Reckitt Benckiser

1 STUDY REPORT TITLE PAGE

EudraCT/IND Number:	2010-019414-24
Study Number:	GA0921
Protocol Title:	A single centre, randomised, partially-blind, placebo-controlled 3 way crossover pilot study investigating efficacy in terms of heartburn relief after taking (2x250mg) Gaviscon® chewable tablets, (1x20mg) Losec® MUPS® tablet and (2x) Placebo tablets in subjects with heartburn following a refluxogenic meal.
Study Phase:	II
Date First Subject Enrolled:	21 July 2010
Date Last Subject Completed:	18 August 2010
Report Date:	19 May 2011
Principal Investigator:	Dr Salvatore Febbraro
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

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2 SYNOPSIS

Name of Sponsor/ Company: Reckitt Benckiser Healthcare (UK) Ltd	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority use only)**
Name of Finished Product: Gaviscon® chewable tablets, placebo chewable tablets, Losec® MUPS® tablets	**Volume:**	
Name of Active Ingredient(s): Sodium alginate, calcium carbonate, sodium bicarbonate	**Page:**	
Title of Trial: A single centre, randomised, partially-blind, placebo-controlled 3 way crossover pilot study investigating efficacy in terms of heartburn relief after taking (2x250mg) Gaviscon® chewable tablets, (1x20mg) Losec® MUPS® tablet and (2x) Placebo tablets in subjects with heartburn following a refluxogenic meal.		
Investigator(s): Dr Salvatore Febbraro		
Trial Site(s): Simbec Research Limited, Merthyr Tydfil CF48 4DR		
Publication (reference): None		
Studied Period: 4 weeks **Date first subject enrolled:** 21 July 2010 **Date last subject completed:** 18 August 2010		**Phase of Development: II**
Objectives: The primary objective of the study was to assess the method used to measure efficacy in terms of relief from heartburn with a new Gaviscon® formulation. The secondary objectives were to determine the onset of relief, duration of action, and overall assessment of the study medication compared to a Placebo and Losec® MUPS®.		
Methodology: The Simbec volunteer database was searched for potential volunteers who met the key study criteria. Participation comprised two Screening Visits, three Treatment Visits and a Post-Study follow-up Visit. Screening Visit 1 consisted of routine screening procedures following signed informed consent. At Screening Visit 2, subjects consumed a standardised refluxogenic meal, after which subjects were asked to evaluate the severity of their heartburn symptoms on a 4-point categorical scale (none, mild, moderate, and severe) over a period of 60 minutes. Those who confirmed their heartburn symptoms to be of at least moderate severity within this time were eligible for the dosing phase of the study. At least 48 hours after the second screening visit, subjects attended the clinic, received a light breakfast and then fasted for at least four hours before receiving a standardised refluxogenic meal. Subjects were asked to attract the attention of the study nurse when they experienced at least moderate symptoms of heartburn, at which time they were dosed with the randomised treatment allocated for that visit. At the time of dosing, two stopwatches were started and subjects were asked to stop the first stopwatch when first perceptible heartburn relief was felt and the second when that relief became "meaningful". Prior to dosing and at specified timepoints throughout the 4-hour study period, the subjects were required to answer heartburn relief questionnaires and complete VAS heartburn intensity pages. A period of 2-7 days was required between each of the three Treatment Visits and 3-7 days between the third Treatment Visit and the Post study Visit.		
Number of Subjects: **Planned:** 20 **Analysed**: 18		
Diagnosis and Main Criteria for Inclusion: Male and female subjects aged 18 – 65 years, inclusive, who had a tendency to experience symptoms of heartburn (a burning sensation behind the breastbone) of moderate severity associated with reflux, following some meals. To be eligible subjects had to experience at least moderate heartburn within 60 minutes following ingestion of a standardised refluxogenic meal at the second screening visit.		

Name of Sponsor/ Company: Reckitt Benckiser Healthcare (UK) Ltd	**Individual Trial Table Referring to Part of the Dossier**	**(For National Authority use only)**
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Name of Active Ingredient(s): Sodium alginate, calcium carbonate, sodium bicarbonate	**Page:**	

Test Product: Gaviscon® chewable tablets

Duration of Treatment: Single dose of each treatment

Reference Therapy: Placebo chewable tablets, Losec® MUPS® 10mg

Criteria for Evaluation:

Efficacy: The primary efficacy end-point was the area under the Heartburn Relief curve from 0 to 60 minutes post dose, computed using the trapezoid method ($AUCPR_{0-60}$). The secondary endpoints in this study were:

- Time to first perceptible relief
- Time to meaningful relief (onset of relief),
- Time to confirmed perceptible relief (where 'time to confirmed perceptible relief' is the time to first perceptible relief for those subjects who also reported 'meaningful relief')
- Heartburn relief using the Heartburn Relief Scale ('no relief', 'slight relief', 'mild relief', 'moderate relief', 'considerable relief', 'almost complete relief', 'complete relief'), assessed at 5, 10, 15, 20, 25, 30, 35, 40, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 minutes post dosing
- The area under the Heartburn Relief curve from 0 to 120 minutes post dose, computed using the trapezoid method ($AUCPR_{0-120}$)
- The area under the Heartburn Relief curve from 0 to 180 minutes post dose, computed using the trapezoid method ($AUCPR_{0-180}$)
- The area under the Heartburn Relief curve from 0 to 240 minutes post dose, computed using the trapezoid method ($AUCPR_{0-240}$)
- Heartburn intensity based on the VAS scale (based on a 100mm VAS scale where 0 = 'no pain' and 100 = 'worst pain imaginable' at 5, 10, 15, 20, 25, 30, 35, 40, 45, 60, 75 90, 105, 120, 150, 180, 210, and 240 minute post dosing
- The area under the VAS heartburn intensity curve from 0 to 60 minutes post dose, computed using the trapezoid method ($AUCVASHI_{0-60}$)
- The area under the VAS heartburn intensity curve from 0 to 120 minutes post dose, computed using the trapezoid method ($AUCVASHI_{0-120}$)
- The area under the VAS heartburn intensity curve from 0 to 180 minutes post dose, computed using the trapezoid method ($AUCVASHI_{0-180}$)
- The area under the VAS heartburn intensity curve from 0 to 240 minutes post dose, computed using the trapezoid method ($AUCVASHI_{0-24}$)
- Subjects' overall assessment of study medication assessed at 240 minutes post dose
- Proportion of subjects who achieved 'complete relief' on the Heartburn Relief Scale within 240 minutes post dose
- Responses to Subjective Relief Questionnaire 1, once the second stopwatch has been

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Name of Active Ingredient(s): Sodium alginate, calcium carbonate, sodium bicarbonate	**Page:**	

stopped (as described in Appendix IV of Protocol)

- Proportion of subjects who reported they would be willing to use the product again.
- Proportion of subjects who reported they would be willing to replace their current therapy with this product

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 if they had any symptoms or complaints since the previous visit and again when the subject returned to the research unit for their post-study follow up visit. Safety was also evaluated using data obtained from monitoring ECGs, vital signs and laboratory tests at screening and at the post-study follow up visit.

Statistical Methods: In all statistical models used to analyse the primary and secondary endpoints, the two comparisons of interests were:

- Gaviscon® chewable tablets vs. Placebo chewable tablets,
- Gaviscon® chewable tablets vs. Losec® tablets.

The above mentioned comparisons were to be considered as statistically significant if the associated test probabilities (p-values) were less then 0.05. As this is an exploratory study, no correction for multiple testing was applied.

Analysis of the Primary endpoint: The area under the Heartburn Relief curve from 0 to 60 minutes post dose ($AUCPR_{0-60}$) was summarised by treatment and analysed using analysis of covariance (ANCOVA) with terms in the model for treatment sequence and treatment as fixed effects, a covariate for period baseline heartburn severity ('moderate' or 'severe') and subject considered as a random factor.

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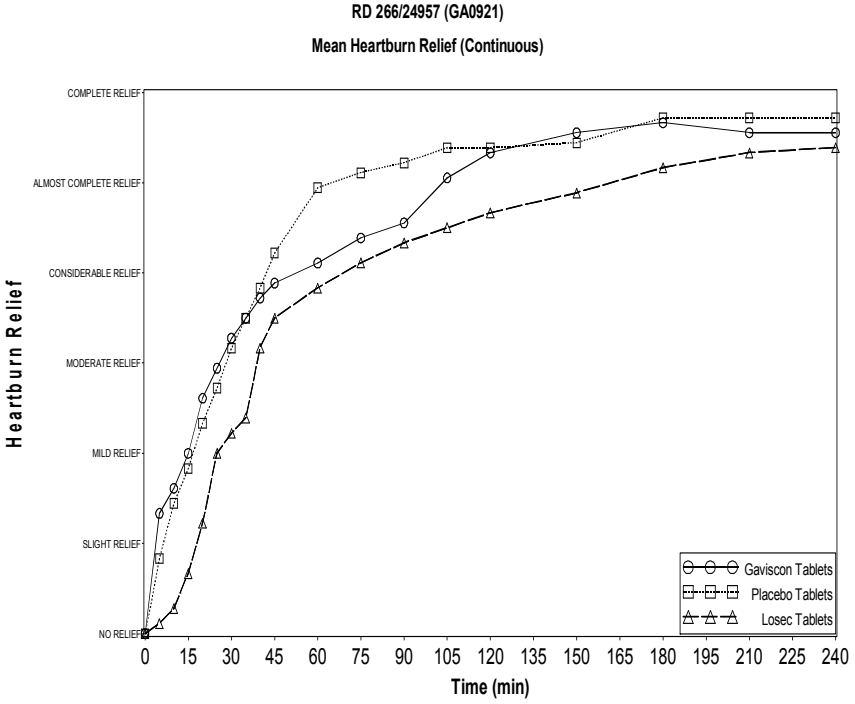
Name of Active Ingredient(s): Sodium alginate, calcium carbonate, sodium bicarbonate	**Page:**	

SUMMARY & CONCLUSIONS

Efficacy Results: *Heartburn Relief:* In terms of the primary endpoint, AUC_{0-60} for heartburn relief, there was no statistically significant difference between Gaviscon® (mean; SD: 174.9; 93.8) and placebo (mean; SD: 177.8; 67.3) (p=0.8883). However, Gaviscon® was statistically significantly more efficacious than Losec® (mean; SD: 124.2; 89.1) (p=0.0163). There was no significant difference between Gaviscon® and placebo in terms of AUC for heartburn relief for the periods 0-15, 0-30, 0-120, 0-180 or 0-240 minutes, although the AUC_{0-15} and AUC_{0-30} values were greater for Gaviscon® than placebo (19.9 vs. 16.2 for AUC_{0-15} and 60.9 vs. 54.1 for AUC_{0-30}). Gaviscon® was statistically significantly more efficacious than Losec in terms of AUC for heartburn relief for the periods 0-15 (p<0.0001) and 0-30 minutes (p=0.0003). There was no statistically significant difference between Gaviscon® and placebo at any individual timepoint, whereas Gaviscon® was statistically significantly more efficacious than Losec® at all timepoints up to and including 35 minutes.

Figure S1 Heartburn Relief (Continuous) for study GA0921



Heartburn Intensity (VAS): There was no statistically significant difference between Gaviscon® and placebo in terms of AUC for heartburn intensity (VAS) for the periods 0-15, 0-30, 0-60, 0-120, 0-180 or 0-240 minutes, whereas Gaviscon® was statistically significantly more efficacious than Losec for the periods 0-15 (p=0.0021), 0-30 (p=0.0010), 0-60 (p=0.0113), 0-120 (p=0.0368) and 180 minutes (p=0.0494). There was no statistically significant difference between Gaviscon® and placebo at any individual timepoint, whereas Gaviscon® was statistically significantly more efficacious than Losec® at all timepoints up to and including 35

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minutes.

Stopwatch Assessments: In terms of the Kaplan-Meier (KM) median time to first perceptible relief, there was no statistically significant difference between Gaviscon® (median; 95%CI: 4.74; 3.60-18.85 minutes) and placebo (median; 95%CI: 6.29; 3.93-19.05 minutes) (KM p value=0.6156, PH p value=0.1875), whereas the time was significantly longer for Losec (median; 95%CI: 22.67; 18.80-27.60 minutes) (KM p value=0.0044, PH p value=0.0003) than for Gaviscon®. In terms of the KM median time to meaningful relief, there was no statistically significant difference between Gaviscon® (median; 95%CI: 30.90; 16.90-38.50 minutes) and placebo (median; 95%CI: 29.20; 14.75-35.20 minutes) (KM p value=0.9901, PH p value=0.8844), whereas the time was significantly longer for Losec (median; 95%CI: 34.47; 27.03-53.62 minutes) than for Gaviscon® using the Cox proportional hazards analysis (PH p value=0.0085) but not according to the KM analysis (KM p value=0.1008).

Other Endpoints: There was no significant difference between Gaviscon® and placebo or between Gaviscon® and Losec® in terms of subjects' overall assessment, the proportion of subjects who attained complete relief or the proportion of subjects who would be willing to use the product again. In terms of the proportion of subjects who were prepared to replace their current therapy with treatment and the proportion that obtained soothing relief, cooling relief and an instant soothing effect, there was no statistically significant difference between Gaviscon® and placebo, whereas the difference between Gaviscon® and Losec® was statistically significant in favour of Gaviscon®.

Safety Results: No clinically significant safety issues were identified and no clinically significant treatment-emergent AEs were reported. There were no clinically significant changes in laboratory evaluations, vital signs or ECGs.

CONCLUSION: The AUC_{0-60} Heartburn Relief with Gaviscon® (174.9) was statistically significantly greater compared with Losec® (124.2) but not compared with placebo (177.8). Gaviscon® demonstrated a statistically significantly earlier onset of of first perceptible relief (4.74 minutes) compared with Losec® (22.67 minutes) but not compared with placebo (6.29 minutes). For the first 30 minutes post-dosing, heartburn relief was greater with Gaviscon® than placebo, whereas from 30 – 240 minutes, heartburn relief tended to be greater with placebo than with Gaviscon®. These differences failed to reach statistical significance.

The inability of the model in this pilot study to distinguish between Gaviscon® and Placebo may be due to a number of confounding factors such as the low severity of heartburn in the study population, the self-limiting nature of the condition and the mint flavour of the placebo.

Date of the report: 19 May 2011

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Abbreviation in Full
AUC	Area under the curve
AE	Adverse event
BPM	Beats per minute
CRF	Case report form
CV	Curriculum vitae
ECG	Electrocardiogram
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IMSU	Investigational Material Supplies Unit
ITT	Intent-to-treat
OTC	Over the Counter
PPI	Proton Pump Inhibitor
RB	Reckitt Benckiser Healthcare (UK) Ltd
SAE	Serious adverse event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
UK	United Kingdom (of Great Britain and Northern Ireland)
VAS	Visual Analogue Scale

5 ETHICS

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

The name and full address of the South East Wales Research Ethics Committee 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), Panel D, in a letter dated 18th June 2010.

5.2 Ethical Conduct of the Study

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

5.3 Subject Information and Consent

Copies of a representative subject information sheet and a blank consent form (Version 2, dated 16th June 2010) are provided in Appendix 16.1.3.

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 or designee 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 vita (CV) of the Investigator is also included in the Appendix.

The study was carried out at Simbec Research Limited under the guidance of the Principal Investigator, Dr S Febbraro. Some study-related activities were delegated to suitably qualified Simbec personnel. Data management and statistical analysis were conducted by the Statistical Analysis Group, all 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, (RB) Dansom Lane, Hull, HU8 7DS. Study project management was contracted to Dr Sandie Reader, Clearcut Clinical Consulting, Nottingham, UK and the writing of the

clinical study report was contracted to Simbec Research Ltd. Monitoring was performed by Ann Ring, Clinical Research Consultant, and RB was responsible for the expedited reporting of any serious adverse events 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) presentations/formulations to offer consumer choice of flavours and dosing formats. Gaviscon® tablets are currently not considered pleasant to take by some antacid users and thereby have contributed to a lack in volume growth of the Gaviscon® tablet range. To address this issue, RB has conducted qualitative market research to define the ideal tablet. Based on the feedback from consumers, RB have developed a new tablet to improve the organoleptic experience such that the tablet has an improved mouthfeel but still has the same active ingredients at the same doses as the current Gaviscon® tablets.

To support the efficacy of the new Gaviscon® product, Reckitt Benckiser wished to pilot a new technique designed to generate data on speed and duration of action of the product. The results of this study will allow further efficacy studies to be designed which can provide data that will form part of the Summary of Product Characteristics (SmPC) for Gaviscon® Chewable tablets.

This pilot study was conducted with a view to performing a pivotal study to confirm the findings of the pilot study regarding the time of onset and duration of heartburn relief following treatment with the latest Gaviscon® tablet formulation. In addition, the study will provide information on the efficacy of Gaviscon® chewable tablets when compared to a Placebo tablet and the Proton Pump Inhibitor (PPI) Losec®.

The placebo tablet had been formulated to be comparable to the test product and provide information on the efficacy of the active ingredients and validity of the test method.

Losec® MUPS® was included in the study as RB wished to understand the difference in the efficacy of PPIs and Gaviscon® products. PPIs inhibit the proton pump in the parietal cells of the stomach thereby inhibiting the production of acid. This causes a dramatic reduction in stomach acid production, which in turn results in effective long term treatment of ulcers and reflux oesophagitis.

The population to be studied were healthy subjects who have a tendency to suffer from postprandial heartburn. Subjects were provided with a refluxogenic meal to induce the symptoms of heartburn.

Previously the 2-stopwatch technique had been shown to be a valid method to assess heartburn; subjects were asked to stop one of the stopwatches when they first perceived a soothing effect and the other stopwatch when they first perceived a

cooling effect from the administered treatment.[1,2] In this randomised, crossover, single dose study, the 2-stopwatch technique was used to assess the onset of action in terms of relief with Gaviscon® chewable tablets compared to a Placebo and Losec® MUPS®.

The study was partially blinded, this was achieved by matching the appearance of the Gaviscon® Chewable Tablet and the Placebo and having a member of Simbec staff not associated with the study administer the study medication. Losec® tablets were open-label due to the nature of the commercial packaging and dosing.

The potential risks to subjects taking part in the present study were considered to be low. The adverse reactions that occur very rarely (<1/10,000) as a result of taking Gaviscon® products are allergic manifestations such as urticaria or bronchospasm, anaphylactic or anaphylactoid reactions as a result of a subject being sensitive to any of the active substances (sodium alginate, sodium bicarbonate/sodium hydrogen carbonate, and calcium carbonate) or any of the excipients (e.g. hydroxybenzoates (parabens)). Other adverse reactions include:

1. Sodium bicarbonate/sodium hydrogen carbonate – increased plasma sodium levels especially for those with renal and cardiovascular conditions on a highly restricted salt diet

2. Calcium carbonate – high doses of calcium may cause alkalosis, hypercalcaemia, acid rebound, milk alkali syndrome or constipation

Losec® MUPS® is well tolerated and adverse reactions have generally been mild and reversible. The following have been reported, but in many cases a relationship to treatment with Omeprazole has not been established. The most commonly reported side effects ($\geq$ 1/100) include headache, diarrhoea, constipation, abdominal pain, nausea/vomiting and flatulence. Uncommonly (between 1/1000 and 1/100) dizziness, paraesthesia, light headedness, feeling faint, drowsiness, insomnia and vertigo, increased liver enzymes, rash, dermatitis, malaise. Rarely serious adverse events have been reported.

Since healthy volunteers (with a history of suffering from heartburn) were recruited to the study the risk benefit balance for the current study is considered to be acceptable.

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

8 STUDY OBJECTIVES

The primary objective of the study was to assess the method used to measure efficacy in terms of relief from heartburn with a new Gaviscon® formulation.

The secondary objectives were to determine the onset of relief, duration of action, and overall assessment of the study medication compared to a Placebo and Losec® MUPS®.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan – Description

The study Protocol (incorporating Amendment 1) is included as Appendix 16.1.1. Unique pages from the case report form (CRF) are included as Appendix 16.1.2.

This was a single-centre randomised, partially-blind, placebo-controlled crossover pilot study investigating the efficacy of Gaviscon® chewable tablets (2 x 250mg), placebo tablets and Losec® MUPS® tablet (1 x 20mg) in subjects who displayed at least moderate heartburn following a refluxogenic meal. There was a minimum 2-day and a maximum 7-day period between each of the treatments.

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

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

Allocation of treatments to visits was based on a Latin Square design using three 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:

Medication A: Gaviscon® chewable tablets (test formulation), contains 250mg sodium alginate, 133.5mg sodium bicarbonate, and 80mg calcium carbonate per tablet, Formulation Reference No: 0261731.

Medication B: Placebo Chewable Tablets, Reference No: 01107/096

Medication C: Losec® MUPS® tablets, containing 20mg Omeprazole, PL 17901/0138

Medication A and B were manufactured to GMP standards by Reckitt Benckiser Healthcare (UK) Limited, Dansom Lane, Hull, HU8 7DS, UK.

Medication C was manufactured to GMP standards by AstraZeneca UK Ltd., 600 Capability Green, Luton, LU1 3LU, UK.

All drug supplies were packed and labelled to GMP standards by the Investigational Material Supplies Unit (IMSU), Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS, UK. The Gaviscon® and Placebo products were supplied as blinded. Losec® was supplied as open label in original packaging.

All test products together with the stopwatches were supplied by Reckitt Benckiser Healthcare UK Ltd, Dansom Lane, Hull HU8 7DS, UK and shipped directly from the IMSU to Simbec Research Ltd.

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 effect in the throat/oesophagus (foodpipe), and the other to record the time when the relief was meaningful to them. The subjects were instructed to stop each of the 2 stopwatches at the appropriate time point i.e., when the first perceptible relief was experienced and when the relief was meaningful to him /her.

Just prior to the allocated medication being administered the subjects were required to answer a Heartburn Intensity Visual Analogue Scale (VAS) questionnaire (Appendix II of study protocol). Following dosing with the appropriate medication the subjects were then required to complete a Heartburn Intensity VAS questionnaire and also a Heartburn Relief Scale questionnaire (Appendix I of study protocol) at the following time points relative to the dosing: 5, 10, 15, 20, 25, 30, 35, 40, 45, 60, 75, 90, 105, 120, 150, 180, 210 and 240 minutes. At the end of this period the subjects were then required to give their overall assessment of the study medication on a five

point scale (Appendix III of study protocol) and also their response to the Subjective Relief Questionnaire II (Appendix V of study protocol). When the subject had stopped the second of the 2 stopwatches he/she was also required to respond to the Subjective Relief Questionnaire I (Appendix IV of study protocol).

Adverse events that occurred during/ following treatment with the study medications were also collected at this stage.

A washout period of at least 2 and no more than 7 days was required between each of the treatment visits.

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

9.3 Selection of Study Population

Simbec Research Ltd searched their volunteer database for potential subjects and then contacted them to establish interest and ask them to present for screening.

9.3.1 Inclusion Criteria

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

1) Age: ≥ 18 years ≤ 65 years
2) Sex: Male and female subjects were eligible for entry.
3) Subjects who had a tendency to experience symptoms of heartburn (a burning sensation behind the breastbone) of moderate severity associated with 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 second screening visit.
5) Subjects who gave written informed consent.

9.3.2 Exclusion Criteria

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

1) Those who had suffered a recent, significant unexplained weight loss of 6-7kg in the previous 6 months.
2) Those who had experienced any gastrointestinal bleeding within the previous 12 months.
3) Those who had taken any antacids, H_2-receptor antagonists, motility stimulants/prokinetics or other medicines for relief of symptoms of acid reflux within the previous 2 weeks of screening.
4) Those who had taken proton pump inhibitors within the previous 4 weeks of screening.
5) Those who had severe constipation or history of colonic stenosis.
6) Those with known hypophosphataemia or phenylketonuria.
7) Those with a history of drug, solvent or alcohol abuse

8) Those who were receiving treatment for their upper gastrointestinal problems or gastro-oesophageal reflux disease from their GP.
9) Those who were participating in a clinical study or who had participated in any other clinical study within the previous 30 days.
10) Those who had previously participated in this randomised study.
11) Those who had difficulty in swallowing or chewing (e.g. those who had loose teeth, dentures, fillings, etc).
12) Those who had a history of cardiovascular disorders or showed evidence of clinically significant cardiovascular disease.
13) Those who were on steroids or non-steroidal anti-inflammatory drugs.
14) Those who were diabetic.
15) 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.
16) 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 [should the subject become sexually active, she must have agreed to use a double barrier method] or condoms/diaphragm and spermicide). A woman of childbearing potential is 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).
17) Those who were known to be hypersensitive or allergic to any of the active substances (e.g. sodium alginate, sodium bicarbonate, calcium carbonate, Omeprazole), any of the excipients (Gaviscon® Tablets: Poly vinyl pyrrolidone (povidone K30), Acesulfame potassium, Mannitol 100SD, Erythritol, Peppermint Flavour 108406, Colloidal silicon dioxide anhydrous, Polyethylene glycol (Macrogol 20000), Stearic Acid Coarse Powder, Aspartame,
Losec® MUPS® Tablets: Mannitol, Hyprolose, Cellulose Microcrystalline, Anhydrous Lactose, Sodium lauryl Sulphate, Disodium Hydrogen Phosphate Dihydrate, Hypromellose, Methacrylic Acid Copolymer, Macrogol, Colours E171 and E172, Gelatin and Magnesium Stearate.
Placebo Tablets: Acesulfame K, Mannitol 100SD, Erythritol , Peppermint Flavour 108406, Silica Colloidal anhydrous. Polyethylene glycol 20000, Stearic Acid Coarse Powder, Aspartame
18) Those who were vegetarians
19) Those unable in the opinion of the Investigator to comply fully with the study requirements.

9.3.3 Removal of Subjects from Therapy or Assessment

The Investigator was able to 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 is an adverse event)
- violation of the study protocol
- in the Investigator's judgement, was in the subject's best interest
- subject declined further study participation

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

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

- Vital Signs
    - blood pressure (after sitting for 5 minutes; mmHg)
    - heart rate (radial pulse counted for 30 seconds after resting for 5 minutes; beats/minute)
    - oral temperature (ºC).

- Physical examination

- Review of concomitant medication

- Review of adverse events

9.4 Treatments

9.4.1 Treatments Administered

The following medication was supplied:

Medication A: Gaviscon® chewable tablets (test formulation), contains 250mg sodium alginate, 133.5mg sodium bicarbonate, and 80mg calcium carbonate per tablet, Formulation Reference No: 0261731.

Medication B: Placebo Chewable Tablets, Reference No: 01107/096

Medication C: Losec® MUPS® tablets, containing 20mg Omeprazole, PL 17901/0138

Two chewable tablets of A/B were administered orally on two occasions (the actual visit administration being denoted by the Treatment visit number on each of the inner containers) for each product. One tablet of product C was administered orally 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, PL04425/0378, batch number 098, expiry date March 2012, was supplied by Simbec and a single dose of 10ml administered orally to those subjects who required symptomatic relief after experiencing heartburn during the second screening visit and throughout the treatment visits (after the 240 minute time at the treatment visits had been exceeded).

9.4.1.1 Standard Refluxogenic Meal

The standard refluxogenic meal was a heavy fat-laden meal consisting of: deep fried chips, beefburger with cheese and fried onions followed by a jam doughnut.

9.4.2 Identity of Investigational Product(s)

The Gaviscon® chewable tablets and placebo chewable tablets were packed and labelled to GMP standards by the Investigational Material Supplies Unit (IMSU), Reckitt Benckiser Healthcare UK Ltd, Dansom Lane, Hull HU8 7DS, UK. Both of the chewable tablet products were supplied as blinded, the Losec® MUPS® being open label in original packaging. They were shipped directly from the IMSU to Simbec Research Ltd.

9.4.3 Method of Assigning Subjects to Treatment Groups

Drug supplies were randomised according to a computer-produced randomisation schedule provided by the RB Statistician and checked by a statistician not involved in the analysis of the study. When randomised, subjects were allocated a unique subject number in numerical sequence. Assignment of the treatment sequence defined by the randomisation list by subject number ensured a balanced randomisation of study drug to Treatment Visit. The blinded aspect of the treatment code would only be broken for an individual subject in an emergency such as a serious adverse event that required knowledge of what study drug (Gaviscon® chewable tablets or placebo chewable tablets) was taken in order that the SAE could be treated appropriately. If the code for a subject was broken for any reason, the Investigator should have withdrawn the subject from the study, documenting the details of the event in the subject's case report form and promptly have informed the RB Clinical Project Manager.

In order to maintain the partial blinding of the study, the Gaviscon® treatment and Placebo (Medications A and B) were matched in appearance and packaging. The randomised treatment allocation schedule was prepared using the treatment codes A, B and C. In addition, treatment doses were prepared by IMSU in containers labelled by subject number and treatment period. Code break envelopes were provided to enable the investigator to break the code when required.

9.4.4 Selection of Doses in the Study

Each medication was given as a single dose, consisting of two 250mg Gaviscon® chewable tablets, two placebo chewable tablets or one 10mg Losec® MUPS® tablet. On each treatment day, the medication for each subject was administered by the Investigator or delegated individual, who instructed the subject how to take the medication and observed them doing so. Individual doses of the IMP were dispensed, according to the randomisation schedule, to the subject when a moderate degree of heartburn was reported by the subject. For all of the three doses the subjects were dosed whilst in a in a seated position. For both the Gaviscon® chewable tablets and the placebo chewable tablets the second tablet was dispensed to the subject only when the first had been chewed and swallowed. The time of dosing was documented as the time at when the second of the two chewable tablets (Gaviscon® or placebo) was swallowed by the subject.

9.4.5 Selection of Timing of Dose for Each Subject

After attending the clinical unit at approximately 8am on each of the three treatment dosing days the subjects were given a light breakfast. After a period of at least 4 hours had elapsed since eating the breakfast the subjects were given the standard refluxogenic meal to consume. Dosing was staggered between groups of subjects, as required and approximately ten subjects were dosed each day. Following the consumption of the standard refluxogenic meal the subjects were instructed to lie flat on their backs until they experienced what they considered to be a moderate degree of heartburn. After informing a member of staff that they had achieved “moderate” heartburn subjects were administered the appropriate treatment according to the randomisation schedule. Subjects were dosed in a sitting position. The actual time of dosing, noted when the subject had taken their allocated treatment (time of swallowing the second of the 2 chewable tablets for treatments A and B and swallowing the tablet for treatment C), was recorded in the subject’s CRF and signed by the person administering the dose, who also conducted a hand and mouth check.

9.4.6 Blinding

This was a partially blinded study in respect of the Gaviscon®chewable tablets and the placebo chewable tablets. These two treatments (Medications A and B) were matched in appearance and packaging. The randomised treatment allocation schedule was prepared using the treatment codes A, B and C. In addition, treatment doses will be prepared by IMSU in containers labelled by subject number and treatment period. Code break envelopes were provided to enable the investigator to break the code when required.

9.4.7 Prior and Concomitant Therapy

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 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.

9.4.8 Treatment Compliance

Simbec personnel (Physician or appropriately trained staff) watched each subject take the treatment, presented in a suitable plastic dosing cup, conducting a hand and mouth inspection afterwards to ensure compliance with dosing. Any subjects who would not take the medication as required was to be withdrawn from the study.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flowchart

Table 9.5.1 Flowchart of study procedures

Study Period	Pre-study Screening		Treatment Visits			Post Study Visit (3-7 days after treatment visit)
	Visit 1	Visit 2	Treatment 1 Day 1	Treatment 2 Day 2	Treatment 3 Day 3	
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 (incl alcohol)	X		X	X	X	
Eligibility decision		X				
Refluxogenic Meal		X	X	X	X	
Severity rating of heartburn		X	X	X	X	
Rescue Medication		X	X	X	X	
Dosing			X	X	X	
Heartburn relief scale			X*	X*	X*	
Heartburn intensity on the VAS scale			X*	X*	X*	
Stopwatch assessments: 1). time to perceptible relief 2). time to meaningful relief			X	X	X	
Questionnaire 1 (as described in Appendix IV of Protocol)			X[a]	X[a]	X[a]	
Overall Treatment Rating and Questionnaire 2 (as described in Appendix V of Protocol)			X[b]	X[b]	X[b]	
Adverse Events			X[b]	X[b]	X[b]	X

* Completed at, 5, 10, 15, 20, 25, 30, 35, 40, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 minutes post dose

[a] Completed after the second stopwatch has been stopped

[b] Completed at 240 minutes

All assessments were conducted by the Investigator or a delegated individual qualified by education and experience to perform the delegated task(s).

Medical History & Current Medical Status: A medical history was taken at screening visit 1 and the subject's current status as a healthy volunteer was

confirmed by a physician. Smoking, alcohol and drugs of abuse history and use were collected at screening visit 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 screening 1 (baseline).

Concomitant Medication (and history at pre-study): At screening visit 1, the medication and therapy history was recorded together with current medication use and concomitant therapy taken during the previous 14 days. At the study treatment visits, any unscheduled visits and 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 for 30 seconds after resting for 5 minutes (beats/minute) and oral temperature (°C) were assessed at screening visit 1. A12-lead ECG was conducted at screening visit 1 and at the post study follow-up visit.

Physical Examination: A standard physical examination was conducted at screening visit 1. Clinically significant findings were documented in the CRF.

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

Urinalysis: The following tests were conducted using urine samples obtained at screening visit 1: dip-stick test for pH, protein, glucose, ketones, bilirubin, blood and 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 screening visit 1.

Viral Serology: Testing for hepatitis B surface antigen, hepatitis C antibody, and HIV screening was conducted on a blood sample obtained at screening visit 1. Results were reported as positive or negative.

Pregnancy testing: Women of child-bearing potential had a serum pregnancy test at Screening Visit 1 using the standard pregnancy testing method of the unit. At each of the 3 study treatment visits the women of child-bearing potential had a urine pregnancy test. This was performed at screening, before dosing at each treatment visit and at the post study visit.

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 screening visit and "Have you had any symptoms or complaints since you were last asked?" at each treatment visit before dosing and prior to discharge from the unit. They were also asked this question when they attended the follow-up visit.

All adverse events (including clinically significant laboratory abnormalities) were to be followed up whenever 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 study, supportive efficacy questions of subject perception were also asked.

9.5.3 Primary Efficacy Variable(s)

The primary efficacy end-point was the area under the Heartburn Relief curve from 0 to 60 minutes post dose, computed using the trapezoid method ($AUCPR_{0-60}$).

9.5.4 Secondary Efficacy Variables

- Time to first perceptible relief
- Time to meaningful relief (onset of relief),
- Time to confirmed perceptible relief (where 'time to confirmed perceptible relief' is the time to first perceptible relief for those subjects who also reported 'meaningful relief')
- Heartburn relief using the Heartburn Relief Scale ('no relief', 'slight relief', 'mild relief', 'moderate relief', 'considerable relief', 'almost complete relief', 'complete relief'), assessed at 5, 10, 15, 20, 25, 30, 35, 40, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 minutes post dosing
- The area under the Heartburn Relief curve from 0 to 120 minutes post dose, computed using the trapezoid method ($AUCPR_{0-120}$)
- The area under the Heartburn Relief curve from 0 to 180 minutes post dose, computed using the trapezoid method ($AUCPR_{0-180}$)
- The area under the Heartburn Relief curve from 0 to 240 minutes post dose, computed using the trapezoid method ($AUCPR_{0-240}$)
- Heartburn intensity based on the VAS scale (based on a 100mm VAS scale where 0 = 'no pain' and 100 = 'worst pain imaginable' at 5, 10, 15, 20, 25, 30, 35, 40, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 minute post dosing
- The area under the VAS heartburn intensity curve from 0 to 60 minutes post dose, computed using the trapezoid method ($AUCVASHI_{0-60}$)
- The area under the VAS heartburn intensity curve from 0 to 120 minutes post dose, computed using the trapezoid method ($AUCVASHI_{0-120}$)
- The area under the VAS heartburn intensity curve from 0 to 180 minutes post dose, computed using the trapezoid method ($AUCVASHI_{0-180}$)
- The area under the VAS heartburn intensity curve from 0 to 240 minutes post dose, computed using the trapezoid method ($AUCVASHI_{0-24}$)
- Subjects' overall assessment of study medication assessed at 240 minutes post dose
- Proportion of subjects who achieved 'complete relief' on the Heartburn Relief Scale within 240 minutes post dose

- Responses to Subjective Relief Questionnaire 1, once the second stopwatch had been stopped (as described in Appendix IV of Protocol)

- Proportion of subjects who reported they would be willing to use the product again.

- Proportion of subjects who reported they would be willing to replace their current therapy with this product

9.5.4 Drug Concentration Measurements

Drug concentrations were not measured in this study.

9.6 Data Quality Assurance

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

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

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

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

- Physical examination
- AEs
- Concomitant medication

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

9.7.1 Statistical and Analytical Plans

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

Data set to be analysed:

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

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

Intention to Treat Population (ITT): All subjects who were recruited to the study, received at least two doses of study medication and had efficacy data for at least two treatment visits. This population was used for summaries of efficacy data.

Demographic and screening failure data for all consented subjects will be listed in the appendices to the study report.

9.7.2 Determination of Sample Size

As this was a pilot study no statistical justification for the sample size in this study was performed. This study was intended to provide variance and effect estimates from which sample size estimates for future studies were to 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

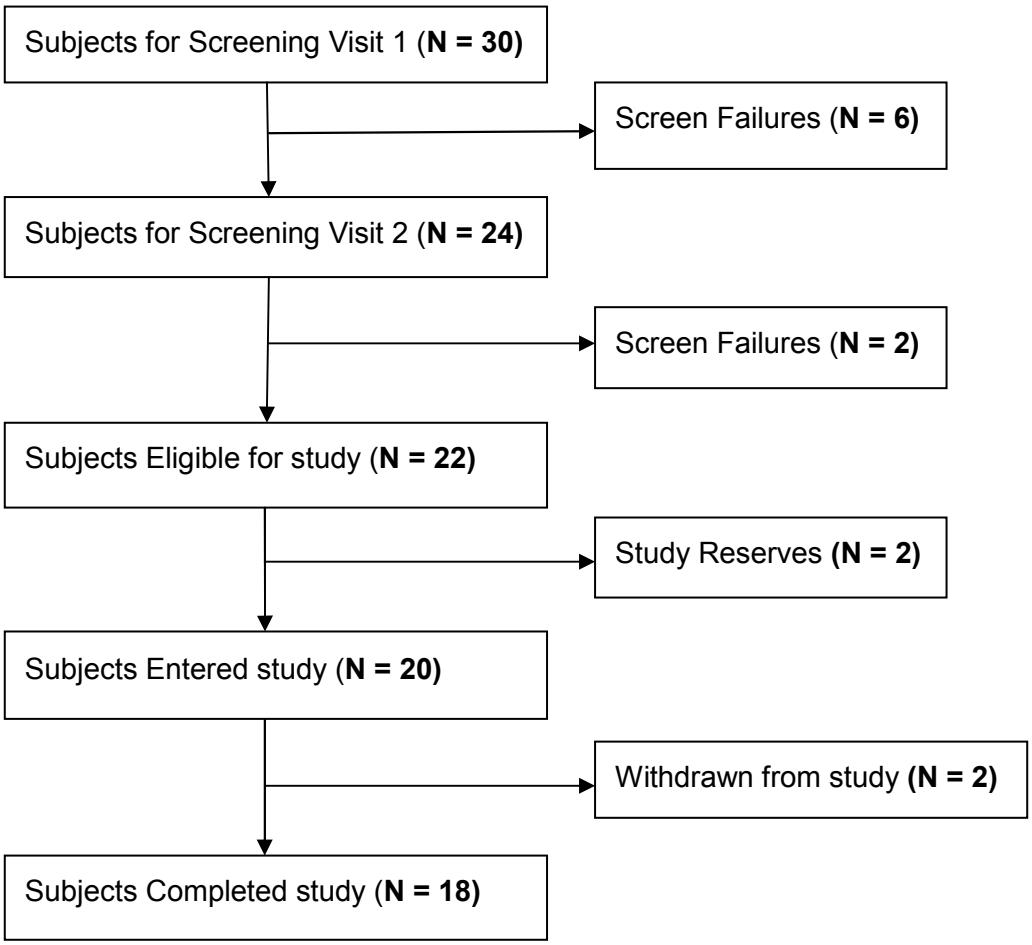
No changes were made in the planned statistical analyses

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 16.2.4 contains a tabular listing of all the study subjects, both in the Safety and ITT populations. 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.

Nineteen out of the 20 subjects who were randomised to treatment received at least one dose of study medication and were included in the Safety Population used for summaries of demography and safety. One subject was not included in the Safety Population as on two dosing visits the subject did not experience any sensation of heartburn following the refluxogenic meal.

Eighteen out of the 20 who were randomised to treatment received at least two doses of study medication and had efficacy data for at least two treatment visits and were included in the ITT Population used for summaries of efficacy data.

11.2 Demographic and Other Baseline Characteristics

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

11.2.1 Demographics

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

Table 11.2.1 Summary of subject demographic data in study GA0921

Variable		Male	Female	All
AGE (YRS)	N	9	10	19
	MEAN	35.0	38.3	36.7
	SD	11.6	13.9	12.6
	MIN	20	19	19
	MEDIAN	32	38	35
	MAX	60	58	60
HEIGHT (CM)	N	9	10	19
	MEAN	176.3	162.3	168.9
	SD	8.2	4.8	9.6
	MIN	165	151	151
	MEDIAN	180	163	166
	MAX	188	167	188
WEIGHT (KG)	N	9	10	19
	MEAN	85.7	67.2	76.0
	SD	14.8	9.3	15.2
	MIN	65.0	53.8	53.8
	MEDIAN	88.3	66.2	70.7
	MAX	110.2	84.0	110.2
BMI (KG/M^2)	N	9	10	19
	MEAN	27.5	25.6	26.5
	SD	3.7	3.9	3.8
	MIN	21.0	19.3	19.3
	MEDIAN	28.1	25.0	26.1
	MAX	31.8	30.6	31.8

All subjects in the study were Caucasian.

11.2.2 Medical History, Physical Examination and Vital Signs

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

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

Subject 6 had raised diastolic blood pressure at the Screening Visit. Subject 12 had raised diastolic blood pressure at the post study visit that required a repeat measurement, but both readings were considered not to be clinically significant.

Subjects 2 and 8 had oral body temperature recordings just below the normal range at the post study visit, both were considered not to be clinically significant.

There were no other clinically meaningful findings in recordings of pulse, blood pressure, oral temperature and 12-lead Electrocardiogram. Subject 10 did have an abnormal QRS recording at the post study visit but this was considered to be not clinically significant. A summary of vital signs pre and post study is provided in Section 14.3.3

11.2.3 Previous Medications and Contraceptive Use

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

Four of the 10 female subjects were taking contraceptive products. Subjects 17 and 19 were taking oral contraceptive pills (Cilest and Cerazette respectively) and subjects 9 and 14 had implanted subdermal products (Implanon). Subject 4 was taking Co-cyprindiol for the treatment of acne.

11.2.4 Concomitant Medications

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

Subjects 4 and 13 took Paracetamol, and Ibuprofen, respectively, for treatment of a headache. Paracetamol was also taken by subjects 3 and 9 for treatment of sinusitis and migraine respectively. Subject 4 used “After Bite” topically for treatment of an insect bite and subject 7 took “Paramol” (Paracetamol and Dihydrocodeine) for toothache. A course of antibiotic medication, Amoxycillin, was taken by subject 7 during the study.

A single dose of Maalox (10mLs), the rescue medication, was taken by a number of subjects (twelve) at Screening Visit 2 following ingestion of the standard refluxogenic meal at which heartburn was induced.

11.3 Measurements of Treatment Compliance

All subjects were administered the study treatments by a member of Simbec staff not associated with the study and were observed during dosing. The subjects were instructed that when being dosed with Treatments A and B, which consisted of 2 chewable tablets in each case, that they should chew and swallow the first tablet before being administered the second. Once the second chewable tablet had been swallowed the subjects immediately signalled (by raising their arm) to the person administering the dose. Treatment C (Losec® MUPS® tablet) was administered with 50mLs of unchilled water. Mouth inspections were performed at each dosing visit to ensure compliance.

11.4 Efficacy Results

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

11.4.1 Analysis of Efficacy

11.4.1.1 Primary Endpoint

From Table 11.4.1 below, it can be seen that the Primary Endpoint of the study which is the mean heartburn relief values at AUC 0-60 are higher for the placebo (177.8) compared to Gaviscon® chewable tablets (174.9) and Losec® tablets (124.2).

11.4.1.2 Secondary Endpoints

Area under the heartburn relief curve across all time-points

Losec®, in particular, shows very poor heartburn relief throughout the 240 minute study period when compared to both the Gaviscon® and the placebo tablets. For instance, the AUC-0-240 values are 1122.3, 1164.4 and 994.6 for Gaviscon®, Placebo and Losec® respectively.

Table 11.4.1 Heartburn Relief values in study GA0921

Parameter	Treatment	N	Mean	Std Dev	Min	Median	Max
$AUCPR_{0-15}$	Gaviscon Tablets	18	19.9	18.3	0	15	65
	Placebo Tablets	18	16.2	13.5	0	17	33
	Losec Tablets	18	3.7	5.5	0	0	15
p=0.2849*, p<0.0001**							
$AUCPR_{0-30}$	Gaviscon Tablets	18	60.9	42.6	0	61	155
	Placebo Tablets	18	54.1	32.8	3	60	103
	Losec Tablets	18	27.2	29.8	0	15	95
p=0.4192*, p=0.0003**							
$AUCPR_{0-60}$	Gaviscon Tablets	18	174.9	93.8	8	169	335
	Placebo Tablets	18	177.8	67.3	50	172	270
	Losec Tablets	18	124.2	89.1	0	126	275
p=0.8883*, p=0.0163**							
$AUCPR_{0-120}$	Gaviscon Tablets	18	455.6	166.6	158	434	695
	Placebo Tablets	18	491.1	124.0	193	520	630
	Losec Tablets	18	382.1	204.8	0	428	635
p=0.4384*, p=0.1118**							
$AUCPR_{0-180}$	Gaviscon Tablets	18	787.3	195.2	470	772	1055
	Placebo Tablets	18	821.1	178.3	373	880	990
	Losec Tablets	18	676.2	299.8	75	775	995
p=0.5995*, p=0.0895**							
$AUCPR_{0-240}$	Gaviscon Tablets	18	1122.3	206.4	770	1132	1415
	Placebo Tablets	18	1164.4	216.2	553	1240	1350
	Losec Tablets	18	994.6	365.8	158	1135	1355
p=0.5859*, p=0.0942**							

* Comparison of Gaviscon vs Placebo; ** Comparison of Gaviscon vs Losec

Indeed this trend for the placebo to outperform the Gaviscon® product, in terms of the perceived relief continues in the mean AUC values for the 0- 120 minutes, 0-180 minutes and 0-240 minutes. However, this trend is not the case when additional calculations (within the 0-30 minute period) were made i.e., 0-15 minutes and 0-30 minutes. For both of these time periods the Gaviscon® product shows the greatest relief from the heartburn pain. For AUC 0-15 minute period the Gaviscon relief is 19.9 compared to 16.2 for the placebo and 3.7 for the Losec®. This is also true for the AUC 0-30 minute period where the Gaviscon® relief was 60.9, the Placebo and Losec® being 54.1 and 27.2 respectively.

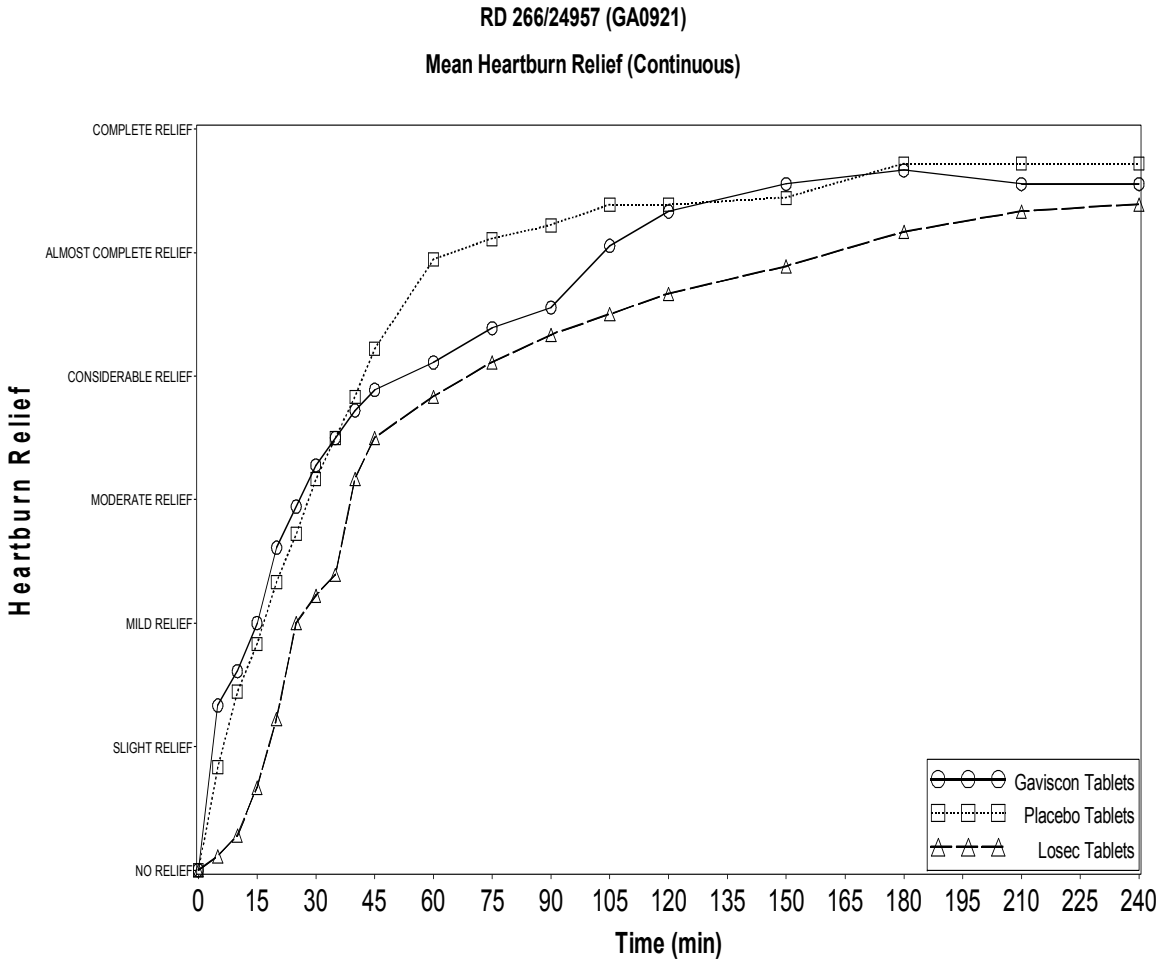
Comparing Gaviscon® and placebo, there were no statistically significant differences in AUC heartburn relief across all time points (p>0.2). However, post-treatment,

Gaviscon® was observed to give greater relief up to 30 minutes, whilst placebo was observed to give greater relief at 60 minutes and at all later time points.

Compared to Losec®, there was significant evidence that Gaviscon® gave higher AUC heartburn relief after 15 (p<0.0001), 30 (p=0.0003) and 60 (p=0.0163) minutes with higher mean AUC heartburn relief that approached statistical significance at 120 (p=0.1118), 180 (p=0.0895) and 240 (p=0.0942) minutes.

The trend for the heartburn relief can be seen in the figure 11.4.1 below.

Figure 11.4.1 Heartburn Relief (Continuous) for study GA0921



Time to first perceptible and meaningful relief

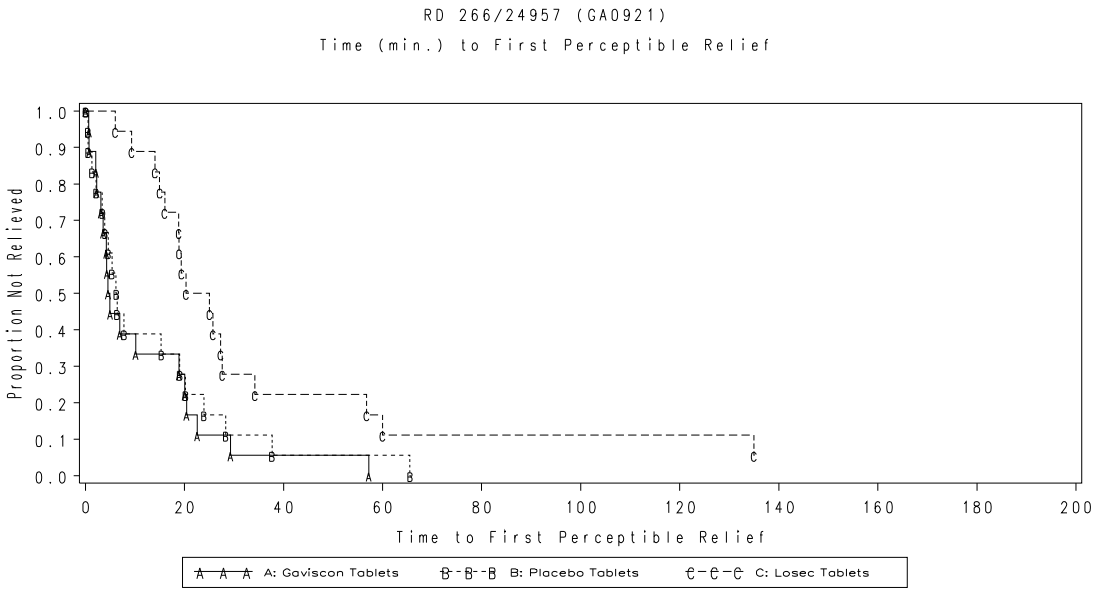
The times to first perceived relief and meaningful relief with each treatment are summarised below in Table 11.4.1.1 and Figure 11.4.1.1.

Table 11.4.1.1 Summary of Time to Heartburn Relief in study GA0921

Treatment	N	No. Censored	Mean	SD	Minimium	Maximum	KM Median	KM 95% CI	KM p-value	PH p-value
Time (min.) to First Perceptible Relief										
Gaviscon Tablets	18	0	11.99	14.33	0.67	57.20	4.74	3.60 – 18.85		
Placebo Tablets	18	0	14.00	16.78	0.50	65.53	6.29	3.93 – 19.05	0.6156 *	0.1875 *
Losec Tablets	18	1	42.74	57.41	6.03	240.00	22.67	18.80 – 27.60	0.0044 **	0.0003 **
Time (min.) to Meaningful Relief										
Gaviscon Tablets	18	0	30.72	21.96	3.62	86.22	30.90	16.90 – 38.50		
Placebo Tablets	18	0	31.38	23.44	8.25	104.80	29.20	14.75 – 35.20	0.9901 *	0.8844 *
Losec Tablets	18	1	62.50	65.09	14.02	240.00	34.47	27.03 – 53.62	0.1008 **	0.0085 **
Time (min.) to First Perceptible Relief (Additional Analysis)										
Gaviscon Tablets	18	0	10.34	13.78	0.67	57.20	4.74	3.60 – 6.90		
Placebo Tablets	18	0	9.66	8.90	0.50	28.32	5.78	3.93 – 15.32	0.8214 *	0.2724 *
Losec Tablets	18	0	30.92	33.39	5.00	134.98	19.12	14.02 – 27.32	0.0040 **	<0.0001 **

* Comparison of Gaviscon vs Placebo; ** Comparison of Gaviscon vs Losec®

Figure 11.4.1.1 Time to First Perceptible Relief (minutes) in study GA0921



The Kaplan-Meier (KM) median times (Table 11.4.1.1) to first perceptible heartburn relief experienced by the subjects for all three products, Gaviscon® (4.74; 95% CI 3.60-18.85), placebo (6.29; 95% CI 3.93-19.05) and Losec® (22.67; 95% CI 18.80-27-60) show that the initial effect of the Gaviscon® was superior following dosing. However, the placebo did have a definite perceptible relief slightly inferior to that of Gaviscon® (means of 11.99 for Gaviscon® and 14.00 for the placebo). The overall difference between the Gaviscon® and placebo treatments for the time to first perceived relief was not found to be statistically significant, statistical significance PH p-value 0.1875 (Figure 11.4.1.1). However, the data did show statistical significance for first perceptible relief when the Gaviscon® data was compared to Losec® (mean time 42.74 minutes), the PH p-value being 0.0003.

The time to first perceptible heartburn relief was observed to be shorter for Gaviscon compared to Placebo (KM median times: Gaviscon® = 4.74 minutes; Placebo = 6.29 minutes) although this difference was not statistically significant (Log rank test: p=0.6156, PH p=0.1875). Gaviscon® demonstrated a significant decrease in the time to first perceptible relief compared to Losec (Log rank test: p=0.0044, PH p=0.0003) which had a KM median time of 22.67 minutes.

From Table 11.4.1.1 and Figure 11.4.1.2 it can be seen that the KM median times to meaningful heartburn relief experienced by the subjects for the three products, Gaviscon® (30.90; 95% CI 16.90-38.50), placebo (29.20; 95% CI 14.75-35.20) and Losec® (34.47; 95% CI 27.03-53.62) again demonstrate that there was very little difference between the Gaviscon® and placebo medications (the mean times being 30.72 and 31.38 minutes respectively) and there was no statistically significance

between the results for these two products. As for first perceptible relief the analysis comparing the Gaviscon® and the Losec® medications for meaningful relief showed statistical significance (PH p-value of 0.0085 for the Losec®), the mean time for the Losec® being 62.50 minutes.

Due to some inconsistencies in the response from some subjects (where there was a time for meaningful relief but not for first perceptible relief due to the stopwatch not being stopped by the subject, in error), an additional analysis (Table 11.4.1.1 and Figure 11.4.1.3) using the times from the Heartburn Relief scale was performed to take this into account such that the time to first perceptible relief was censored to be the time point at which least slight relief was recorded on the heartburn relief scale.

These subjects were subject 1 (Treatment Visits 1 and 2), subject 4 (Treatment Visits 2), subject 5 (Treatment Visits 1 and 3), subject 9 (Treatment Visit 1), subject 11 (Treatment Visit 3), subject 15 (Treatment Visit 2 and 3) and subject 20 (Treatment Visit 3).

This demonstrated that the Kaplan-Meier times for the three products, Gaviscon® (4.74; 95% CI 3.60-6.90), placebo (5.78; 95% CI 3.93-15.32) and Losec® (19.12; 95% CI 14.02-27.32) remained similar although the placebo time to first perceptible relief (14.02 – 27.32) was now shorter in comparison to the Gaviscon® (10.34 and 9.66 minutes respectively). This was considered not to be of statistical significance unlike the comparison between Gaviscon® and Losec® which was statistically significant (PH p-value <0.0001). However, this additional analysis had little effect on the results apart from slightly reducing the KM median times to first perceptible relief for both placebo (6.29 to 5.78 minutes) and Losec (22.67 to 19.12 minutes), whilst for Gaviscon® this remained unchanged (4.74 minutes) and still lower than the other two treatments. The same statistical inferences were made as for the original analysis with no evidence of a difference between Gaviscon® and placebo (Log rank test: p=0.8214, PH p=0.2724) and Gaviscon® statistically superior to Losec® (Log rank test: p=0.0040, PH p<0.0001).

The time to meaningful heartburn relief was very similar for Gaviscon® and Placebo (KM median times: Gaviscon® = 30.90 minutes; Placebo = 29.20 minutes) with no significant difference. Compared to Losec®, which had a KM median time to meaningful relief of 34.47 minutes, the time taken for Gaviscon® was significantly lower when evaluating the PH model results (p=0.0085) and this difference approached significance when using the results of the Log-Rank test (p=0.1008).

Figure 11.4.1.2 Time to Meaningful Relief (minutes) in study GA0921

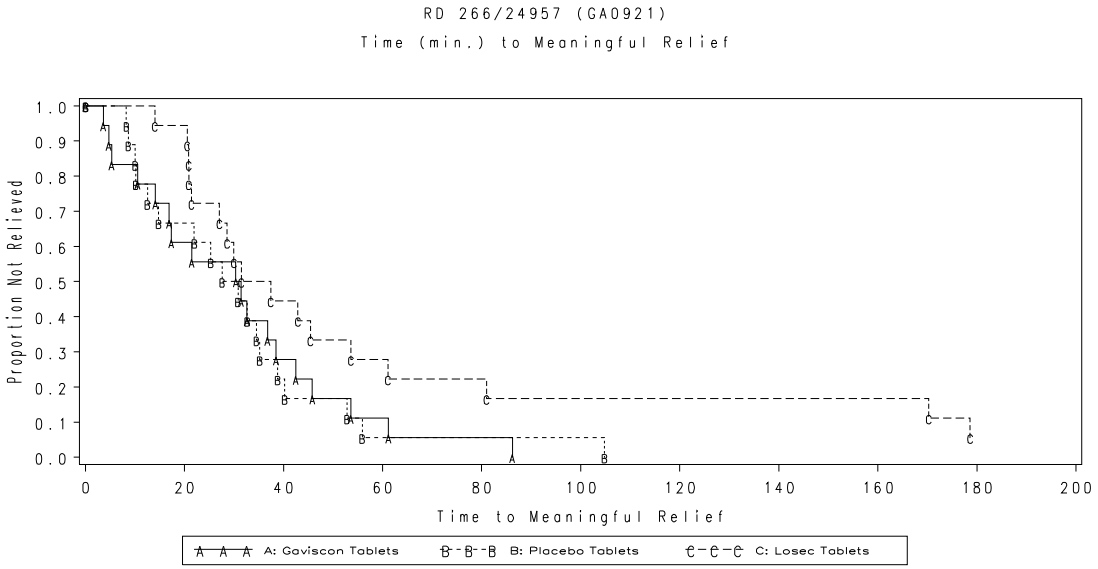
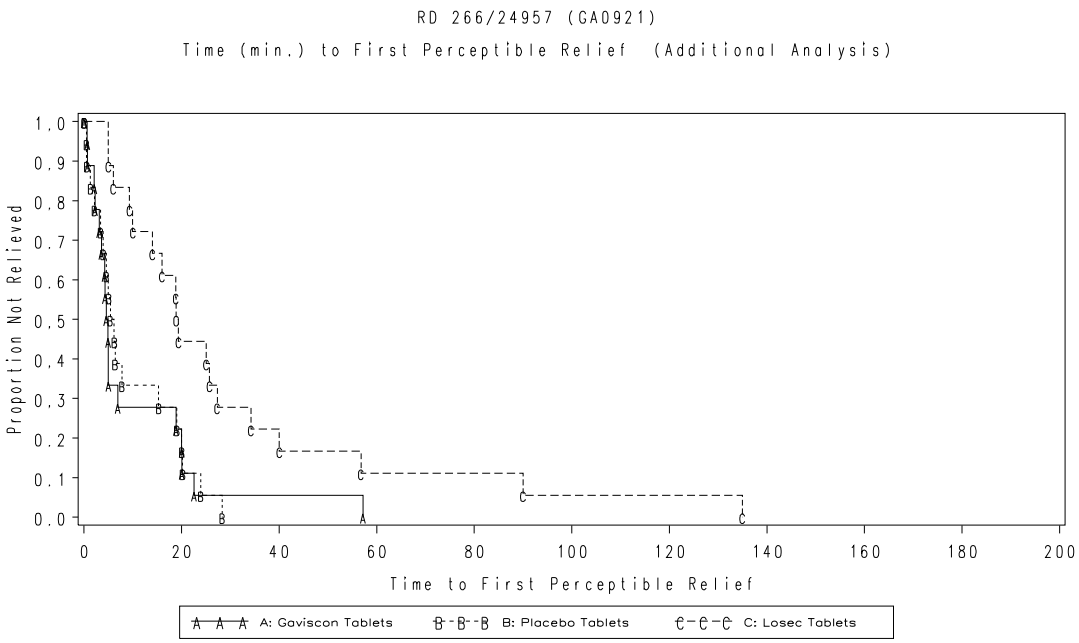


Figure 11.4.1.3 Additional Analysis of Time to First Perceptible Relief (minutes) in study GA0921



The summary of heartburn relief using the Heartburn Relief Scale (where 'no relief' = 0, 'slight relief' = 1, 'mild relief' = 2, 'moderate relief' = 3, 'considerable relief' = 4, 'almost complete relief' = 5, 'complete relief' = 6) for Gaviscon®, placebo and Losec®

are shown below in Tables 11.4.1.2, 11.4.1.3, 11.4.1.4 and the AUC data in Tables, 11.4.1.5, 11.4.1.6, 11.4.1.7, 11.4.1.8 and 11.4.1.9 below.

Table 11.4.1.2 Summary of Heartburn Relief (Continuous) for Gaviscon Tablets in study GA0921

		N	Mean	Std Dev	Min	Median	Max	L 95% CI	U 95% CI
Treatment	Time								
Gaviscon Tablets	5 MIN POST DOSE	18	1.3	1.4	0	1	4	0.6	2.0
	10 MIN POST DOSE	18	1.6	1.6	0	1	6	0.8	2.4
	15 MIN POST DOSE	18	2.0	1.6	0	2	6	1.2	2.8
	20 MIN POST DOSE	18	2.6	1.8	0	3	6	1.7	3.5
	25 MIN POST DOSE	18	2.9	1.8	0	3	6	2.0	3.9
	30 MIN POST DOSE	18	3.3	1.9	0	3	6	2.3	4.2
	35 MIN POST DOSE	18	3.5	2.0	0	3	6	2.5	4.5
	40 MIN POST DOSE	18	3.7	2.0	0	4	6	2.7	4.7
	45 MIN POST DOSE	18	3.9	1.9	0	4	6	2.9	4.9
	60 MIN POST DOSE	18	4.1	1.7	1	4	6	3.3	4.9
	75 MIN POST DOSE	18	4.4	1.6	1	5	6	3.6	5.2
	90 MIN POST DOSE	18	4.6	1.5	2	5	6	3.8	5.3
	105 MIN POST DOSE	18	5.1	1.1	3	6	6	4.5	5.6
	120 MIN POST DOSE	18	5.3	0.9	4	6	6	4.9	5.8
	150 MIN POST DOSE	18	5.6	0.8	4	6	6	5.2	5.9
	180 MIN POST DOSE	18	5.7	0.7	4	6	6	5.3	6.0
	210 MIN POST DOSE	18	5.6	1.0	2	6	6	5.1	6.0
	240 MIN POST DOSE	18	5.6	1.0	2	6	6	5.1	6.0

Table 11.4.1.3 Summary of Heartburn Relief (Continuous) for placebo tablets in study GA0921

		N	Mean	Std Dev	Min	Median	Max	L 95% CI	U 95% CI	p-value *
Treatment	Time									
Placebo Tablets	5 MIN POST DOSE	18	0.8	0.8	0	1	2	0.4	1.2	0.0522
	10 MIN POST DOSE	18	1.4	1.3	0	1	3	0.8	2.1	0.6129
	15 MIN POST DOSE	18	1.8	1.4	0	2	4	1.1	2.5	0.6447
	20 MIN POST DOSE	18	2.3	1.4	0	3	5	1.6	3.0	0.5124
	25 MIN POST DOSE	18	2.7	1.6	0	3	5	1.9	3.5	0.6135
	30 MIN POST DOSE	18	3.2	1.5	1	3	6	2.4	3.9	0.7961
	35 MIN POST DOSE	18	3.5	1.6	1	4	6	2.7	4.3	1.0000
	40 MIN POST DOSE	18	3.8	1.5	1	4	6	3.1	4.6	0.8271
	45 MIN POST DOSE	18	4.2	1.5	1	5	6	3.5	5.0	0.4966
	60 MIN POST DOSE	18	4.9	1.3	2	5	6	4.3	5.6	0.1117
	75 MIN POST DOSE	18	5.1	1.3	2	6	6	4.5	5.7	0.1673
	90 MIN POST DOSE	18	5.2	1.3	2	6	6	4.6	5.9	0.1752
	105 MIN POST DOSE	18	5.4	1.2	3	6	6	4.8	6.0	0.4727
	120 MIN POST DOSE	18	5.4	1.2	3	6	6	4.8	6.0	0.8983
	150 MIN POST DOSE	18	5.4	1.1	3	6	6	4.9	6.0	0.7736
	180 MIN POST DOSE	18	5.7	0.8	3	6	6	5.3	6.1	0.8475
	210 MIN POST DOSE	18	5.7	0.8	3	6	6	5.3	6.1	0.6130
	240 MIN POST DOSE	18	5.7	0.8	3	6	6	5.3	6.1	0.6076

* Comparison of Gaviscon vs Placebo

Table 11.4.1.4 Summary of Heartburn Relief (Continuous) for Losec® tablets in study GA0921

Treatment	Time	N	Mean	Std Dev	Min	Median	Max	L 95% CI	U 95% CI	p-value **
Losec® Tablets	5 MIN POST DOSE	18	0.1	0.3	0	0	1	-0.0	0.3	<0.0001
	10 MIN POST DOSE	18	0.3	0.5	0	0	1	0.0	0.5	0.0003
	15 MIN POST DOSE	18	0.7	1.1	0	0	4	0.1	1.2	0.0009
	20 MIN POST DOSE	18	1.2	1.6	0	1	5	0.4	2.0	0.0022
	25 MIN POST DOSE	18	2.0	2.1	0	1	6	1.0	3.0	0.0297
	30 MIN POST DOSE	18	2.2	2.1	0	2	6	1.2	3.3	0.0134
	35 MIN POST DOSE	18	2.4	2.1	0	2	6	1.3	3.4	0.0220
	40 MIN POST DOSE	18	3.2	2.2	0	3	6	2.1	4.2	0.2742
	45 MIN POST DOSE	18	3.5	2.2	0	4	6	2.4	4.6	0.3994
	60 MIN POST DOSE	18	3.8	2.2	0	4	6	2.8	4.9	0.6103
	75 MIN POST DOSE	18	4.1	2.2	0	5	6	3.0	5.2	0.5888
	90 MIN POST DOSE	18	4.3	2.1	0	5	6	3.3	5.4	0.6486
	105 MIN POST DOSE	18	4.5	2.0	0	6	6	3.5	5.5	0.2585
	120 MIN POST DOSE	18	4.7	1.9	0	6	6	3.7	5.6	0.1383
	150 MIN POST DOSE	18	4.9	1.8	1	6	6	4.0	5.8	0.0938
	180 MIN POST DOSE	18	5.2	1.5	1	6	6	4.4	5.9	0.0727
	210 MIN POST DOSE	18	5.3	1.4	1	6	6	4.7	6.0	0.3695
	240 MIN POST DOSE	18	5.4	1.2	1	6	6	4.8	6.0	0.4603

** Comparison of Gaviscon vs Losec

The comparison of Gaviscon® with placebo in terms of the heartburn relief recorded via the answers given by the subjects does not demonstrate any statistically significant difference in terms of heartburn relief between the Gaviscon® and placebo at any of the time-points. However, statistical significance is shown between the Gaviscon® when compared to the Losec® tablet. From Table 11.4.1.4 a statistical significance is demonstrated in favour of the Gaviscon® over placebo up to and including the 35 minute timepoint on the questionnaires. After the 35 minute timepoint statistical significance is not demonstrated.

There were no statistically significant differences in the level of heartburn relief between Gaviscon® (Table 11.4.1.2) and Placebo across all time points. It was observed that when comparing the mean heartburn relief scores (Table 11.4.1.3), Gaviscon® was 0.5 higher than Placebo after 5 minutes post dose. This difference reduced until the means were the same after 35 minutes and Placebo was 0.8 higher than Gaviscon® after 60 minutes. This difference in means then reduced and became very close from 120 minutes onwards.

Compared to Losec® (Table 11.4.1.4), up to and including 35 minutes post dose, Gaviscon® (Table 11.4.1.2) provided statistically superior heartburn relief (Tables 11.4.1.5, 11.4.1.6, 11.4.1.7, 11.4.1.8 and 11.4.1.9), whereas at all subsequent time points, although higher mean heartburn relief scores were recorded (decreasing difference with time), these differences were not significant

Table 11.4.1.5 Summary of Heartburn Relief (Frequency from 5min-20min) for Gaviscon Tablets, placebo tablets and Losec® tablet in study GA0921

		Number of Subjects (%)		
		Gaviscon Tablets (n=18)	Placebo Tablets (n=18)	Losec® Tablets (n=18)
Time	Heartburn Relief			
5 MIN POST DOSE	NO RELIEF	6 (33.3)	7 (38.9)	16 (88.9)
	SLIGHT RELIEF	6 (33.3)	7 (38.9)	2 (11.1)
	MILD RELIEF	3 (16.7)	4 (22.2)	0
	CONSIDERABLE RELIEF	3 (16.7)	0	0
10 MIN POST DOSE	NO RELIEF	5 (27.8)	6 (33.3)	13 (72.2)
	SLIGHT RELIEF	5 (27.8)	4 (22.2)	5 (27.8)
	MILD RELIEF	4 (22.2)	2 (11.1)	0
	MODERATE RELIEF	2 (11.1)	6 (33.3)	0
	CONSIDERABLE RELIEF	1 (5.6)	0	0
	COMPLETE RELIEF	1 (5.6)	0	0
15 MIN POST DOSE	NO RELIEF	4 (22.2)	5 (27.8)	11 (61.1)
	SLIGHT RELIEF	3 (16.7)	2 (11.1)	4 (22.2)
	MILD RELIEF	4 (22.2)	3 (16.7)	2 (11.1)
	MODERATE RELIEF	5 (27.8)	7 (38.9)	0
	CONSIDERABLE RELIEF	1 (5.6)	1 (5.6)	1 (5.6)
	COMPLETE RELIEF	1 (5.6)	0	0
20 MIN POST DOSE	NO RELIEF	2 (11.1)	2 (11.1)	8 (44.4)
	SLIGHT RELIEF	4 (22.2)	4 (22.2)	5 (27.8)
	MILD RELIEF	3 (16.7)	2 (11.1)	1 (5.6)
	MODERATE RELIEF	3 (16.7)	7 (38.9)	2 (11.1)
	CONSIDERABLE RELIEF	3 (16.7)	2 (11.1)	1 (5.6)
	ALMOST COMPLETE RELIEF	2 (11.1)	1 (5.6)	1 (5.6)
	COMPLETE RELIEF	1 (5.6)	0	0

Table 11.4.1.6 Summary of Heartburn Relief (Frequency from 25min-40min) for Gaviscon Tablets, placebo tablets and Losec® tablet in study GA0921

		Number of Subjects (%)		
		Gaviscon Tablets (n=18)	Placebo Tablets (n=18)	Losec® Tablets (n=18)
Time	Heartburn Relief			
25 MIN POST DOSE	NO RELIEF	1 (5.6)	1 (5.6)	6 (33.3)
	SLIGHT RELIEF	4 (22.2)	4 (22.2)	4 (22.2)
	MILD RELIEF	3 (16.7)	3 (16.7)	1 (5.6)
	MODERATE RELIEF	3 (16.7)	4 (22.2)	3 (16.7)
	CONSIDERABLE RELIEF	3 (16.7)	3 (16.7)	0
	ALMOST COMPLETE RELIEF	2 (11.1)	3 (16.7)	3 (16.7)
	COMPLETE RELIEF	2 (11.1)	0	1 (5.6)
30 MIN POST DOSE	NO RELIEF	1 (5.6)	0	4 (22.2)
	SLIGHT RELIEF	2 (11.1)	3 (16.7)	5 (27.8)
	MILD RELIEF	4 (22.2)	3 (16.7)	2 (11.1)
	MODERATE RELIEF	4 (22.2)	5 (27.8)	3 (16.7)
	CONSIDERABLE RELIEF	1 (5.6)	3 (16.7)	0
	ALMOST COMPLETE RELIEF	3 (16.7)	3 (16.7)	2 (11.1)
	COMPLETE RELIEF	3 (16.7)	1 (5.6)	2 (11.1)
35 MIN POST DOSE	NO RELIEF	1 (5.6)	0	4 (22.2)
	SLIGHT RELIEF	2 (11.1)	3 (16.7)	4 (22.2)
	MILD RELIEF	3 (16.7)	1 (5.6)	2 (11.1)
	MODERATE RELIEF	4 (22.2)	5 (27.8)	3 (16.7)
	CONSIDERABLE RELIEF	2 (11.1)	4 (22.2)	1 (5.6)
	ALMOST COMPLETE RELIEF	1 (5.6)	3 (16.7)	2 (11.1)
	COMPLETE RELIEF	5 (27.8)	2 (11.1)	2 (11.1)
40 MIN POST DOSE	NO RELIEF	1 (5.6)	0	3 (16.7)
	SLIGHT RELIEF	2 (11.1)	1 (5.6)	2 (11.1)
	MILD RELIEF	2 (11.1)	2 (11.1)	1 (5.6)
	MODERATE RELIEF	4 (22.2)	5 (27.8)	5 (27.8)
	CONSIDERABLE RELIEF	2 (11.1)	4 (22.2)	1 (5.6)
	ALMOST COMPLETE RELIEF	1 (5.6)	3 (16.7)	2 (11.1)
	COMPLETE RELIEF	6 (33.3)	3 (16.7)	4 (22.2)

Table 11.4.1.7 Summary of Heartburn Relief (Frequency from 45min-90min) for Gaviscon Tablets, placebo tablets and Losec® tablet in study GA0921

		Number of Subjects (%)		
		Gaviscon Tablets (n=18)	Placebo Tablets (n=18)	Losec® Tablets (n=18)
Time	Heartburn Relief			
45 MIN POST DOSE	NO RELIEF	1 (5.6)	0	3 (16.7)
	SLIGHT RELIEF	1 (5.6)	1 (5.6)	1 (5.6)
	MILD RELIEF	2 (11.1)	1 (5.6)	1 (5.6)
	MODERATE RELIEF	5 (27.8)	4 (22.2)	3 (16.7)
	CONSIDERABLE RELIEF	1 (5.6)	3 (16.7)	4 (22.2)
	ALMOST COMPLETE RELIEF	2 (11.1)	5 (27.8)	1 (5.6)
	COMPLETE RELIEF	6 (33.3)	4 (22.2)	5 (27.8)
60 MIN POST DOSE	NO RELIEF	0	0	2 (11.1)
	SLIGHT RELIEF	1 (5.6)	0	2 (11.1)
	MILD RELIEF	2 (11.1)	2 (11.1)	1 (5.6)
	MODERATE RELIEF	5 (27.8)	1 (5.6)	1 (5.6)
	CONSIDERABLE RELIEF	2 (11.1)	1 (5.6)	4 (22.2)
	ALMOST COMPLETE RELIEF	2 (11.1)	6 (33.3)	2 (11.1)
	COMPLETE RELIEF	6 (33.3)	8 (44.4)	6 (33.3)
75 MIN POST DOSE	NO RELIEF	0	0	2 (11.1)
	SLIGHT RELIEF	1 (5.6)	0	1 (5.6)
	MILD RELIEF	2 (11.1)	1 (5.6)	1 (5.6)
	MODERATE RELIEF	2 (11.1)	2 (11.1)	2 (11.1)
	CONSIDERABLE RELIEF	4 (22.2)	1 (5.6)	3 (16.7)
	ALMOST COMPLETE RELIEF	2 (11.1)	4 (22.2)	1 (5.6)
	COMPLETE RELIEF	7 (38.9)	10 (55.6)	8 (44.4)
90 MIN POST DOSE	NO RELIEF	0	0	1 (5.6)
	SLIGHT RELIEF	0	0	2 (11.1)
	MILD RELIEF	1 (5.6)	1 (5.6)	1 (5.6)
	MODERATE RELIEF	5 (27.8)	2 (11.1)	1 (5.6)
	CONSIDERABLE RELIEF	3 (16.7)	1 (5.6)	2 (11.1)
	ALMOST COMPLETE RELIEF	1 (5.6)	2 (11.1)	3 (16.7)
	COMPLETE RELIEF	8 (44.4)	12 (66.7)	8 (44.4)

Table 11.4.1.8 Summary of Heartburn Relief (Frequency from 105min-180min) for Gaviscon Tablets, placebo tablets and Losec® tablet in study GA0921

		Number of Subjects (%)		
		Gaviscon Tablets (n=18)	Placebo Tablets (n=18)	Losec® Tablets (n=18)
Time	Heartburn Relief			
105 MIN POST DOSE	NO RELIEF	0	0	1 (5.6)
	SLIGHT RELIEF	0	0	2 (11.1)
	MODERATE RELIEF	2 (11.1)	3 (16.7)	2 (11.1)
	CONSIDERABLE RELIEF	4 (22.2)	1 (5.6)	1 (5.6)
	ALMOST COMPLETE RELIEF	3 (16.7)	0	3 (16.7)
	COMPLETE RELIEF	9 (50.0)	14 (77.8)	9 (50.0)
120 MIN POST DOSE	NO RELIEF	0	0	1 (5.6)
	SLIGHT RELIEF	0	0	1 (5.6)
	MILD RELIEF	0	0	1 (5.6)
	MODERATE RELIEF	0	3 (16.7)	1 (5.6)
	CONSIDERABLE RELIEF	5 (27.8)	1 (5.6)	2 (11.1)
	ALMOST COMPLETE RELIEF	2 (11.1)	0	2 (11.1)
	COMPLETE RELIEF	11 (61.1)	14 (77.8)	10 (55.6)
150 MIN POST DOSE	SLIGHT RELIEF	0	0	2 (11.1)
	MILD RELIEF	0	0	1 (5.6)
	MODERATE RELIEF	0	2 (11.1)	1 (5.6)
	CONSIDERABLE RELIEF	3 (16.7)	2 (11.1)	0
	ALMOST COMPLETE RELIEF	2 (11.1)	0	3 (16.7)
	COMPLETE RELIEF	13 (72.2)	14 (77.8)	11 (61.1)
180 MIN POST DOSE	SLIGHT RELIEF	0	0	1 (5.6)
	MODERATE RELIEF	0	1 (5.6)	2 (11.1)
	CONSIDERABLE RELIEF	2 (11.1)	0	1 (5.6)
	ALMOST COMPLETE RELIEF	2 (11.1)	2 (11.1)	2 (11.1)
	COMPLETE RELIEF	14 (77.8)	15 (83.3)	12 (66.7)

Table 11.4.1.9 Summary of Heartburn Relief (Frequency from 210min-240min) for Gaviscon Tablets, placebo tablets and Losec® tablet in study GA0921

		Number of Subjects (%)		
		Gaviscon Tablets (n=18)	Placebo Tablets (n=18)	Losec® Tablets (n=18)
Time	Heartburn Relief			
210 MIN POST DOSE	SLIGHT RELIEF	0	0	1 (5.6)
	MILD RELIEF	1 (5.6)	0	0
	MODERATE RELIEF	0	1 (5.6)	1 (5.6)
	CONSIDERABLE RELIEF	0	0	1 (5.6)
	ALMOST COMPLETE RELIEF	4 (22.2)	2 (11.1)	2 (11.1)
	COMPLETE RELIEF	13 (72.2)	15 (83.3)	13 (72.2)
240 MIN POST DOSE	SLIGHT RELIEF	0	0	1 (5.6)
	MILD RELIEF	1 (5.6)	0	0
	MODERATE RELIEF	0	1 (5.6)	0
	CONSIDERABLE RELIEF	0	0	1 (5.6)
	ALMOST COMPLETE RELIEF	4 (22.2)	2 (11.1)	4 (22.2)
	COMPLETE RELIEF	13 (72.2)	15 (83.3)	12 (66.7)

From the summary of heartburn intensity (Tables 11.4.1.10, 11.4.1.11 and 11.4.1.12 below) scores using the 100mm VAS Scale (where 0 = 'no pain' and 100 = 'worst pain imaginable' at 5, 10, 15, 20, 25, 30, 35, 40, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 minute post dosing) for the three products it can be seen that there is no statistical significance between the Gaviscon® and placebo products but, similar to the heartburn relief data, the heartburn intensity data also shows a statistical significance between Gaviscon® and Losec® up to and including 35 minutes post dose, with non-significant higher mean heartburn intensity scores at later time points. This is also presented in graph form in Figure 11.4.1.4.

Table 11.4.1.10 Summary of Heartburn Intensity (VAS scale) for Gaviscon Tablets in study GA0921

		N	Mean	Std Dev	Min	Median	Max	L 95% CI	U 95% CI
Treatment	Time								
Gaviscon Tablets	PRE-DOSE	18	49.7	18.2	25	49	77	40.6	58.7
	5 MIN POST DOSE	18	41.1	19.3	16	35	77	31.5	50.7
	10 MIN POST DOSE	18	37.6	21.4	6	38	77	27.0	48.2
	15 MIN POST DOSE	18	33.4	23.5	3	34	76	21.7	45.1
	20 MIN POST DOSE	18	30.4	23.5	1	29	74	18.7	42.1
	25 MIN POST DOSE	18	27.7	23.6	1	28	70	15.9	39.4
	30 MIN POST DOSE	18	25.9	22.5	0	26	69	14.8	37.1
	35 MIN POST DOSE	18	24.0	21.5	0	24	67	13.3	34.7
	40 MIN POST DOSE	18	23.2	22.7	0	21	71	12.0	34.5
	45 MIN POST DOSE	18	20.8	21.3	0	18	65	10.2	31.4
	60 MIN POST DOSE	18	17.2	18.0	0	13	57	8.3	26.2
	75 MIN POST DOSE	18	14.5	16.2	0	11	54	6.4	22.6
	90 MIN POST DOSE	18	11.2	13.7	0	7	46	4.4	18.0
	105 MIN POST DOSE	18	7.7	12.0	0	2	46	1.7	13.6
	120 MIN POST DOSE	18	6.6	10.3	0	2	37	1.4	11.7
	150 MIN POST DOSE	18	4.9	9.6	0	0	36	0.2	9.7
	180 MIN POST DOSE	18	2.8	7.1	0	0	27	-0.7	6.3
	210 MIN POST DOSE	18	2.7	6.0	0	0	24	-0.3	5.7
	240 MIN POST DOSE	18	1.8	3.9	0	0	15	-0.1	3.7

Table 11.4.1.11 Summary of Heartburn Intensity (VAS scale) for placebo tablets in study GA0921

		N	Mean	Std Dev	Min	Median	Max	L 95% CI	U 95% CI	p-value*
Treatment	Time									
Placebo Tablets	PRE-DOSE	18	51.1	17.3	18	55	75	42.5	59.6	0.5700
	5 MIN POST DOSE	18	46.2	17.9	13	50	72	37.3	55.1	0.1477
	10 MIN POST DOSE	18	41.2	18.7	5	43	69	31.9	50.5	0.3553
	15 MIN POST DOSE	18	38.0	19.8	5	38	69	28.2	47.8	0.2226
	20 MIN POST DOSE	18	34.0	20.3	2	31	64	23.9	44.1	0.3249
	25 MIN POST DOSE	18	28.6	22.0	3	30	62	17.7	39.6	0.7993
	30 MIN POST DOSE	18	26.0	21.3	1	26	60	15.4	36.6	0.9887
	35 MIN POST DOSE	18	23.3	21.2	0	16	58	12.7	33.8	0.8577
	40 MIN POST DOSE	18	20.4	21.1	0	14	56	9.9	30.9	0.5490
	45 MIN POST DOSE	18	18.5	18.9	0	14	50	9.1	27.9	0.6258
	60 MIN POST DOSE	18	12.4	15.9	0	2	41	4.5	20.3	0.3769
	75 MIN POST DOSE	18	8.3	13.6	0	0	39	1.5	15.0	0.2238
	90 MIN POST DOSE	18	7.0	12.8	0	1	37	0.6	13.4	0.3701
	105 MIN POST DOSE	18	6.2	11.2	0	1	31	0.6	11.8	0.7422
	120 MIN POST DOSE	18	5.6	10.9	0	0	32	0.1	11.0	0.8026
	150 MIN POST DOSE	18	4.3	8.6	0	0	26	-0.0	8.6	0.8354
	180 MIN POST DOSE	18	2.7	6.1	0	0	21	-0.3	5.8	0.9654
	210 MIN POST DOSE	18	2.5	6.3	0	0	24	-0.6	5.6	0.9292
	240 MIN POST DOSE	18	2.2	5.5	0	0	22	-0.5	5.0	0.8588

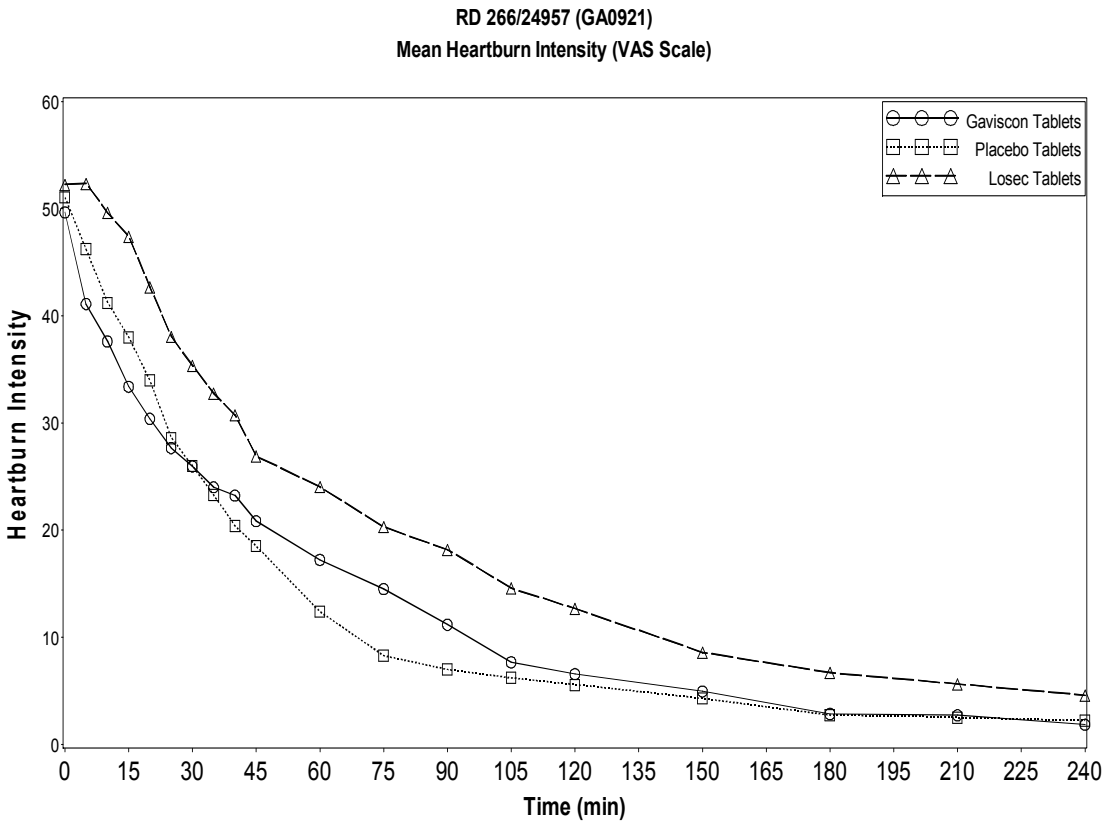
* Comparison of Gaviscon vs Placebo

Table 11.4.1.12 Summary of Heartburn Intensity (VAS scale) for Losec® tablets in study GA0921

		N	Mean	Std Dev	Min	Median	Max	L 95% CI	U 95% CI	p-value**
Treatment	Time									
Losec Tablets	PRE-DOSE	18	52.2	18.1	21	55	75	43.2	61.2	0.2656
	5 MIN POST DOSE	18	52.3	19.4	17	57	75	42.7	62.0	0.0023
	10 MIN POST DOSE	18	49.6	21.0	13	54	75	39.2	60.0	0.0034
	15 MIN POST DOSE	18	47.4	22.2	2	47	78	36.3	58.4	0.0006
	20 MIN POST DOSE	18	42.7	23.0	1	44	75	31.2	54.1	0.0014
	25 MIN POST DOSE	18	38.1	25.1	0	40	80	25.6	50.6	0.0056
	30 MIN POST DOSE	18	35.3	24.7	0	39	73	23.1	47.6	0.0167
	35 MIN POST DOSE	18	32.7	23.0	0	35	72	21.3	44.2	0.0292
	40 MIN POST DOSE	18	30.7	25.0	0	35	75	18.3	43.2	0.1102
	45 MIN POST DOSE	18	26.9	23.8	0	27	69	15.1	38.7	0.1749
	60 MIN POST DOSE	18	24.0	24.1	0	20	70	12.0	36.0	0.1774
	75 MIN POST DOSE	18	20.3	24.0	0	12	77	8.3	32.2	0.1969
	90 MIN POST DOSE	18	18.2	21.3	0	10	63	7.6	28.8	0.1043
	105 MIN POST DOSE	18	14.6	19.8	0	1	58	4.7	24.4	0.1179
	120 MIN POST DOSE	18	12.7	18.6	0	3	61	3.4	21.9	0.1094
	150 MIN POST DOSE	18	8.6	15.2	0	1	53	1.0	16.1	0.2283
	180 MIN POST DOSE	18	6.7	13.3	0	0	50	0.0	13.3	0.1048
	210 MIN POST DOSE	18	5.6	13.1	0	0	51	-0.9	12.1	0.1782
	240 MIN POST DOSE	18	4.6	11.4	0	0	47	-1.1	10.2	0.1433

** Comparison of Gaviscon vs Losec

Figure 11.4.1.4 Graph of Mean Heartburn Intensity (VAS) scale in study GA0921



With reference to the heartburn intensity experienced by the subjects the summary data of AUC heartburn intensity for the time periods 0-60, 0-120, 0-180 and 0-240 are presented below in Tables 11.4.1.13. The area under the respective curves for each treatment can be compared in Figure 11.4.1.4 above.

There were no statistically significant differences in the AUC heartburn intensity between Gaviscon® and Placebo across all time points.

In a similar fashion to the heartburn relief summary (Table 11.4.1.1 intensity summaries (Tables 11.4.1.10 – 11.4.1.12), there was a lower mean AUC heartburn intensity for the Gaviscon® product compared to the placebo up to 30 minutes post dose (Table 11.4.1.13). However, unlike with the mean intensity and relief values, the mean AUC value also remained slightly lower than Placebo at the 60 minute timepoint. After this time the mean AUC values for the placebo became lower (indicating a lower intensity of the heartburn discomfort) than those for the Gaviscon® product.

The extra comparisons of the mean AUC s for 0-15 minutes and 0-30 minutes again, like those for the relief intensity and relief values, showed an observed lower heartburn intensity for the Gaviscon® product compared to placebo.

Following the same trend as the intensity and relief scores the AUC heartburn intensity scores for Gaviscon® were markedly lower compared to Losec® across all timepoints (Table 11.4.1.13). This indicates a distinctly higher heartburn intensity in those subjects that were administered Losec® than those administered the Gaviscon® product throughout the study period of 240 minutes. These differences were all statistically significant apart from the comparison at 0-240 minutes, which was approaching significance (p=0.0518)

Table 11.4.1.13 Summary of AUC values for Heartburn Intensity in study GA0921

		N	Mean	Std Dev	Min	Median	Max
Parameter	Treatment						
$AUCVASHI_{0-15}$	Gaviscon Tablets	18	601.6	296.3	260	546	1153
	Placebo Tablets	18	660.2	266.9	173	687	1058
	Losec® Tablets	18	759.0	297.1	253	819	1118
p=0.2295*, p=0.0021**							
$AUCVASHI_{0-30}$	Gaviscon Tablets	18	1040.2	640.4	295	1004	2235
	Placebo Tablets	18	1133.2	561.9	215	1077	1988
	Losec® Tablets	18	1369.4	621.0	270	1253	2270
p=0.3281*, p=0.0010**							
$AUCVASHI_{0-60}$	Gaviscon Tablets	18	1678.6	1232.7	308	1559	4150
	Placebo Tablets	18	1694.4	1081.1	230	1578	3343
	Losec® Tablets	18	2223.9	1273.3	270	2285	4403
p=0.9410*, p=0.0113**							
$AUCVASHI_{0-120}$	Gaviscon Tablets	18	2357.0	1945.9	308	2145	6468
	Placebo Tablets	18	2151.5	1670.1	245	1608	5178
	Losec® Tablets	18	3293.8	2425.7	270	3079	8355
p=0.6548*, p=0.0368**							
$AUCVASHI_{0-180}$	Gaviscon Tablets	18	2646.2	2374.8	308	2228	8133
	Placebo Tablets	18	2404.0	2097.0	245	1608	6588
	Losec® Tablets	18	3840.5	3248.6	270	3139	11610
p=0.6997*, p=0.0494**							
$AUCVASHI_{0-240}$	Gaviscon Tablets	18	2797.8	2599.5	308	2228	9483
	Placebo Tablets	18	2553.2	2386.1	245	1616	7953
	Losec® Tablets	18	4177.2	3901.8	270	3139	14595
p=0.7416*, p=0.0518**							

* Gaviscon - Placebo

** Gaviscon - Losec

The responses of the subjects overall assessment of the study medication administered at the end of each study period is captured in Table 11.4.1.14 below.

At 240 minutes post dose the subjects were required to give their overall assessment of the study medication administered on that day, the answers being one of the

following: poor, fair, good, very good or excellent. From the table it can be seen that the proportion of subjects that reported the Gaviscon® treatment to be “very good” was higher than that for the placebo and Losec® (44.4% compared to 27.8% and 22.2% respectively) although these values were not considered to be statistically significant. This is summarised in Table 11.4.1.14 below.

There were no statistically significant differences in response when comparing Gaviscon® with either Placebo (p=0.4043) or Losec® (p=0.5177), (Table 11.4.1.14). The only observed difference between the treatments was that Losec® had a lower percentage of patients rating the medication at least ‘Very Good’ (22.2%) compared to Gaviscon® (44.4%) and Placebo (27.8%) which were comparable.

Table 11.4.1.14 Summary of Subjects Overall Assessment of Study Medication in study GA0921

	Number of Subjects (%)		
	Gaviscon Tablets (n=18)	Placebo Tablets (n=18)	Losec® Tablets (n=18)
Overall Assessment of Study Medication			
MISSING	0	1 (5.6)	0
POOR	2 (11.1)	2 (11.1)	2 (11.1)
FAIR	4 (22.2)	4 (22.2)	5 (27.8)
GOOD	3 (16.7)	3 (16.7)	5 (27.8)
VERY GOOD	8 (44.4)	5 (27.8)	4 (22.2)
EXCELLENT	1 (5.6)	3 (16.7)	2 (11.1)
p=0.4043 *			
p=0.5177 **			

* Comparison of Gaviscon vs Placebo

** Comparison of Gaviscon vs Losec

There was no statistically significant difference between Gaviscon® and placebo or between Gaviscon® and Losec® in terms of the proportion of subjects who achieved complete relief (77.8% for Gaviscon®, 83.3% for placebo and 72.2% for Losec®), Table 11.4.1.15.

Table 11.4.1.15 Summary of Proportion of Subjects who Achieved Complete Relief in study GA0921

	Number of Subjects (%)		
	Gaviscon Tablets (n=18)	Placebo Tablets (n=18)	Losec® Tablets (n=18)
Complete Relief			
Yes	14 (77.8)	15 (83.3)	13 (72.2)
No	4 (22.2)	3 (16.7)	5 (27.8)
p=0.5217 *			
p=0.6201 **			

* Comparison of Gaviscon vs Placebo

** Comparison of Gaviscon vs Losec

Once the study subjects had stopped the second stopwatch (therefore a meaningful heartburn relief had been achieved) they were then required to give their response to the Subjective Relief Questionnaire 1. This consisted of three questions to which the answer was yes or no with regard to the product that had been administered i.e. did you feel a soothing relief, did you feel a cooling relief and did you feel an instant soothing effect when you took the product?

The answers to this questionnaire are summarised in Table 11.4.1.16 below.

Table 11.4.1.16 Summary of Subjective Relief Questionnaire 1 in study GA0921

		Number of Subjects (%)		
		Gaviscon Tablets (n=18)	Placebo Tablets (n=18)	Losec® Tablets (n=19)
Parameter	Response			
Soothing Relief	YES	14 (77.8)	12 (66.7)	7 (38.9)
	NO	4 (22.2)	6 (33.3)	9 (50.0)
	MISSING	0	0	2 (11.1)
p=0.3128 *				
p=0.0373 **				
Cooling Relief	YES	12 (66.7)	13 (72.2)	1 (5.6)
	NO	6 (33.3)	5 (27.8)	15 (83.3)
	MISSING	0	0	2 (11.1)
p=0.6514 *				
P<0.0001 **				
Instant Soothing Effect	YES	5 (27.8)	3 (16.7)	0
	NO	13 (72.2)	15 (83.3)	16 (88.9)
	MISSING	0	0	2 (11.1)
p=0.4136 *				
P<0.0001 **				

These results above do indeed give an indication that Gaviscon® (77.8% for soothing and 66.7% for cooling) gave a soothing and a cooling effect when compared to Losec® (38.9% for soothing and 5.6% for cooling). However, these percentages are much closer but remain in favour of the Gaviscon® when compared to the placebo for the soothing effect (77.8% v 66.7%) but in favour of the placebo over Gaviscon® (66.7% v 72.2%) for cooling. At the end of the treatment period (240 minutes after being administered the assigned study medication) the subjects were asked two questions (Subjective Relief Questionnaire II) i.e. would you be willing to use the product again? and also would you be prepared to replace your current therapy with this product?

The responses to these questions is summarised in Table 11.4.1.17 below.

Table 11.4.1.17 Summary of Future Product Use (Subjective Relief Questionnaire II) in study GA0921

		Number of Subjects (%)		
		Gaviscon Tablets (n=18)	Placebo Tablets (n=18)	Losec® Tablets (n=18)
Parameter	Response			
Willing to Use Product Again	YES	15 (83.3)	14 (77.8)	10 (55.6)
	NO	3 (16.7)	4 (22.2)	8 (44.4)
p=0.3930 *				
p=0.0518 **				
Prepared to Replace Current Therapy with this Product	YES	12 (66.7)	9 (50.0)	6 (33.3)
	NO	6 (33.3)	9 (50.0)	12 (66.7)
p=0.1554 *				
p=0.0376 **				

The results give a favourable result in terms of the Gaviscon® product in relation to Losec® with 83.3% of subjects willing to use the Gaviscon® again against 55.6% for Losec®. However, this was not of statistical significance.

This is again reflected in the numbers of subjects who would be willing to replace their current heartburn therapy with Gaviscon® rather than Losec® (66.7% to 33.3%).

11.4.2 Analytical Issues

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

11.4.2.1 Adjustments for Covariates

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

11.4.2.2 Handling of Dropouts or Missing Data

Subject 7 had missing data for Treatment Visit 3 as a result of testing positive for drugs of abuse prior to Treatment Visit 3. Subject 12 did not have any treatment visit data due to not experiencing any heartburn symptoms following the standard refluxogenic meal at both Treatment Visits 1 and 2 and was therefore withdrawn from the study. These results were treated as missing in the analysis. It is considered that with so few missing items of data there will be no impact on the results of the study.

11.4.2.3 Interim Analyses and Data Monitoring

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

11.4.2.4 Multi-site Studies

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

11.4.2.5 Multiple Comparison/Multiplicity

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

11.4.2.6 Use of an "Efficacy Subset" of Subjects

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

11.4.2.7 Active-Control Studies Intended to Show Equivalence

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

11.4.2.8 Examination of Subgroups

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

11.4.3 Tabulation of Individual Response Data

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

From the results of the study it was clear that the Gaviscon® product had a statistically significantly faster onset of action compared to the Losec® tablet. However, when compared to the placebo chewable tablet, the Gaviscon® product did initially better in terms of relief i.e., up to approximately 30 minutes after dosing, from which time the placebo's relief scores exceeded those of the Gaviscon®. Indeed, the AUC 0-15 and 0-30 minute data shows that the Gaviscon® product out performs the placebo in terms of the relief induced. Statistically significant differences were not demonstrated for any of the above data points when comparing Gaviscon® and placebo.

According to the subjective assessments the Gaviscon® and placebo chewable tablets the subjects were prepared to use these products in the future when compared to the Losec® product, the same being true for willingness of the subjects to replace their current heartburn therapy with the Gaviscon® as opposed to the Losec®.

However, overall this study did not substantiate claims for Gaviscon® chewable tablets, in relation to the placebo tablets, being able to provide a meaningful relief for heartburn discomfort.

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

Eighteen subjects received a single dose of all three study medications, one subject received one dose of the study medications and one subject did not receive any of the study treatments as no heartburn was induced on the first 2 study treatment

visits, the subject therefore being withdrawn from the study at treatment visit 2, as per study protocol.

Thus, eighteen subjects received Gaviscon® chewable tablets (2 x 250mg), eighteen subjects received Placebo chewable tablets (x2) and nineteen subjects received Losec® MUPS® (10mg) tablet.

12.2 Adverse Events (AEs)

All adverse events for each subject, including the same event on several occasions are listed in Appendix 16.2.7, giving both the original terms used by the investigator and the preferred terms according to MedDRA Version 13.0 dictionary.

The tables that follow describe adverse events occurring after the initiation of treatment with study medication. Only treatment emergent AEs are included in the summary tables.

12.2.1 Brief Summary of Events

Ten subjects reported a total of 15 treatment emergent adverse events. All events except one resolved with no sequelae, this event (sinusitis) not being considered to be related to the study medication. Seven were mild, seven were moderate and one (nausea) was classed as severe. Eleven events were categorised by the Investigator as not related or as unlikely to be related to treatment. Four events (diarrhoea, 2 instances of abdominal pain, vomiting) were classed as possibly related to treatment. No events were classed as probably related 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 of the 15 treatment emergent adverse events that occurred during the study categorised by MedDRA body system and preferred term is provided in Section 14.4.

12.2.3 Analysis of Adverse Events

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

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

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

12.3.1 Listing of Deaths, other Serious Adverse Events, and other Significant Adverse Events

12.3.1.1 Deaths

There were no deaths in this study.

12.3.1.2 Other Serious Adverse Events

There were no other serious adverse events in this study.

12.3.1.3 Other Significant Adverse Events

There were no significant adverse events in this study.

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

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

12.3.3 Analysis and Discussion of Deaths, other Serious Adverse Events and other Significant Adverse Events

12.4 Clinical Laboratory Evaluation

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

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

No abnormal laboratory value was deemed by the Investigator to be clinically significant. However, subject 8 was recorded initially as having a clinically significant microbiology result from the urine sample taken at the screening visit (elevated white blood count, positive for the presence of bacteria and positive sensitivity to Escherischia coli). The subject was asymptomatic and the result was later amended to not clinically significant by the investigator. A listing of individual laboratory measurements by subject is given in Appendix 16.2.8. A summary of the pre-study haematology and biochemistry data is given in Sections 14.3.1 and 14.3.2, respectively. Out of range values for haematology, biochemistry and urinalysis are shown in Sections 14.3.1, 14.3.2 and 14.3.3, respectively.

12.4.2 Evaluation of Each Laboratory Parameter

The active moiety of the study medications used in this study has been licensed for use in man for many years. Their safety profile is very well established. For this

reason, laboratory evaluations were not conducted during the study and no further data are presented here.

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

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

12.6 Safety Conclusions

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

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

This study employed the adapted 2-stopwatch technique that was shown to be effective in 2 previous studies[1,2] for assessing the onset of a sensorial effect in heartburn. However, for these previous studies the 2 stopwatches were used for the subjects to differentiate between the "soothing" and "cooling" sensations induced by the study medications. In this study, subjects dosed as a result of experiencing heartburn of moderate severity after consuming a refluxogenic meal, stopped the first stopwatch when they first perceived any heartburn relief. They stopped the second stopwatch when they perceived heartburn relief that was meaningful. The results showed that Gaviscon® was significantly more efficacious than Losec® both in terms of the primary endpoint, $AUC_{0\text{-}60}$ Heartburn Relief, time to first perceptible pain relief and change from baseline in heartburn intensity. This is expected given that Losec® is intended for use as a heartburn prophylactic as opposed to a treatment for symptom relief.

For the first 30 minutes post-dosing, heartburn relief was greater with Gaviscon® than placebo, whereas from 30 – 240 minutes, heartburn relief tended to be greater with placebo than with Gaviscon®. However, these differences failed to reach statistical significance.

The act of swallowing placebo chewable tablets is likely to have affected subjects' perception of heartburn more than the act of swallowing the Losec® tablets (which do not required chewing), hence accounting for the lack of 'placebo effect' observed with Losec®. This combined with the fact that heartburn is a self-limiting condition that resolves with time could partly explain the inability of the model to distinguish between Gaviscon® and placebo.

Several flaws in the protocol methodology may also have contributed to this. Subjects were aware that they would be dosed only if they achieved moderate heartburn within 60 minutes of the refluxogenic meal and this may have influenced their decision to notify the nurse that moderate heartburn had been attained, resulting in a study population with less severe heartburn than had been intended. Subjects were situated together in one ward and so were aware of when other subjects called the nurse and received medication. A more appropriate method would have been for the nurse to ask the subjects at regular timepoints throughout the 60 minutes post-meal to indicate their heartburn intensity on the heartburn intensity scale. Thus the subject would be unaware that a moderate hearburn was required for dosing and unaware of the heartburn scores indicated by their peers. In addition, the subjects were responsible for ensuring that the heartburn intensity and relief scales were completed at the scheduled timepoints, and their responses were not immediately checked by a member of staff. This led to some discrepancies between the heartburn relief scores and the stopwatch times whereby the subject indicated relief on the scale but had not stopped the stopwatch. This suggests that some subjects had not understood the use of the stopwatches. It is recommended that for future studies of a similar design, a member of staff is with the subjects on completion of the scales so that any discrepancies can be addressed immediately. It should be noted, however, that an additional analysis of time to first perceptible pain relief excluding such discrepancies did not alter the outcome of the Gaviscon® vs. placebo comparison.

13.2 Conclusion

The AUC_{0-60} Heartburn Relief with Gaviscon® (174.9) was statistically significantly greater compared with Losec® (124.2) but not compared with placebo (177.8). Gaviscon® demonstrated a statistically significantly earlier onset of of first perceptible relief (4.74 minutes) compared with Losec® (22.67 minutes) but not compared with placebo (6.29 minutes). The inability of the model in this pilot study to distinguish between Gaviscon® and Placebo may be due to a number of confounding factors such as the low severity of heartburn in the study population, the self-limiting nature of the condition and the influence of the chewable, mint flavoured placebo formulation.

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

14.1 Demographic Data

A summary of pre-study demographics is shown below.

Table 14.1.1 Summary of Pre-Study Demographics

Variable		Male	Female	All
AGE (YRS)	N	9	10	19
	MEAN	35.0	38.3	36.7
	SD	11.6	13.9	12.6
	MIN	20	19	19
	MEDIAN	32	38	35
	MAX	60	58	60
HEIGHT (CM)	N	9	10	19
	MEAN	176.3	162.3	168.9
	SD	8.2	4.8	9.6
	MIN	165	151	151
	MEDIAN	180	163	166
	MAX	188	167	188
WEIGHT (KG)	N	9	10	19
	MEAN	85.7	67.2	76.0
	SD	14.8	9.3	15.2
	MIN	65.0	53.8	53.8
	MEDIAN	88.3	66.2	70.7
	MAX	110.2	84.0	110.2
BMI (KG/M^2)	N	9	10	19
	MEAN	27.5	25.6	26.5
	SD	3.7	3.9	3.8
	MIN	21.0	19.3	19.3
	MEDIAN	28.1	25.0	26.1
	MAX	31.8	30.6	31.8

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14.2 Efficacy Data

Additional efficacy data is shown below:

Table 14.2.1 Summary of AUC Heartburn Intensity

Parameter	Treatment	N	Mean	Std Dev	Min	Median	Max
$AUCVASHI_{0-15}$	Gaviscon Tablets	18	601.6	296.3	260	546	1153
	Placebo Tablets	18	660.2	266.9	173	687	1058
	Losec® Tablets	18	759.0	297.1	253	819	1118
LS Mean Difference (95% CI)							
* -58.6 (-156.1 – 38.9) p=0.2295							
** -162.7 (-261.6 – -63.9) p=0.0021							
$AUCVASHI_{0-30}$	Gaviscon Tablets	18	1040.2	640.4	295	1004	2235
	Placebo Tablets	18	1133.2	561.9	215	1077	1988
	Losec® Tablets	18	1369.4	621.0	270	1253	2270
LS Mean Difference (95% CI)							
* -92.9 (-283.6 – 97.7) p=0.3281							
** -343.0 (-536.4 – -149.7) p=0.0010							
$AUCVASHI_{0-60}$	Gaviscon Tablets	18	1678.6	1232.7	308	1559	4150
	Placebo Tablets	18	1694.4	1081.1	230	1578	3343
	Losec® Tablets	18	2223.9	1273.3	270	2285	4403
LS Mean Difference (95% CI)							
* -15.8 (-446.7 – 415.1) p=0.9410							
** -576.6 (-1013.7 – -139.6) p=0.0113							

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* Gaviscon - Placebo
** Gaviscon - Losec

Table 14.2.1 Summary of AUC Heartburn Intensity(Continued)

Parameter	Treatment	N	Mean	Std Dev	Min	Median	Max
$AUCVASHI_{0-120}$	Gaviscon Tablets	18	2357.0	1945.9	308	2145	6468
	Placebo Tablets	18	2151.5	1670.1	245	1608	5178
	Losec® Tablets	18	3293.8	2425.7	270	3079	8355
LS Mean Difference (95% CI)							
* 205.5 (-722.1 – 1133.1) p=0.6548							
** -1006.4 (-1947.3 – -65.6) p=0.0368							
$AUCVASHI_{0-180}$	Gaviscon Tablets	18	2646.2	2374.8	308	2228	8133
	Placebo Tablets	18	2404.0	2097.0	245	1608	6588
	Losec® Tablets	18	3840.5	3248.6	270	3139	11610
LS Mean Difference (95% CI)							
* 242.2 (-1025.2 – 1509.6) p=0.6997							
** -1289.2 (-2574.8 – 3.7) p=0.0494							
$AUCVASHI_{0-240}$	Gaviscon Tablets	18	2797.8	2599.5	308	2228	9483
	Placebo Tablets	18	2553.2	2386.1	245	1616	7953
	Losec® Tablets	18	4177.2	3901.8	270	3139	14595
LS Mean Difference (95% CI)							
* 244.7 (-1253.6 – 1743.0) p=0.7416							
** -1507.2 (-3027.0 – 12.5) p=0.0518							

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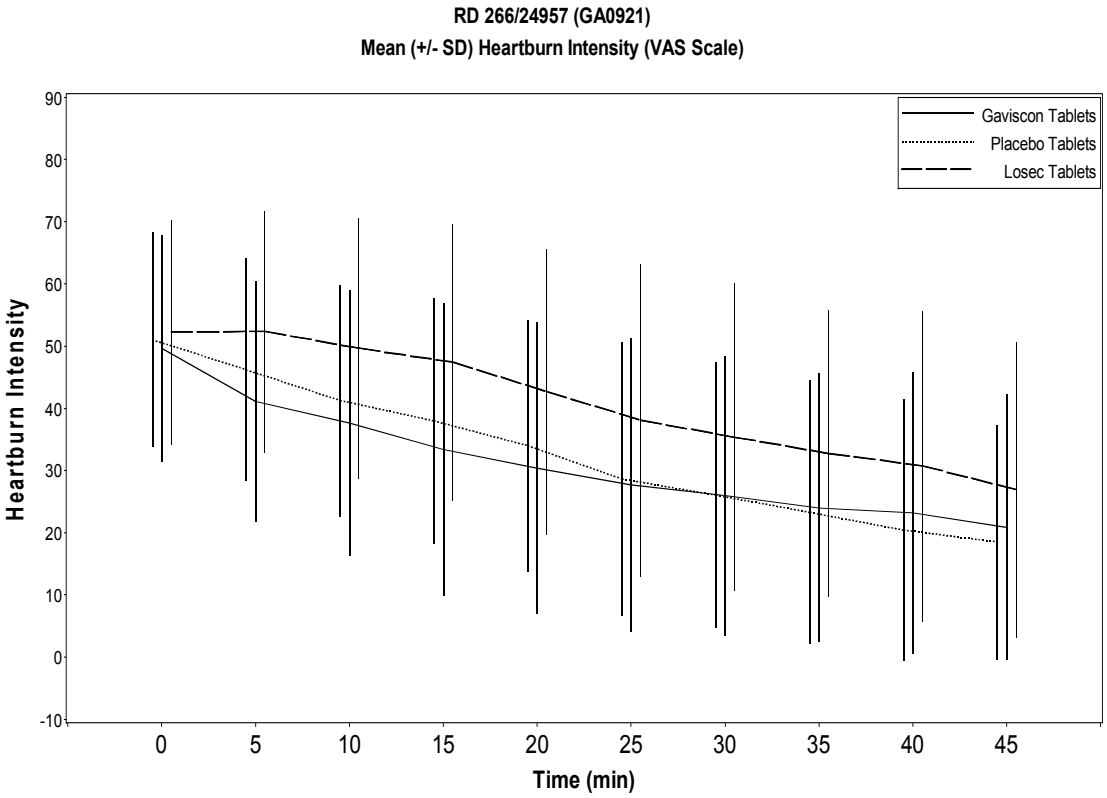
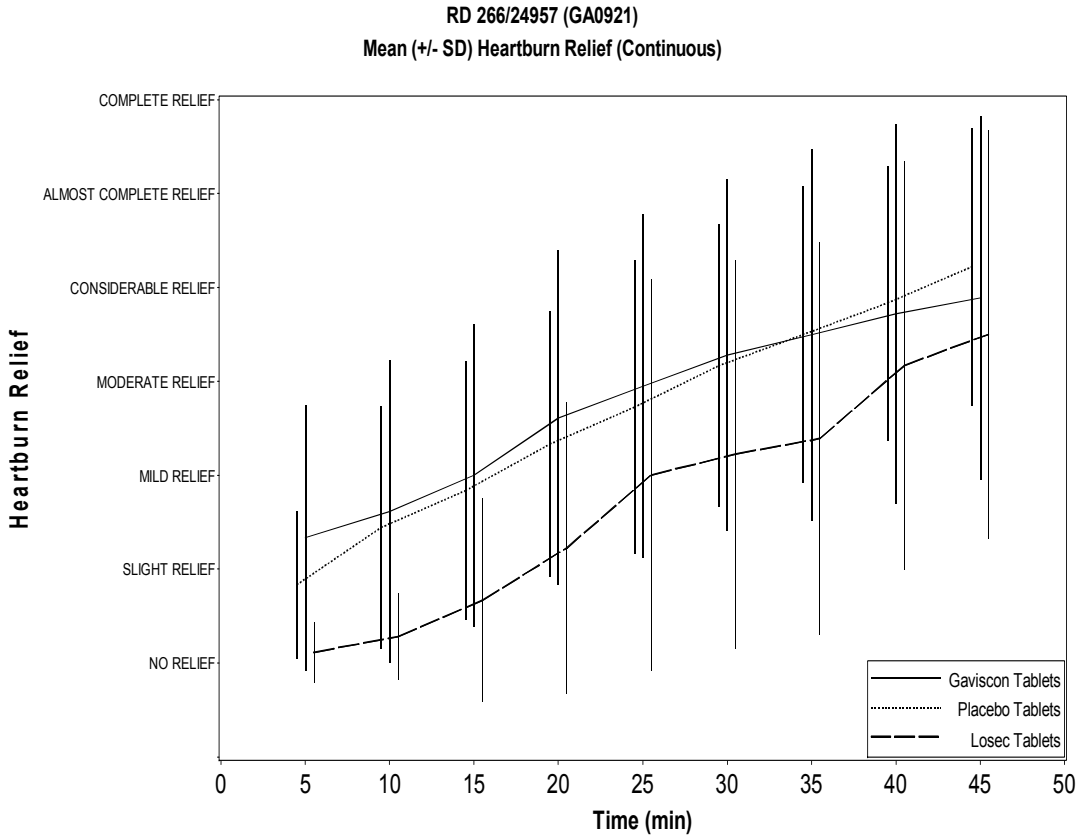
* Gaviscon - Placebo
** Gaviscon - Losec

Figure 14.2.1 Heartburn Intensity (Mean ± SD) (VAS Scale)



Output File: graph_intens_sd, 24FEB2011 15:33, Final

Figure 14.2.2 Heartburn Relief – Continuous (Mean ± SD) (VAS Scale)



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14.3 Safety Data

14.3.1 Summary of Haematology Data

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

Table 14.3.1 Summary of Haematology Data for Study GA0921 (Safety population)

Visit	Parameter	N	Mean	SD	Minimum	Median	Maximum
Pre-Study	Basophils (X10 9.L-1)	19	0.01	0.03	0.0	0.0	0.1
Pre-Study	Eosinophils (X10 9.L-1)	19	0.18	0.10	0.1	0.1	0.4
Pre-Study	Haematocrit (L.L-1)	19	0.4346	0.0316	0.376	0.436	0.474
Pre-Study	Haemoglobin (g.L-1)	19	144.2	10.6	128	145	161
Pre-Study	Lymphocytes (X10 9.L-1)	19	2.05	0.47	1.5	1.9	3.4
Pre-Study	MCH (pg)	19	29.25	1.48	25.9	29.6	31.9
Pre-Study	MCHC (g.L-1)	19	331.6	6.3	320	331	341
Pre-Study	MCV (fL)	19	88.26	4.80	79.4	88.2	98.4
Pre-Study	Monocytes (X10 9.L-1)	19	0.41	0.08	0.2	0.4	0.5
Pre-Study	Neutrophils (X10 9.L-1)	19	4.16	0.99	2.5	4.0	6.5
Pre-Study	Platelets (X10 9.L-1)	19	245.6	47.5	134	242	330
Pre-Study	RBC (X10 12.L-1)	19	4.932	0.365	4.30	4.88	5.72
Pre-Study	WBC (X10 9.L-1)	19	6.95	1.12	4.8	6.9	9.4

14.3.2 Summary of Biochemistry Data

A summary of pre-study biochemistry data are provided in the table 14.3.2 below:

Table 14.3.2 Summary of Biochemistry Data for Study GA0921 (Safety population)

Visit	Parameter	N	Mean	SD	Minimum	Median	Maximum
Pre-Study	Albumin (g.L-1)	19	47.12	1.75	44.9	47.0	50.6
Pre-Study	ALP (IU.L-1)	19	170.46	62.43	60.2	147.7	274.7
Pre-Study	ALT (IU.L-1)	19	24.86	15.65	10.1	20.3	77.2
Pre-Study	Total Bilirubin (mmol.L-1)	19	8.76	3.65	4.0	7.9	16.1
Pre-Study	Calcium (mmol.L-1)	19	2.324	0.075	2.17	2.34	2.44
Pre-Study	Cholesterol (mmol.L-1)	19	5.07	1.23	3.0	5.0	7.4
Pre-Study	Creatine Kinase (IU.L-1)	19	124.55	101.84	48.3	88.3	448.8
Pre-Study	Creatinine (mmol.L-1)	19	68.71	13.25	48.4	69.5	94.3
Pre-Study	GGT (IU.L-1)	19	21.19	16.94	6.4	16.9	85.4
Pre-Study	Glucose (mmol.L-1)	19	4.99	0.45	4.4	5.0	6.2
Pre-Study	HBD (IU.L-1)	19	135.35	19.47	105.9	135.3	185.5
Pre-Study	Potassium (mmol.L-1)	19	4.590	0.291	4.18	4.47	5.14
Pre-Study	Sodium (mmol.L-1)	19	140.65	1.57	138.1	140.5	143.6
Pre-Study	Phosphorus (mmol.L-1)	19	1.160	0.150	0.96	1.12	1.47
Pre-Study	Total Protein (g.L-1)	19	70.99	3.24	66.3	71.0	78.2
Pre-Study	Triglycerides (mmol.L-1)	19	1.216	0.758	0.40	0.90	2.80
Pre-Study	Uric Acid (mmol.L-1)	19	0.294	0.093	0.16	0.29	0.50
Pre-Study	Urea (mmol.L-1)	19	5.17	1.12	3.9	4.7	7.7

14.3.3 Summary of Vital Signs

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

Table 14.3.3 Pre and Post-Study Vital Signs

Variable		Pre-Study	Post-Study	Change
SITTING SBP	N	19	19	19
(MMHG)	MEAN	123.3	118.9	-4.4
	SD	8.4	9.7	6.1
	MIN	111	104	-14
	MEDIAN	123	119	-6
	MAX	139	134	13
SITTING DBP	N	19	19	19
(MMHG)	MEAN	73.1	69.5	-3.5
	SD	7.1	6.6	6.9
	MIN	63	60	-25
	MEDIAN	71	69	-4
	MAX	92	85	5
SITTING	N	19	19	19
PULSE (BPM)	MEAN	62.2	67.4	5.2
	SD	7.0	9.3	5.8
	MIN	49	52	-3
	MEDIAN	65	68	3
	MAX	71	87	16
TEMP. (C)	N	19	19	19
	MEAN	36.43	36.34	-0.09
	SD	0.30	0.32	0.45
	MIN	36.0	35.9	-0.9
	MEDIAN	36.4	36.3	-0.1
	MAX	36.8	36.9	0.8

14.4 Displays of Adverse Events

Additional displays of adverse events are provided below:

Table 14.4.1 Summary of Adverse Events by Preferred Term

		Number of Reports / Subjects (%)		
		Gaviscon Tablets (n=18)	Placebo Tablets (n=18)	Losec® Tablets (n=19)
MedDRA Primary SOC	MedDRA Preferred Term			
Gastrointestinal disorders	ABDOMINAL PAIN	1 / 1 (5.6)	1 / 1 (5.6)	0
	DIARRHOEA	1 / 1 (5.6)	0	0
	NAUSEA	0	1 / 1 (5.6)	0
	TOOTHACHE	0	0	2 / 1 (5.3)
	VOMITING	0	0	1 / 1 (5.3)
Infections and infestations	SINUSITIS	1 / 1 (5.6)	0	0
Injury, poisoning and procedural complications	ARTHROPOD BITE	1 / 1 (5.6)	0	0
Nervous system disorders	DIZZINESS	0	1 / 1 (5.6)	0
	HEADACHE	2 / 2 (11.1)	1 / 1 (5.6)	1 / 1 (5.3)
	MIGRAINE	1 / 1 (5.6)	0	0

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Table 14.4.2 Summary of Adverse Events by Relationship

			Number of Subjects		
			POSSIBLE	UNLIKELY	NONE
Treatment	MedDRA Primary SOC	MedDRA Preferred Term			
Gaviscon Tablets (n=18)	Gastrointestinal disorders	ABDOMINAL PAIN (p=0.5394)	1	0	0
		DIARRHOEA (p=0.6545)	1	0	0
	Infections and infestations	SINUSITIS(p=1.0000)	0	0	1
	Injury, poisoning and procedural complications	ARTHROPOD BITE (p=1.0000)	0	0	1
	Nervous system disorders	HEADACHE (p=1.0000)	0	2	0
		MIGRAINE (p=1.0000)	0	0	1
Placebo Tablets (n=18)	Gastrointestinal disorders	ABDOMINAL PAIN (p=0.5394)	1	0	0
		NAUSEA (p=1.0000)	0	1	0
	Nervous system disorders	DIZZINESS (p=1.0000)	0	1	0
		HEADACHE (p=1.0000)	0	1	0
Losec® Tablets (n=19)	Gastrointestinal disorders	TOOTHACHE (p=1.0000)	0	1	0
		VOMITING (p=1.0000)	1	0	0
	Nervous system disorders	HEADACHE (p=1.0000)	0	1	0

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

Table 14.4.3 Summary of Adverse Events by Severity

			Number of Subjects		
			MILD	MODERATE	SEVERE
Treatment	MedDRA Primary SOC	MedDRA Preferred Term			
Gaviscon Tablets (n=18)	Gastrointestinal disorders	ABDOMINAL PAIN (p=1.0000)	1	0	0
		DIARRHOEA (p=1.0000)	0	1	0
	Infections and infestations	SINUSITIS (p=1.0000)	1	0	0
	Injury, poisoning and procedural complications	ARTHROPOD BITE (p=1.0000)	1	0	0
	Nervous system disorders	HEADACHE (p=1.0000)	2	0	0
		MIGRAINE (p=1.0000)	0	1	0
Placebo Tablets (n=18)	Gastrointestinal disorders	ABDOMINAL PAIN (p=1.0000)	0	1	0
		NAUSEA (p=0.6545)	0	0	1
	Nervous system disorders	DIZZINESS (p=1.0000)	0	1	0
		HEADACHE (p=1.00000)	1	0	0
Losec® Tablets (n=19)	Gastrointestinal disorders	TOOTHACHE (p=1.0000)	0	1	0
		VOMITING (p=1.0000)	1	0	0
	Nervous system disorders	HEADACHE (p=1.0000)	0	1	0

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

14.4.1 Listings of Deaths, other Serious and Significant Adverse Events

Not applicable.

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

Not applicable.

14.4.3 Clinically Significant Abnormal Laboratory Value Listing (each subject)

No clinically significant abnormal laboratory values were found for any subject.

15 REFERENCE LIST

1. GA0706 Clinical Study Report, Reckitt Benckiser, Data on File.

2. GA0821 Clinical Study Report, Reckitt Benckiser, Data on File.