	Post-Study	115	76	60	36.5
9	Pre-Study	147H	70	65	37.2
9	Pre-Study Rpt	145H	76		
9	Post-Study	135	70	66	37.0
10	Pre-Study	102	54	55	36.2
10	Post-Study	109	66	68	36.5

Output File: vs, 28APR2008 11:02, Final

H = Above Normal Range
L = Below Normal Range

RD 266/24573 (GA0706)

Vital Signs Data

Subject Number	Visit	Sitting Systolic Blood Pressure (mmHg)	Sitting Diastolic Blood Pressure (mmHg)	Sitting Pulse Rate (bpm)	Temperature (C)
11	Pre-Study	111	72	72	36.7
11	Post-Study	135	65	67	36.8
12	Pre-Study	136	85	74	37.1
12	Post-Study	126	80	75	37.2
13	Pre-Study	148H	87	70	36.1
13	Pre-Study Rpt	133	77		
13	Post-Study	140	81	63	36.0
14	Pre-Study	133	87	84	35.1L
14	Pre-Study Rpt				35.4L
14	Post-Study	139	88	75	36.0
15	Pre-Study	153H	80	61	36.3
15	Pre-Study Rpt	135	81		
15	Post-Study	146H	77	70	36.3
16	Pre-Study	117	59	62	36.0
16	Post-Study	115	69	70	36.0
17	Pre-Study	130	80	72	37.2
17	Post-Study	140	76	88	36.0
18	Pre-Study	98	54	58	36.6
18	Post-Study	94	51	73	36.6
19	Pre-Study	113	79	70	36.0
19	Post-Study	140	77	68	36.2
20	Pre-Study	100	65	59	36.4
20	Post-Study	101	62	69	37.1

Output File: vs, 28APR2008 11:02, Final

H = Above Normal Range
L = Below Normal Range

RD 266/24573 (GA0706)

Reflux Meal and Heartburn

Subject	Meal Start Time	Meal Stop Time	Onset of Heartburn	Degree of Heartburn
1	12:21	12:41	12:53	SEVERE
2	12:20	12:40	12:43	SEVERE
3	12:19	12:39	13:06	SEVERE
4	12:25	12:45	12:59	MODERATE
5	13:36	13:56	14:27	MODERATE
6	12:20	12:37	12:47	SEVERE
7	12:18	12:27	12:46	SEVERE
8	12:26	12:46	12:58	MODERATE
9	12:25	12:45	12:59	MODERATE
10	12:20	12:37	12:59	SEVERE
11	12:26	12:44	13:01	SEVERE
12	12:27	12:39	12:42	MODERATE
13	12:29	12:44	12:49	MODERATE
14	12:34	12:41	13:03	MODERATE
15	12:26	12:42	12:55	SEVERE
16	12:34	12:52	13:21	MODERATE
17	12:28	12:40	13:00	MODERATE
18	12:34	12:51	13:22	MODERATE
19	13:11	13:23	13:38	SEVERE
20	13:53	14:13	14:21	MODERATE

Output File: reflux, 28APR2008 9:05, Final

APPENDIX 16.2.5 COMPLIANCE AND/OR DRUG CONCENTRATION DATA

In addition to this cover sheet, this appendix contains:

- Dose Administration listing (1 page)
- Visit Dates listing (1 page)

RD 266/24573 (GA0706)

Dose Administration

Subject	Date, Time, Dose 1	Date, Time, Dose 2	Date, Time, Dose 3	Date, Time, Dose 4
1	01FEB2008 13:44 C	04FEB2008 13:44 D	06FEB2008 13:42 B	08FEB2008 13:41 A
2	01FEB2008 13:42 D	04FEB2008 13:40 A	06FEB2008 13:35 C	08FEB2008 13:43 B
3	01FEB2008 13:47 A	04FEB2008 13:49 B	06FEB2008 13:41 D	08FEB2008 13:45 C
4	01FEB2008 13:37 B	04FEB2008 13:47 C	06FEB2008 13:48 A	08FEB2008 13:49 D
5	01FEB2008 15:55 A	04FEB2008 13:56 B	06FEB2008 13:53 D	08FEB2008 13:51 C
6	01FEB2008 13:49 B	04FEB2008 13:52 C	06FEB2008 13:45 A	08FEB2008 13:47 D
7	01FEB2008 14:09 C	04FEB2008 14:13 D	06FEB2008 14:29 B	08FEB2008 14:40 A
8	01FEB2008 14:16 D	04FEB2008 14:18 A	06FEB2008 14:34 C	08FEB2008 14:35 B
9	01FEB2008 14:14 A	04FEB2008 14:20 B	06FEB2008 14:39 D	08FEB2008 14:37 C
10	01FEB2008 14:50 C	04FEB2008 14:26 D	06FEB2008 14:48 B	08FEB2008 14:47 A
11	01FEB2008 14:28 D	04FEB2008 14:24 A	06FEB2008 14:50 C	08FEB2008 13:53 B
12	05FEB2008 13:36 B	07FEB2008 13:25 C	11FEB2008 13:35 A	13FEB2008 13:20 D
13	05FEB2008 14:14 B	07FEB2008 13:41 C	11FEB2008 13:46 A	13FEB2008 13:45 D
14	05FEB2008 13:41 C	07FEB2008 13:31 D	11FEB2008 13:42 B	13FEB2008 13:35 A
15	05FEB2008 13:43 D	07FEB2008 13:34 A	11FEB2008 13:40 C	13FEB2008 13:38 B
16	05FEB2008 14:07 A	07FEB2008 13:39 B	11FEB2008 13:48 D	13FEB2008 13:43 C
17	05FEB2008 14:03 A	07FEB2008 14:34 B	11FEB2008 14:11 D	13FEB2008 14:11 C
18	05FEB2008 14:12 C	07FEB2008 14:45 D	11FEB2008 14:08 B	13FEB2008 14:16 A
19	07FEB2008 14:39 D	11FEB2008 14:16 A	13FEB2008 14:10 C	15FEB2008 14:10 B
20	07FEB2008 14:41 B	11FEB2008 14:27 C	13FEB2008 14:23 A	15FEB2008 14:38 D

Output File: dose, 28APR2008 15:26, Final

Treatment A = Gaviscon Peppermint Liquid
Treatment B = Gaviscon Advance Aniseed Flavour
Treatment C = Gaviscon Double Action Liquid
Treatment D = Control

RD 266/24573 (GA0706)

Visit Dates

Subject	Pre-Study	Pre-Study Repeat	Phase 1 Dosing	Phase 2 Dosing	Phase 3 Dosing	Phase 4 Dosing	Post-Study
1	24JAN2008		01FEB2008	04FEB2008	06FEB2008	08FEB2008	12FEB2008
2	22JAN2008		01FEB2008	04FEB2008	06FEB2008	08FEB2008	13FEB2008
3	22JAN2008		01FEB2008	04FEB2008	06FEB2008	08FEB2008	13FEB2008
4	24JAN2008		01FEB2008	04FEB2008	06FEB2008	08FEB2008	14FEB2008
5	25JAN2008	29JAN2008	01FEB2008	04FEB2008	06FEB2008	08FEB2008	13FEB2008
6	23JAN2008		01FEB2008	04FEB2008	06FEB2008	08FEB2008	13FEB2008
7	25JAN2008		01FEB2008	04FEB2008	06FEB2008	08FEB2008	13FEB2008
8	25JAN2008		01FEB2008	04FEB2008	06FEB2008	08FEB2008	13FEB2008
9	25JAN2008		01FEB2008	04FEB2008	06FEB2008	08FEB2008	13FEB2008
10	24JAN2008		01FEB2008	04FEB2008	06FEB2008	08FEB2008	14FEB2008
11	23JAN2008	28JAN2008	01FEB2008	04FEB2008	06FEB2008	08FEB2008	13FEB2008
12	21JAN2008		05FEB2008	07FEB2008	11FEB2008	13FEB2008	19FEB2008
13	25JAN2008		05FEB2008	07FEB2008	11FEB2008	13FEB2008	19FEB2008
14	24JAN2008	31JAN2008	05FEB2008	07FEB2008	11FEB2008	13FEB2008	21FEB2008
15	24JAN2008	31JAN2008	05FEB2008	07FEB2008	11FEB2008	13FEB2008	19FEB2008
16	28JAN2008		05FEB2008	07FEB2008	11FEB2008	13FEB2008	20FEB2008
17	28JAN2008		05FEB2008	07FEB2008	11FEB2008	13FEB2008	19FEB2008
18	28JAN2008		05FEB2008	07FEB2008	11FEB2008	13FEB2008	20FEB2008
19	30JAN2008		07FEB2008	11FEB2008	13FEB2008	15FEB2008	19FEB2008
20	31JAN2008		07FEB2008	11FEB2008	13FEB2008	15FEB2008	19FEB2008

Output File: visit, 28APR2008 9:04, Final

APPENDIX 16.2.6 INDIVIDUAL EFFICACY RESPONSE DATA

In addition to this cover sheet, this appendix contains:

- Individual Soothing and Cooling data listing (5 pages)

RD 266/24573 (GA0706)

Soothing and Cooling Effect

Subject	Phase	Admin.	Breakfast Time	Meal Start Time	Meal Stop Time	Time of Moderate Heartburn	Dosing Time	Soothing Time	Cooling Time	Time to Soothing (min)	Time to Cooling (min)	Instant Benefit	Mouth/Throat Feel Fresher	Willing to Use Again	Any AEs
1	TREATMENT VISIT 1	C	9:00	13:00	13:20	13:43	13:44:00	13:46:39	13:44:30	2.65	0.50	YES	YES	YES	NO
1	TREATMENT VISIT 2	D	9:00	13:05	13:25	13:42	13:44:00	14:04:00	14:04:30	20.00	20.50	NO	NO	NO	NO
1	TREATMENT VISIT 3	B	9:00	13:05	13:24	13:39	13:42:30	13:46:01	13:44:21	3.52	1.85	YES	NO	YES	NO
1	TREATMENT VISIT 4	A	9:00	13:02	13:22	13:39	13:41:00	13:44:09	13:41:19	3.15	0.32	YES	NO	YES	NO
2	TREATMENT VISIT 1	D	9:00	13:02	13:22	13:41	13:42:00	14:02:27	14:07:10	20.45	25.17	NO	NO	NO	NO
2	TREATMENT VISIT 2	A	9:00	13:07	13:24	13:37	13:40:00	13:47:00	13:43:00	7.00	3.00	NO	YES	YES	NO
2	TREATMENT VISIT 3	C	9:00	13:07	13:24	13:34	13:35:00	13:37:58	13:36:35	2.97	1.58	YES	YES	YES	NO
2	TREATMENT VISIT 4	B	9:00	13:04	13:22	13:41	13:43:15	13:44:39	13:44:36	1.40	1.35	YES	YES	YES	NO
3	TREATMENT VISIT 1	A	9:00	13:04	13:21	13:46	13:47:21	13:47:31	13:47:57	0.17	0.60	YES	YES	YES	NO
3	TREATMENT VISIT 2	B	9:00	13:09	13:23	13:48	13:49:00	13:49:23	13:49:11	0.38	0.18	YES	YES	YES	NO
3	TREATMENT VISIT 3	D	9:00	13:08	13:24	13:39	13:41:00	13:49:56		8.93	30.00	NO	NO	NO	NO
3	TREATMENT VISIT 4	C	9:00	13:04	13:22	13:44	13:45:30	13:45:52	13:46:29	0.37	0.98	YES	YES	YES	NO
4	TREATMENT VISIT 1	B	9:00	13:06	13:24	13:37	13:37:00	13:38:13	13:38:25	1.22	1.42	YES	YES	YES	NO
4	TREATMENT VISIT 2	C	9:20	13:11	13:27	13:45	13:47:00	13:48:29	13:47:18	1.48	0.30	YES	YES	YES	NO
4	TREATMENT VISIT 3	A	9:00	13:09	13:29	13:46	13:48:00	13:49:06	13:48:24	1.10	0.40	YES	YES	YES	NO
4	TREATMENT VISIT 4	D	9:00	13:06	13:24	13:47	13:49:00			30.00	30.00	NO	NO	NO	NO

Output File: sooth, 28APR2008 15:39, Final

Treatment A = Gaviscon Peppermint Liquid
Treatment B = Gaviscon Advance Aniseed Flavour
Treatment C = Gaviscon Double Action Liquid
Treatment D = Control

RD 266/24573 (GA0706)

Soothing and Cooling Effect

Subject	Phase	Admin.	Breakfast Time	Meal Start Time	Meal Stop Time	Time of Moderate Heartburn	Dosing Time	Soothing Time	Cooling Time	Time to Soothing (min)	Time to Cooling (min)	Instant Benefit	Mouth/Throat Feel Fresher	Willing to Use Again	Any AEs
5	TREATMENT VISIT 1	A	9:00	13:08	13:27	13:54	13:55:09	13:55:59	13:55:21	0.83	0.20	YES	YES	YES	NO
5	TREATMENT VISIT 2	B	9:00	13:13	13:31	13:55	13:56:00	13:59:35	13:56:40	3.58	0.67	NO	NO	NO	NO
5	TREATMENT VISIT 3	D	9:00	13:09	13:29	13:52	13:53:30			30.00	30.00	NO	NO	NO	NO
5	TREATMENT VISIT 4	C	9:00	13:06	13:26	13:50	13:51:15	13:52:10	13:51:29	0.92	0.23	YES	YES	YES	NO
6	TREATMENT VISIT 1	B	9:00	13:10	13:25	13.48	13:49:50	14:04:26	14:05:27	14.60	15.62	NO	YES	NO	NO
6	TREATMENT VISIT 2	C	9:00	13:15	13:28	13:51	13:52:00	13:53:01	13:52:16	1.02	0.27	YES	YES	YES	NO
6	TREATMENT VISIT 3	A	9:00	13:09	13:29	13.44	13:45:30	13:49:00	13:49:08	3.50	3.63	NO	YES	NO	NO
6	TREATMENT VISIT 4	D	9:00	13:06	13:24	13.45	13:47:30			30.00	30.00	NO	NO	NO	NO
7	TREATMENT VISIT 1	C	9:00	13:32	13:50	14:08	14:09:03	14:10:16	14:09:25	1.22	0.37	NO	YES	YES	NO
7	TREATMENT VISIT 2	D	9:00	13:32	13.49	14.11	14:13:30			30.00	30.00	NO	NO	NO	NO
7	TREATMENT VISIT 3	B	9:00	14:02	14:19	14:28	14:29:00	14:29:19	14:29:36	0.32	0.60	YES	YES	YES	NO
7	TREATMENT VISIT 4	A	10:00	14:08	14:23	14:39	14:40:30	14:41:21	14:40:43	0.85	0.22	YES	YES	YES	NO
8	TREATMENT VISIT 1	D	9:00	13:34	13:54	14:15	14:16:00			30.00	30.00	NO	NO	NO	NO
8	TREATMENT VISIT 2	A	9:00	13:34	13:54	14:15	14:18:00	14:18:22	14:19:01	0.37	1.02	YES	YES	YES	NO
8	TREATMENT VISIT 3	C	9:00	14:05	14:21	14:33	14:34:00	14:34:48	14:34:14	0.80	0.23	YES	YES	YES	NO
8	TREATMENT VISIT 4	B	10:00	14:09	14:25	14:34	14:35:15	14:35:56	14:35:31	0.68	0.27	YES	YES	YES	NO

Output File: sooth, 28APR2008 15:39, Final

Treatment A = Gaviscon Peppermint Liquid
Treatment B = Gaviscon Advance Aniseed Flavour
Treatment C = Gaviscon Double Action Liquid
Treatment D = Control

RD 266/24573 (GA0706)

Soothing and Cooling Effect

Subject	Phase	Admin.	Breakfast Time	Meal Start Time	Meal Stop Time	Time of Moderate Heartburn	Dosing Time	Soothing Time	Cooling Time	Time to Soothing (min)	Time to Cooling (min)	Instant Benefit	Mouth/Throat Feel Fresher	Willing to Use Again	Any AEs
9	TREATMENT VISIT 1	A	9:00	13:36	13:56	14:13	14:14:12	14:14:54	14:14:32	0.70	0.33	NO	YES	YES	NO
9	TREATMENT VISIT 2	B	9:00	13:36	13:54	14:18	14:20:00	14:20:48	14:20:43	0.80	0.72	NO	YES	NO	NO
9	TREATMENT VISIT 3	D	9:00	14:08	14:26	14:38	14:39:00			30.00	30.00	NO	NO	NO	NO
9	TREATMENT VISIT 4	C	10:00	14:08	14:25	14:36	14:37:15	14:37:42	14:37:32	0.45	0.28	YES	YES	YES	NO
10	TREATMENT VISIT 1	C	9:00	13:38	13:56	14:49	14:50:27	14:57:50	14:51:00	7.38	0.55	YES	NO	NO	NO
10	TREATMENT VISIT 2	D	9:00	13:38	13:57	14:24	14:26:00			30.00	30.00	NO	NO	NO	NO
10	TREATMENT VISIT 3	B	9:00	14:11	14:27	14:47	14:48:30	14:52:01	14:49:09	3.52	0.65	YES	NO	YES	NO
10	TREATMENT VISIT 4	A	10:00	14:09	14:24	14:46	14:47:30	14:47:46	14:48:18	0.27	0.80	YES	NO	YES	NO
11	TREATMENT VISIT 1	D	9:00	13:40	13:59	14:27	14:28:30			30.00	30.00	NO	NO	NO	NO
11	TREATMENT VISIT 2	A	9:00	13:40	13:59	14:22	14:24:00	14:25:38	14:24:32	1.63	0.53	NO	NO	NO	NO
11	TREATMENT VISIT 3	C	9:00	14:14	14:27	14:49	14:50:00	14:51:03	14:50:30	1.05	0.50	NO	NO	YES	NO
11	TREATMENT VISIT 4	B	9:00	13:06	13:25	13:52	13:53:00	13:54:15	13:53:28	1.25	0.47	NO	NO	NO	NO
12	TREATMENT VISIT 1	B	9:00	13:06	13:19	13:34	13:36:00	13:37:42	13:36:14	1.70	0.23	YES	NO	YES	NO
12	TREATMENT VISIT 2	C	9:00	13:02	13:14	13:22	13:25:01	13:28:07	13:25:40	3.10	0.65	NO	NO	YES	NO
12	TREATMENT VISIT 3	A	9:00	13:05	13:20	13:32	13:35:00	13:37:14	13:36:11	2.23	1.18	NO	NO	NO	NO
12	TREATMENT VISIT 4	D	9:00	13:03	13:14	13:19	13:20:30			30.00	30.00	NO	NO	NO	NO

Output File: sooth, 28APR2008 15:39, Final

Treatment A = Gaviscon Peppermint Liquid
Treatment B = Gaviscon Advance Aniseed Flavour
Treatment C = Gaviscon Double Action Liquid
Treatment D = Control

RD 266/24573 (GA0706)

Soothing and Cooling Effect

Subject	Phase	Admin.	Breakfast Time	Meal Start Time	Meal Stop Time	Time of Moderate Heartburn	Dosing Time	Soothing Time	Cooling Time	Time to Soothing (min)	Time to Cooling (min)	Instant Benefit	Mouth/Throat Feel Fresher	Willing to Use Again	Any AEs
13	TREATMENT VISIT 1	B	9:00	13:07	13:22	14:12	14:14:00	14:15:17	14:15:55	1.28	1.92	YES	YES	YES	NO
13	TREATMENT VISIT 2	C	9:00	13:02	13:19	13:40	13:41:15	13:42:59	13:41:46	1.73	0.52	NO	NO	NO	NO
13	TREATMENT VISIT 3	A	9:00	13:06	13:23	13:44	13:46:15	13:48:19	13:47:43	2.07	1.47	NO	NO	NO	NO
13	TREATMENT VISIT 4	D	9:00	13:04	13:18	13:44	13:45:30			30.00	30.00	NO	NO	NO	NO
14	TREATMENT VISIT 1	C	9:00	13:08	13:19	13:39	13:41:00	13:41:29	13:42:16	0.48	1.27	NO	YES	YES	NO
14	TREATMENT VISIT 2	D	9:00	13:04	13:14	13:29	13:31:00			30.00	30.00	NO	NO	NO	NO
14	TREATMENT VISIT 3	B	9:00	13:05	13:15	13:41	13:42:30	13:43:45	13:43:02	1.25	0.53	NO	YES	YES	NO
14	TREATMENT VISIT 4	A	9:00	13:03	13:10	13:34	13:35:30	13:36:23	13:35:50	0.88	0.33	NO	YES	YES	NO
15	TREATMENT VISIT 1	D	9:00	13:07	13:22	13:41	13:43:00	13:50:29	13:48:18	7.48	5.30	NO	NO	NO	NO
15	TREATMENT VISIT 2	A	9:00	13:04	13:20	13:32	13:34:00	13:36:54	13:34:30	2.90	0.50	YES	NO	YES	NO
15	TREATMENT VISIT 3	C	9:00	13:05	13:21	13:39	13:40:45	13:45:45	13:41:12	5.00	0.45	YES	NO	YES	NO
15	TREATMENT VISIT 4	B	9:00	13:04	13:22	13:35	13:38:00	13:42:41	13:38:40	4.68	0.67	YES	NO	YES	NO
16	TREATMENT VISIT 1	A	9:00	13:31	13:48	14:05	14:07:00	14:12:35	14:09:23	5.58	2.38	YES	YES	YES	NO
16	TREATMENT VISIT 2	B	9:00	13:06	13:20	13:37	13:39:05	13:42:52	13:41:09	3.78	2.07	YES	YES	YES	NO
16	TREATMENT VISIT 3	D	9:00	13:07	13:22	13:45	13:48:00			30.00	30.00	NO	NO	NO	NO
16	TREATMENT VISIT 4	C	9:00	13:05	13:21	13:41	13:43:30	13:44:37	13:43:52	1.12	0.37	YES	YES	YES	NO

Output File: sooth, 28APR2008 15:39, Final

Treatment A = Gaviscon Peppermint Liquid
Treatment B = Gaviscon Advance Aniseed Flavour
Treatment C = Gaviscon Double Action Liquid
Treatment D = Control

RD 266/24573 (GA0706)

Soothing and Cooling Effect

Subject	Phase	Admin.	Breakfast Time	Meal Start Time	Meal Stop Time	Time of Moderate Heartburn	Dosing Time	Soothing Time	Cooling Time	Time to Soothing (min)	Time to Cooling (min)	Instant Benefit	Mouth/Throat Feel Fresher	Willing to Use Again	Any AEs
17	TREATMENT VISIT 1	A	9:00	13:31	13:45	14:01	14:03:00	14:05:16	14:05:02	2.27	2.03	NO	YES	YES	NO
17	TREATMENT VISIT 2	B	9:00	14:04	14:21	14:32	14:34:00	14:40:05		6.08	30.00	NO	NO	NO	NO
17	TREATMENT VISIT 3	D	9:30	13:36	13:51	14:10	14:11:30			30.00	30.00	NO	NO	NO	NO
17	TREATMENT VISIT 4	C	9:15	13:36	13:52	14:11	14:12:00	14:13:27	14:12:25	1.45	0.42	YES	YES	YES	NO
18	TREATMENT VISIT 1	C	9:00	13:31	13:47	14:11	14:12:30	14:12:43	14:12:57	0.22	0.45	YES	YES	YES	NO
18	TREATMENT VISIT 2	D	9:00	14:03	14:20	14:45	14:45:30			30.00	30.00	NO	NO	NO	NO
18	TREATMENT VISIT 3	B	9:30	13:35	13:52	14:06	14:08:00	14:08:16		0.27	30.00	YES	YES	NO	NO
18	TREATMENT VISIT 4	A	9:15	13:35	13:52	14:15	14:16:15	14:17:10	14:16:38	0.92	0.38	YES	YES	YES	NO
19	TREATMENT VISIT 1	D	9:00	14:03	14:19	14:38	14:39:00			30.00	30.00	NO	NO	NO	NO
19	TREATMENT VISIT 2	A	9:30	13:35	13:51	14:14	14:16:00	14:16:48	14:16:28	0.80	0.47	YES	YES	YES	NO
19	TREATMENT VISIT 3	C	9:15	13:35	13:52	14:08	14:10:00	14:10:30	14:10:14	0.50	0.23	YES	YES	YES	NO
19	TREATMENT VISIT 4	B	9:00	13:32	13:49	14:08	14:10:00	14:12:33		2.55	30.00	NO	NO	NO	NO
20	TREATMENT VISIT 1	B	9:00	14:04	14:23	14:40	14:41:30	14:42:21	14:45:09	0.85	3.65	YES	YES	YES	NO
20	TREATMENT VISIT 2	C	9:30	13:36	13:53	14:23	14:27:15	14:33:10		5.92	30.00	NO	YES	YES	NO
20	TREATMENT VISIT 3	A	9:15	13:35	13:53	14:21	14:23:00	14:28:33	14:29:21	5.55	6.35	YES	YES	YES	NO
20	TREATMENT VISIT 4	D	9:00	13:32	13:49	14:37	14:38:00			30.00	30.00	NO	NO	NO	NO

Output File: sooth, 28APR2008 15:39, Final

Treatment A = Gaviscon Peppermint Liquid
Treatment B = Gaviscon Advance Aniseed Flavour
Treatment C = Gaviscon Double Action Liquid
Treatment D = Control

APPENDIX 16.2.7 ADVERSE EVENT LISTINGS

In addition to this cover sheet, this appendix contains:

- The adverse event listing (2 pages)

RD 266/24573 (GA0706)

Listing of Adverse Events

SUBJECT	ADVERSE EVENT (ORGAN SYSTEM)	ADVERSE EVENT (PREFERRED TERM)	ADVERSE EVENT (REPORTED TERM)	DATE OF ONSET	DATE OF RESOLUTION	TIME POST DOSE	DURATION	OUTCOME	SEVERITY	ACTION	RELATIONSHIP TO STUDY DRUG
Prior to Dosing											
15	Infections and infestations	UPPER RESPIRATORY TRACT INFECTION	UPPER RESPIRATORY TRACT INFECTION	30JAN2008		< -6.4 days	Not Available	N/K	MODERATE	Symptomatic Therapy	NONE
Gaviscon Peppermint Liquid											
9	Gastrointestinal disorders	NAUSEA	NAUSEA	01FEB2008	02FEB2008	1 8 hours	10 5 hours	RESOLVED	MODERATE	None	UNLIKELY
9	Gastrointestinal disorders	CONSTIPATION	CONSTIPATION	02FEB2008	09FEB2008	< 1.4 days	< 7 5 days	RESOLVED	SEVERE	Symptomatic Therapy	POSSIBLE
18	Gastrointestinal disorders	NAUSEA	NAUSEA	16FEB2008	19FEB2008	2 9 days	2 8 days	RESOLVED	MILD	None	UNLIKELY
Gaviscon Advance Aniseed Flavour											
13	Gastrointestinal disorders	ABDOMINAL PAIN	ABDOMINAL PAIN	05FEB2008	05FEB2008	1.8 hours	20 mins	RESOLVED	MILD	None	UNLIKELY

RD 266/24573 (GA0706)

Listing of Adverse Events

SUBJECT	ADVERSE EVENT (ORGAN SYSTEM)	ADVERSE EVENT (PREFERRED TERM)	ADVERSE EVENT (REPORTED TERM)	DATE OF ONSET	DATE OF RESOLUTION	TIME POST DOSE	DURATION	OUTCOME	SEVERITY	ACTION	RELATIONSHIP TO STUDY DRUG
Gaviscon Double Action Liquid											
4	Gastrointestinal disorders	GASTROOESOPHAGEAL REFLUX DISEASE	GASTRO OESOPHAGIAL REFLUX	04FEB2008	05FEB2008	5.2 hours	13.0 hours	RESOLVED	MODERATE	None	UNLIKELY
12	Gastrointestinal disorders	DYSPEPSIA	HEARTBURN	07FEB2008	07FEB2008	2.6 hours	2.0 hours	RESOLVED	MILD	None	UNLIKELY
12	Gastrointestinal disorders	VOMITING	VOMITING	07FEB2008	07FEB2008	2.6 hours	2.0 hours	RESOLVED	MILD	None	UNLIKELY
13	Gastrointestinal disorders	DYSPEPSIA	HEARTBURN	10FEB2008	10FEB2008	3.3 days	1.0 hour	RESOLVED	MILD	None	NONE
Control											
8	Nervous system disorders	HEADACHE	HEADACHE	01FEB2008	02FEB2008	1.7 hours	17.1 hours	RESOLVED	MILD	None	POSSIBLE
8	Gastrointestinal disorders	NAUSEA	NAUSEA	01FEB2008	02FEB2008	1.7 hours	17.1 hours	RESOLVED	MILD	None	POSSIBLE
8	Gastrointestinal disorders	NAUSEA	NAUSEA	04FEB2008	04FEB2008	3.0 days	5.0 hours	RESOLVED	MILD	None	UNLIKELY
12	Infections and infestations	NASOPHARYNGITIS	COMMON COLD	16FEB2008	18FEB2008	2.8 days	2.0 days	RESOLVED	MILD	Symptomatic Therapy	NONE

APPENDIX 16.2.8 LISTING OF INDIVIDUAL LABORATORY MEASUREMENTS BY SUBJECT

In addition to this cover sheet, this appendix contains:

- Summary of biochemistry data (1 page)
- Biochemistry results listing (2 pages)
- Biochemistry out of range results (1 page)
- Summary of haematology data (1 page)
- Haematology results listing (1 pages)
- Haematology out of range results (1 page)
- Urinalysis results (1 page)
- Urinalysis out of range results (1 page)
- Urinalysis microscopy results (1page)
- Drugs of Abuse and Pregnancy Test Results (1 page)
- Virology Test Results (1 page)

RD 266/24573 (GA0706)

Summary of Biochemistry Data

Visit	Parameter	N	Mean	SD	Minimum	Median	Maximum
Pre-Study	Albumin (g.L-1)	20	46.09	3.07	39.5	45.6	53.4
Pre-Study	ALP (IU.L-1)	20	174.32	54.01	76.4	173.3	276.9
Pre-Study	ALT (IU.L-1)	20	23.56	15.03	11.4	17.7	74.6
Pre-Study	Total Bilirubin (mmol.L-1)	20	10.28	6.25	2.9	8.7	29.5
Pre-Study	Calcium (mmol.L-1)	20	2.368	0.079	2.23	2.37	2.53
Pre-Study	Cholesterol (mmol.L-1)	20	4.86	0.97	3.1	4.6	7.3
Pre-Study	Creatine Kinase (IU.L-1)	20	101.28	64.06	43.8	77.5	251.5
Pre-Study	Creatinine (mmol.L-1)	20	67.59	12.59	47.6	65.1	98.9
Pre-Study	GGT (IU.L-1)	20	22.21	18.86	3.9	15.7	84.5
Pre-Study	Glucose (mmol.L-1)	20	4.78	0.43	4.1	4.9	5.7
Pre-Study	HBD (IU.L-1)	20	130.75	16.60	99.0	129.9	162.2
Pre-Study	Potassium (mmol.L-1)	20	4.535	0.279	4.04	4.52	5.12
Pre-Study	Sodium (mmol.L-1)	20	140.16	2.20	136.0	140.4	143.3
Pre-Study	Phosphorus (mmol.L-1)	20	1.145	0.164	0.83	1.12	1.43
Pre-Study	Total Protein (g.L-1)	20	76.52	5.11	68.3	76.3	88.7
Pre-Study	Triglycerides (mmol.L-1)	20	1.240	0.624	0.40	1.05	2.80
Pre-Study	Uric Acid (mmol.L-1)	20	0.254	0.069	0.16	0.24	0.39
Pre-Study	Urea (mmol.L-1)	20	4.37	1.00	2.4	4.7	5.7

Output File: tab_bio, 28APR2008 11:50, Final

RD 266/24573 (GA0706)

Biochemistry Results

SUBJECT	VISIT	SAMPLEID	TP g/L	ALB g/L	BIL-T umol/L	ALT IU/L	CREA umol/L	GLU mmol/L	GGT IU/L	NA mmol/L	K mmol/L	CA mmol/L	UREA mmol/L	PHOS mmol/L	ALP IU/L	HBD IU/L	CK IU/L	CHOL mmol/L	TRIG mmol/L	UA mmol/L
1	Pre-Study	Z00101887	72.4	44.6	7.1	11.5	59.7	4.3	7.3d	140.4	4.49	2.30	4.7	1.39	186.3	125.1	73.8	3.12	0.40	0.20
2	Pre-Study	Z00101843	71.6	46.5	4.1	17.1	70.1	4.8	14.2	143.3h	4.35	2.31	5.7	1.31	110.6	162.2	228.1h	4.20	0.90	0.21
3	Pre-Study	Z00101825	88.7h	53.4h	21.1	20.5	73.9	5.3	20.7	138.4	4.18	2.41	4.6	1.05	183.9	120.5	117.6	4.32	0.80	0.34
4	Pre-Study	Z00101922	68.3	39.5	5.2	17.2	61.1	5.0	33.6	141.4	4.74	2.23d	4.8	1.09	257.8h	124.2	109.0	5.33h	2.00	0.34
5	Pre-Study	Z00101925	70.2	43.7	8.0	16.1	53.8d	5.7h	10.7	136.4	4.38	2.32	4.0	1.23	76.4d	131.9	58.1	6.45h	0.80	0.19
5	Pre-Study Rpt	Z00101957					62.7	5.4							105.9			6.33h		
6	Pre-Study	Z00101882	75.9	45.4	8.2	14.4	58.2	4.5	11.2	140.2	4.27	2.45	5.6	1.12	133.1	110.5	84.0	5.09	0.60	0.25
7	Pre-Study	Z00101919	80.5	47.2	8.6	43.3h	69.4	5.0	34.3	136.0	4.50	2.44	4.8	0.88	172.4	99.0	55.9	5.67h	1.90	0.29
8	Pre-Study	Z00101917	72.6	45.8	7.7	16.1	65.0	4.5	3.9d	137.9	4.57	2.44	3.2	1.23	221.5	113.2	50.3	4.60	0.80	0.26
9	Pre-Study	Z00101924	85.8h	52.0h	9.4	17.9	61.4	5.3	23.3	140.4	4.79	2.53	2.4	1.43	265.7h	148.5	82.0	5.50h	0.70	0.21
10	Pre-Study	Z00101892	79.7	47.2	8.7	19.9	70.7	4.5	11.2	140.1	4.04	2.30	3.7	1.08	115.2	116.4	62.6	4.63	1.30	0.19

Output File: bio, 28APR2008 12:17, Final

h = Above Normal Range
d = Below Normal Range

RD 266/24573 (GA0706)

Biochemistry Results

SUBJECT	VISIT	SAMPLEID	TP g/L	ALB g/L	BIL-T umol/L	ALT IU/L	CREA umol/L	GLU mmol/L	GGT IU/L	NA mmol/L	K mmol/L	CA mmol/L	UREA mmol/L	PHOS mmol/L	ALP IU/L	HBD IU/L	CK IU/L	CHOL mmol/L	TRIG mmol/L	UA mmol/L
11	Pre-Study	Z00101859	75.8	48.1	5.9	22.0	65.1	4.1	17.9	142.8h	4.31	2.41	3.4	1.14	204.3	143.8	72.4	7.32h	2.80h	0.23
11	Pre-Study Rpt	Z00101945																7.15h		
11	Pre-Study Rpt	Z00102040																6.76h		
12	Pre-Study	Z00101799	78.8	45.4	9.0	17.3	61.4	4.6	22.5	139.7	5.12	2.36	3.2	1.03	151.9	149.1	65.2	4.20	1.20	0.18
13	Pre-Study	Z00101918	76.7	45.3	11.1	24.1	47.6d	4.9	15.6	136.5	4.48	2.33	5.0	1.02	202.5	155.0	231.1h	4.41	0.70	0.22
14	Pre-Study	Z00101894	78.1	46.8	17.2	74.6h	98.9	4.9	84.5h	142.6	4.72	2.37	5.3	0.83	109.5d	143.4	64.7	4.49	1.70	0.39
14	Pre-Study Rpt	Z00102008	75.9	46.3	15.3	43.6			54.8											
15	Pre-Study	Z00101890	76.8	46.8	9.5	45.0	89.3	5.3	51.1	140.4	4.53	2.38	5.3	0.96	134.7	131.3	155.2	6.01h	1.90	0.29
15	Pre-Study Rpt	Z00102006																5.17		
16	Pre-Study	Z00101948	77.9	44.8	12.4	17.4	61.8	4.1	7.3d	139.1	5.04	2.43	4.0	1.22	182.4	120.3	81.2	3.94	1.00	0.20
17	Pre-Study	Z00101954	74.5	41.6	2.9d	20.1	67.9	4.9	15.7	141.9	4.63	2.36	5.4	1.12	276.9h	136.3	86.7	4.78	1.80	0.30
18	Pre-Study	Z00101947	74.9	45.2	13.8	14.9	56.0	4.4	11.9	142.8h	4.20	2.29	2.6	1.11	162.5	113.7	52.4	4.82	1.10	0.24
19	Pre-Study	Z00101996	80.7	48.1	29.5	30.3	88.7	4.5	36.5	141.8	4.77	2.46	5.1	1.31	164.6	142.1	251.5	4.05	1.70	0.39
20	Pre-Study	Z00102005	70.4	44.4	6.1	11.4	71.8	4.9	10.8	141.0	4.58	2.23d	4.6	1.36	174.2	128.5	43.8	4.17	0.70	0.16

Output File: bio, 28APR2008 12:17, Final

h = Above Normal Range
d = Below Normal Range

RD 266/24573 (GA0706)

Biochemistry Out of Range Results

Subject	Visit	Parameter	Result	Low Range	High Range	Units
1	Pre-Study	GGT (IU.L-1)	7.3	7.8	46.8	IU/L
2	Pre-Study	Creatine Kinase (IU.L-1)	228.1	35.1	227.9	IU/L
2	Pre-Study	Sodium (mmol.L-1)	143.3	135.4	142.5	MMOL/L
3	Pre-Study	Albumin (g.L-1)	53.4	42.0	50.5	G/L
3	Pre-Study	Total Protein (g.L-1)	88.7	66.7	80.8	G/L
4	Pre-Study	ALP (IU.L-1)	257.8	84.6	253.4	IU/L
4	Pre-Study	Calcium (mmol.L-1)	2.23	2.24	2.66	MMOL/L
4	Pre-Study	Cholesterol (mmol.L-1)	5.33	0.0	5.2	MMOL/L
5	Pre-Study	ALP (IU.L-1)	76.4	84.6	253.4	IU/L
5	Pre-Study	Cholesterol (mmol.L-1)	6.45	0.0	5.2	MMOL/L
5	Pre-Study	Creatinine (umol.L-1)	53.8	56.0	92.2	UMOL/L
5	Pre-Study	Glucose (mmol.L-1)	5.7	3.8	5.5	MMOL/L
5	Pre-Study Rpt	Cholesterol (mmol.L-1)	6.33	0.0	5.2	MMOL/L
7	Pre-Study	ALT (IU.L-1)	43.3	8.9	32.6	IU/L
7	Pre-Study	Cholesterol (mmol.L-1)	5.67	0.0	5.2	MMOL/L
8	Pre-Study	GGT (IU.L-1)	3.9	7.8	46.8	IU/L
9	Pre-Study	Albumin (g.L-1)	52.0	39.3	48.5	G/L
9	Pre-Study	ALP (IU.L-1)	265.7	84.6	253.4	IU/L
9	Pre-Study	Cholesterol (mmol.L-1)	5.50	0.0	5.2	MMOL/L
9	Pre-Study	Total Protein (g.L-1)	85.8	66.1	81.1	G/L
11	Pre-Study	Cholesterol (mmol.L-1)	7.32	0.0	5.2	MMOL/L
11	Pre-Study	Sodium (mmol.L-1)	142.8	135.4	142.5	MMOL/L
11	Pre-Study	Triglycerides (mmol.L-1)	2.80	0.0	2.3	MMOL/L
11	Pre-Study Rpt	Cholesterol (mmol.L-1)	7.15	0.0	5.2	MMOL/L
11	Pre-Study Rpt	Cholesterol (mmol.L-1)	6.76	0.0	5.2	MMOL/L
13	Pre-Study	Creatine Kinase (IU.L-1)	231.1	35.1	227.9	IU/L
13	Pre-Study	Creatinine (umol.L-1)	47.6	56.0	92.2	UMOL/L
14	Pre-Study	ALP (IU.L-1)	109.5	124.9	294.3	IU/L
14	Pre-Study	ALT (IU.L-1)	74.6	13.0	67.2	IU/L
14	Pre-Study	GGT (IU.L-1)	84.5	10.0	69.7	IU/L
15	Pre-Study	Cholesterol (mmol.L-1)	6.01	0.0	5.2	MMOL/L
16	Pre-Study	GGT (IU.L-1)	7.3	7.8	46.8	IU/L
17	Pre-Study	ALP (IU.L-1)	276.9	84.6	253.4	IU/L
17	Pre-Study	Total Bilirubin (umol.L-1)	2.9	3.6	22.0	UMOL/L
18	Pre-Study	Sodium (mmol.L-1)	142.8	135.4	142.5	MMOL/L
20	Pre-Study	Calcium (mmol.L-1)	2.23	2.24	2.66	MMOL/L

Output File: bio_oor, 28APR2008 14:35, Final

RD 266/24573 (GA0706)

Summary of Haematology Data

Visit	Parameter	N	Mean	SD	Minimum	Median	Maximum
Pre-Study	Basophils (X10 9.L-1)	20	0.05	0.05	0.0	0.0	0.1
Pre-Study	Eosinophils (X10 9.L-1)	20	0.14	0.07	0.0	0.1	0.3
Pre-Study	Haematocrit (L.L-1)	20	0.4160	0.0304	0.358	0.421	0.464
Pre-Study	Haemoglobin (g.L-1)	20	142.0	12.0	120	143	160
Pre-Study	Lymphocytes (X10 9.L-1)	20	2.19	0.42	1.4	2.3	2.7
Pre-Study	MCH (pg)	20	30.73	1.95	25.8	31.0	33.7
Pre-Study	MCHC (g.L-1)	20	341.3	9.0	328	341	363
Pre-Study	MCV (fL)	20	90.04	4.97	77.2	90.7	96.1
Pre-Study	Monocytes (X10 9.L-1)	20	0.34	0.09	0.2	0.3	0.6
Pre-Study	Neutrophils (X10 9.L-1)	20	4.46	1.13	2.5	4.0	7.0
Pre-Study	Platelets (X10 9.L-1)	20	291.8	47.4	230	285	372
Pre-Study	RBC (X10 12.L-1)	20	4.626	0.300	4.02	4.59	5.16
Pre-Study	WBC (X10 9.L-1)	20	7.32	1.29	5.7	6.9	10.0

Output File: tab_haem, 28APR2008 11:49, Final

RD 266/24573 (GA0706)

Haematology Results

SUBJECT	VISIT	SAMPLEID	HB g/L	HCT L/L	RBC 10^12/L	MCV fL	MCH pg	MCHC g/L	WBC 10^9/L	NEUT 10^9/L	LYMP 10^9/L	MONO 10^9/L	EOS 10^9/L	BASO 10^9/L	PLT 10^9/L
1	Pre-Study	Z00101887	122	0.365	4.51	80.9	27.0	334	7.6	4.3	2.6	0.3	0.2	0.0	236
2	Pre-Study	Z00101843	133	0.400	4.72	84.7	28.2	333	9.9	6.4	2.4	0.6	0.3	0.1	294
3	Pre-Study	Z00101825	160	0.464	5.13	90.4	31.1	344	5.7	3.4	1.6	0.3	0.2	0.1	242
4	Pre-Study	Z00101922	130	0.396	4.38	90.5	29.7	328	9.3	6.0	2.7	0.3	0.1	0.1	319
5	Pre-Study	Z00101925	131	0.384	4.31	89.2	30.4	341	6.9	5.2	1.4	0.2	0.0	0.0	310
6	Pre-Study	Z00101882	128	0.379	4.02	94.3	31.9	338	7.5	4.0	2.7	0.4	0.2	0.0	237
7	Pre-Study	Z00101919	145	0.423	4.53	93.3	32.1	344	8.3	5.0	2.5	0.4	0.1	0.0	304
8	Pre-Study	Z00101917	144	0.418	4.47	93.5	32.3	345	6.6	3.9	2.1	0.3	0.1	0.0	271
9	Pre-Study	Z00101924	142	0.428	4.52	94.8	31.4	332	10.0	7.0	2.3	0.5	0.1	0.1	343
10	Pre-Study	Z00101892	146	0.436	4.89	89.2	29.9	335	8.4	5.7	2.1	0.3	0.2	0.1	230
11	Pre-Study	Z00101859	145	0.436	4.77	91.5	30.4	332	6.9	3.9	2.4	0.3	0.1	0.1	364h
12	Pre-Study	Z00101799	154h	0.437	4.88	89.6	31.5	352h	6.2	3.9	1.6	0.3	0.2	0.0	276
13	Pre-Study	Z00101918	154h	0.441	4.87	90.7	31.8	350	6.1	4.0	1.7	0.2	0.1	0.1	246
14	Pre-Study	Z00101894	156	0.430	5.16	83.2	30.2	363H*	7.1	4.9	1.6	0.4	0.1	0.0	297
15	Pre-Study	Z00101890	152	0.458	4.92	93.1	30.9	332	6.0	2.5	2.6	0.4	0.1	0.1	240
16	Pre-Study	Z00101948	141	0.405	4.34	93.4	32.5	348	6.6	3.8	2.3	0.3	0.1	0.0	372h
17	Pre-Study	Z00101954	120	0.358d	4.64	77.2d	25.8d	335	6.9	3.9	2.4	0.3	0.1	0.1	350
18	Pre-Study	Z00101947	137	0.403	4.45	90.6	30.8	340	7.9	4.6	2.6	0.3	0.2	0.0	362h
19	Pre-Study	Z00101996	160	0.457	4.75	96.1	33.7h	351	5.9	3.3	1.9	0.4	0.1	0.0	266
20	Pre-Study	Z00102005	140	0.402	4.25	94.6	33.0	348	6.5	3.6	2.3	0.3	0.2	0.0	276

Output File: haem, 28APR2008 11:56, Final

H* = Above Alert Range
h = Above Normal Range
d = Below Normal Range
D* = Below Alert Range

RD 266/24573 (GA0706)

Haematology Out of Range Results

Subject	Visit	Parameter	Result	Low Range	High Range	Units
11	Pre-Study	Platelets (X10 9.L-1)	364	169	357	10**9/L
12	Pre-Study	Haemoglobin (g.L-1)	154	120	152	G/L
12	Pre-Study	MCHC (g.L-1)	352	320	350	G/L
13	Pre-Study	Haemoglobin (g.L-1)	154	120	152	G/L
14	Pre-Study	MCHC (g.L-1)	363	323	360	G/L
16	Pre-Study	Platelets (X10 9.L-1)	372	169	357	10**9/L
17	Pre-Study	Haematocrit (L.L-1)	0.358	0.362	0.450	L/L
17	Pre-Study	MCH (pg)	25.8	26.5	33.1	PG
17	Pre-Study	MCV (fL)	77.2	78.3	100.1	FL
18	Pre-Study	Platelets (X10 9.L-1)	362	169	357	10**9/L
19	Pre-Study	MCH (pg)	33.7	27.5	33.6	PG

Output File: haem_oor, 28APR2008 14:59, Final

RD 266/24573 (GA0706)

Urinalysis Results

SUBJECT	VISIT	SAMPLEID	PH	PROTEIN	GLUCOSE	KETONES	BILI-RUBIN	BLOOD	UROB-ILINOGEN umol/L
1	Pre-Study	Z00101887	6.5	Neg	Neg	Neg	Neg	Neg	3.2
2	Pre-Study	Z00101843	7.5	Neg	Neg	Neg	Neg	Trace	3.2
3	Pre-Study	Z00101825	7.0	Neg	Neg	Neg	Neg	Neg	3.2
4	Pre-Study	Z00101922	7.0	Neg	Neg	Neg	Neg	Neg	3.2
5	Pre-Study	Z00101925	8.0	Neg	Neg	Neg	Neg	Neg	3.2
6	Pre-Study	Z00101882	7.5	Neg	Neg	Neg	Neg	Neg	3.2
7	Pre-Study	Z00101919	7.0	Neg	Neg	Neg	Neg	Trace	3.2
8	Pre-Study	Z00101917	8.5h	Neg	Neg	Neg	Neg	Neg	3.2
9	Pre-Study	Z00101924	8.0	Neg	Neg	Neg	Neg	Trace	3.2
10	Pre-Study	Z00101892	6.5	Neg	Neg	Neg	Neg	Neg	3.2
11	Pre-Study	Z00101859	8.0	Neg	Neg	Neg	Neg	Neg	3.2
12	Pre-Study	Z00101799	7.5	Neg	Neg	Neg	Neg	+	3.2
13	Pre-Study	Z00101918	7.5	Neg	Neg	Neg	Neg	Trace	3.2
14	Pre-Study	Z00101894	6.5	Neg	Neg	Neg	Neg	Neg	3.2
15	Pre-Study	Z00101890	7.0	Neg	Neg	Neg	Neg	Neg	3.2
16	Pre-Study	Z00101948	7.0	Neg	Neg	Neg	Neg	Neg	3.2
17	Pre-Study	Z00101954	7.0	Neg	Neg	Neg	Neg	Neg	3.2
18	Pre-Study	Z00101947	8.5h	Neg	Neg	Neg	Neg	Neg	3.2
19	Pre-Study	Z00101996	8.0	Neg	Neg	Neg	Neg	Neg	16.0
20	Pre-Study	Z00102005	6.5	Neg	Neg	Neg	Neg	Neg	3.2

Output File: ur, 28APR2008 11:00, Final

h = Above Normal Range
d = Below Normal Range

RD 266/24573 (GA0706)

Urinalysis Out of Range Results

Subject	Visit	Parameter	Result	Normal Range
2	Pre-Study	Blood	Trace	Negative
7	Pre-Study	Blood	Trace	Negative
8	Pre-Study	pH	8.5	Negative
9	Pre-Study	Blood	Trace	Negative
12	Pre-Study	Blood	+	Negative
13	Pre-Study	Blood	Trace	Negative
18	Pre-Study	pH	8.5	Negative

Output File: ur_oor, 28APR2008 12:27, Final

RD 266/24573 (GA0706)

Microscopy Results

SUBJECT	VISIT	SAMPLEID	WBC /HPF	RBC /HPF	CASTS /HPF	CRYSTALS	EPITHELIAL CELLS /HPF	BACT
2	Pre-Study	Z00101843	<=2	<=2	NIL	NIL	<=2	NEGATIVE
7	Pre-Study	Z00101919	<=2	<=2	NIL	NIL	2-5	NEGATIVE
9	Pre-Study	Z00101924	2-5	<=2	NIL	NIL	5-10	NEGATIVE
12	Pre-Study	Z00101799	<=2	<=2	NIL	NIL	2-5	NEGATIVE
13	Pre-Study	Z00101918	<=2	<=2	NIL	NIL	<=2	NEGATIVE

Output File: micro, 28APR2008 9:57, Final

RD 266/24573 (GA0706)

DOA and Pregnancy Test Results

	--- Pre-Study ---		--- Phase 1 ---		--- Phase 2 ---		--- Phase 3 ---		--- Phase 4 ---	
Subject	DOA	Pregnancy	DOA	Pregnancy	DOA	Pregnancy	DOA	Pregnancy	DOA	Pregnancy
1	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
2	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
3	Negative	N/A	Negative	N/A	Negative	N/A	Negative	N/A	Negative	N/A
4	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
5	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
6	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
7	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
8	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
9	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
10	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
11	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
12	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
13	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Positive	Negative
14	Negative	N/A	Negative	N/A	Negative	N/A	Negative	N/A	Negative	N/A
15	Negative	N/A	Negative	N/A	Negative	N/A	Negative	N/A	Negative	N/A
16	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
17	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
18	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
19	Negative	N/A	Negative	N/A	Negative	N/A	Negative	N/A	Negative	N/A
20	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative

Output File: doa, 28APR2008 15:06, Final

RD 266/24573 (GA0706)

Virology Test Results

Subject	Hep B	Hep C	HIV
1	NEGATIVE	NEGATIVE	NEGATIVE
2	NEGATIVE	NEGATIVE	NEGATIVE
3	NEGATIVE	NEGATIVE	NEGATIVE
4	NEGATIVE	NEGATIVE	NEGATIVE
5	NEGATIVE	NEGATIVE	NEGATIVE
6	NEGATIVE	NEGATIVE	NEGATIVE
7	NEGATIVE	NEGATIVE	NEGATIVE
8	NEGATIVE	NEGATIVE	NEGATIVE
9	NEGATIVE	NEGATIVE	NEGATIVE
10	NEGATIVE	NEGATIVE	NEGATIVE
11	NEGATIVE	NEGATIVE	NEGATIVE
12	NEGATIVE	NEGATIVE	NEGATIVE
13	NEGATIVE	NEGATIVE	NEGATIVE
14	NEGATIVE	NEGATIVE	NEGATIVE
15	NEGATIVE	NEGATIVE	NEGATIVE
16	NEGATIVE	NEGATIVE	NEGATIVE
17	NEGATIVE	NEGATIVE	NEGATIVE
18	NEGATIVE	NEGATIVE	NEGATIVE
19	NEGATIVE	NEGATIVE	NEGATIVE
20	NEGATIVE	NEGATIVE	NEGATIVE

Output File: virol, 28APR2008 9:09, Final

APPENDIX 16.3 CASE REPORT FORMS

No subjects died, experienced other serious adverse events, withdrew because of adverse events, or experienced other significant adverse events so this appendix is not present.

APPENDIX 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.