Reckitt Benckiser

1 STUDY REPORT TITLE PAGE

EudraCT Number:	2012-000678-44		
Study Number:	GA1116	**Project Name:**	501
Study Phase:	II	**Study Country:**	United Kingdom (UK)
Indication:	Not Applicable.		
Test Product:	Gaviscon® Double Action Aniseed Liquid (PL 00063/0543) Gaviscon® Advance Aniseed Liquid (PL 00063/0097)		
Reference Product:	Placebo Aniseed Liquid		
Date of First Subject Visit:	18 Sep 2012		
Date of Last Subject Visit:	08 May 2013		
Principal Investigator:	Dr Simon Singer, BSc MB, ChB MRCS (from 01 Mar 2012 until 13 Mar 2013). Dr Peter Dewland, BSc, MA, MBBS, FFPM, DCPSA (from 13 Mar 2013 until 17 Apr 2013). Dr Pui Man Leung, MBChB, MRCP (UK), MFPM, DPM (from 17 Apr 2013 until 21 May 2013). ICON Development Solutions, Skelton House, Lloyd Street North, Manchester, M15 6SH, UK.		
Study Title:	A single-centre, randomised, four-way crossover study to investigate the measurement of the acid pocket and subsequent gastro-oesophageal reflux episodes using a novel pH/impedance catheter in subjects receiving Gaviscon® Double Action, Gaviscon® Advance and Placebo Liquid versus no treatment		
Short Study Title:	Gaviscon® Double Action Acid Pocket Investigation		
Report Date:	18 July 2014		
Report Version:	Final		
Study Conduct Statement:	This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and the ethical principles contained within the Declaration of Helsinki, as referenced in European Union (EU) Directive 2001/20/EC.		
Confidentiality Statement:	**The information contained in this document is privileged and confidential. Do not copy, circulate or otherwise distribute without written authority from the Reckitt Benckiser Clinical Project Manager function.**		

2 REPORT APPROVAL

Reviewed and Agreed by:

Reckitt Benckiser Healthcare (UK) Ltd

Clinical Project Manager Function:		**Statistical Manager:**	
Dr Stacey V. Fergusson PhD	25 Jul-2014 Date	Mr Gary Smith MSc	22/JUL/2014 Date

ICON Development Solutions/ICON Clinical Research

Statistician:		**Report Author:**	
Dr Colm Farrell, PhD ICON Development Solutions	Date	Mr Leon Conradie, BA Hons ICON Clinical Research	Date

Reviewed and Approved by:

R&D Senior Clinical Manager, Health:		**RB Global Medical Director:**	
Dr Sue Aspley PhD	Date	Dr Bernard Ng MD, MBA	Date

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Reviewed and Approved by:

R&D Senior Clinical Manager, Health:		**RB Global Medical Director:**	
Dr Sue Aspley PhD	Date	Dr Bernard Ng MD, MBA	23 Jul 2014 Date

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Reviewed and Approved by:

R&D Senior Clinical Manager, Health:		**RB Global Medical Director:**	
Sue Aspley 23 July 14			
Dr Sue Aspley PhD	Date	Dr Bernard Ng MD, MBA	Date

3 SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/ Company:
Reckitt Benckiser Healthcare (UK) Ltd</td><td rowspan="3">Individual Trial Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority use only)</td></tr>
<tr><td colspan="2">Name of Finished Products:
Gaviscon® Double Action Aniseed Liquid
Gaviscon® Advance Aniseed Liquid</td></tr>
<tr><td colspan="2">Name of Active Ingredients:
Gaviscon® Double Action Aniseed Liquid: Sodium alginate, sodium hydrogen carbonate and calcium carbonate
Gaviscon® Advance Aniseed Liquid: Sodium alginate and potassium hydrogen carbonate</td></tr>
<tr><td colspan="4">Title of Trial: A single-centre, randomised, four-way crossover study to investigate the measurement of the acid pocket and subsequent gastro-oesophageal reflux episodes using a novel pH/impedance catheter in subjects receiving Gaviscon® Double Action, Gaviscon® Advance and Placebo Liquid versus no treatment</td></tr>
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Dr Peter Dewland, BSc, MA, MBBS, FFPM, DCPSA (from 13 Mar 2013 until 17 Apr 2013).

Dr Pui Man Leung, MBChB, MRCP (UK), MFPM, DPM (from 17 Apr 2013 until 21 May 2013).</td></tr>
<tr><td colspan="4">Trial Site: This study was conducted at the Phase 1 unit of ICON Development Solutions, Manchester Royal Infirmary Campus, Oxford Road, Manchester, M13 9WL, UK.</td></tr>
<tr><td colspan="4">Publication (reference): None</td></tr>
<tr><td colspan="3">Studied Period: The duration of the study was approximately 8 months.

Date first subject enrolled: 18 Sep 2012

Date last subject completed: 08 May 2013</td><td>Phase of Development: II</td></tr>
<tr><td colspan="4">Objectives: The objectives of this study were to assess the formation of the acid pocket, following a high fat test meal, and associated reflux episodes in subjects receiving no treatment and when dosed with Gaviscon® Advance Aniseed Liquid, Gaviscon® Double Action Aniseed Liquid or Placebo Aniseed Liquid.</td></tr>
<tr><td colspan="4">Methodology:

Validation Phase:

Subjects in the Validation Phase of the study attended the ICON clinical pharmacology unit (CPU) on 3 separate occasions: a screening visit, one data collection visit (including 2 overnight stays) and a post-study visit. Subjects who took part in the Validation Phase were not able to participate in the Clinical Phase of the study.

After written informed consent had been given by the subjects, the following screening assessments took place to confirm subject eligibility: an assessment using High Resolution Manometry (HiRM) to determine the presence/absence of hiatus hernia. Subjects were also assessed for demographic</td></tr>
</table>

Name of Sponsor/ Company: Reckitt Benckiser Healthcare (UK) Ltd	**Individual Trial Table Referring to Part of the Dossier** **Volume:**	**(For National Authority use only)**
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data, vital signs, medical history, medication and therapy history, physical examination, drugs of abuse test, alcohol breath test, pregnancy test and laboratory investigations.

On Day 1 of the Validation Phase, subjects reported to the CPU, had vital signs recorded and were required to stay in the CPU and fast from approximately 22:00 until they were provided with a drink and meal the next day. The fasting period lasted approximately 12 to 14 hours (including sleep time).

On the morning of Day 2, fasted subjects had the pH and impedance catheter inserted under endoscopic guidance. It was positioned in relation to the lower oesophageal sphincter and a fluoroscopic assessment was performed to confirm the position of the catheter for comparison later in the day. A minimum of 30 minutes after catheter insertion, pH and impedance monitoring commenced for 30 minutes to enable the pH readings to stabilise and a baseline dataset to be produced. Data recording was halted whilst subjects consumed a high fat meal, and data recording resumed immediately after completion of the meal and continued for 4 hours 15 minutes. Following implementation of non-substantial protocol amendment No. 4, dated 10 Jan 2013, data recording was continued whilst subjects consumed a high fat meal, with markers placed on the trace to identify the start and stop of eating.

Following the recording period, the subjects were disconnected from the recording device, but the catheter was left in place. A repeat fluoroscopic assessment was performed to confirm catheter position. During the remainder of the day and night, subjects remained under the supervision of the CPU staff. Subjects were provided with food and drink (outside of the high fat meal administered during the treatment period, high fat food was avoided, i.e., total fat content of meals was less than 30% per meal and spicy food was avoided). From approximately 22:00 onwards, subjects were required to fast.

On the morning of Day 3, the subjects were reconnected to the recording device and baseline readings were taken for 30 minutes. Subjects were then provided with the same high fat refluxogenic meal at approximately the same time of day as on Day 2.

On completion of the recording period, a repeat fluoroscopic assessment was performed and the pH and impedance catheter was removed.

The subjects were provided with a light meal and vital signs were assessed before the subjects were discharged. Subjects returned 3 to 7 days later for a follow-up visit.

Clinical Phase:

Subjects in the Clinical Phase of the study attended the CPU on a total of 4 separate occasions: a screening visit, 2 dosing visits (each including 2 overnight stays) and a post-study visit.

The procedures described for the Validation Phase were repeated with the addition of a dosing step 15 minutes after completion of the meal. Fluoroscopic assessments were not performed in the Clinical Phase of the study.

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Name of Active Ingredients: Gaviscon® Double Action Aniseed Liquid: Sodium alginate, sodium hydrogen carbonate and calcium carbonate Gaviscon® Advance Aniseed Liquid: Sodium alginate and potassium hydrogen carbonate		

Subjects were dosed with Gaviscon® Advance Aniseed Liquid, Gaviscon® Double Action Aniseed Liquid, Placebo Aniseed Liquid or left untreated. After dosing, pH and impedance monitoring commenced for 4 hours. Data recording continued during dosing.

As with the Validation Phase, the subjects remained under the supervision of CPU staff. On Day 3, a second refluxogenic meal and an alternative treatment was given.

Following Treatment Period 1, subjects entered a minimum 5-day wash-out period before re-entering for repeat procedures with the remaining 2 treatments. Subjects returned 3 to 7 days after Treatment Period 2 for a follow-up visit.

Throughout the study, at various time-points, subjects were asked whether they had experienced any symptoms or complaints. Any spontaneously reported or observed adverse events (AEs) were recorded. Any concomitant medication taken by the subject during the study was recorded.

Number of Subjects:

Planned: Eight subjects were to be assessed in the Validation Phase. Sixteen subjects were considered to be sufficient to meet the objectives of the Clinical Phase of the study.

Analysed: Ten subjects were enrolled in the Validation Phase of the study, and 8 (80.0%) subjects completed the Validation Phase. Sixteen subjects were enrolled in the Clinical Phase of the study. The study was terminated early due to quality issues being identified across a number of RB studies and, as such, 14 (87.5%) subjects completed the Clinical Phase. One subject (Subject C011) completed Treatment Period 1, but was withdrawn from the study due to a positive drugs of abuse test in Treatment Period 2.

Diagnosis and Main Criteria for Inclusion: Male or female subjects, aged ≥ 18 to ≤ 50 years, who had used over-the-counter medication to treat for heartburn, typically at least twice a month for the previous 3 months and who gave written informed consent, were included in the study.

Main criteria for exclusion were:

- A history of gastro-oesophageal reflux disease or active gastrointestinal disease (gastroduodenal ulcer, gastrointestinal haemorrhage, mechanical obstruction or perforation) within the last year.
- Clinically significant allergic, pulmonary, neurological, renal, hepatic, cardiovascular, psychiatric, metabolic, endocrine or haematological disease.
- A hiatus hernia with a diameter which exceeded 3 cm at screening.
- A history of basal skull fracture or trans-sphenoidal surgery.
- Hospitalisation within the previous 3 months for major surgery or medical illness.

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Name of Active Ingredients: Gaviscon® Double Action Aniseed Liquid: Sodium alginate, sodium hydrogen carbonate and calcium carbonate Gaviscon® Advance Aniseed Liquid: Sodium alginate and potassium hydrogen carbonate		

- A clinically significant illness within the previous 4 weeks.
- Use of any prescription medication or non-prescription medication (other than hormonal contraceptives) within the last 7 days, prior to the screening visit, which the Principal Investigator considered might interfere with the study.
- Use of H_2 antagonists or motility stimulants 2 weeks prior to enrolment in the study and during the study.
- Use of proton pump inhibitors 4 weeks prior to enrolment into the study and during the study.
- A drug hypersensitivity, which in the opinion of the Principal Investigator might interfere with the study.
- Evidence of columnar lined oesophagus or any other significant abnormality to the gastrointestinal tract (as determined during the endoscopy procedure to place the catheter).
- Woman of childbearing potential, who were pregnant or lactating, seeking pregnancy or failing to take adequate contraceptive precautions. Adequate contraceptive precautions included oral or injectable contraceptives, approved hormonal implants or topical patches, intrauterine devices; barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; true abstinence (true abstinence: when this was in line with the preferred and usual lifestyle of the subject. Periodic abstinence e.g., calendar, ovulation, symptothermal, post ovulation methods and withdrawal were not acceptable methods of contraception. Should the subject become sexually active whilst participating in the study, she and her partner agreed to use a double barrier method or condoms/diaphragms with spermicidal foam/gel/film/cream/ suppository). Subjects were to be informed verbally that a female condom and male condom should not have been used together as friction between the 2 can result in either product failing. A woman of childbearing potential was defined as any female who was less than 2 years postmenopausal or who had not undergone a hysterectomy or surgical sterilisation, e.g. bilateral tubal ligation, bilateral ovariectomy (oophorectomy).

Test Products:

Gaviscon® Advance Aniseed Liquid (300 ml bottles; batch number: 223085) and Gaviscon® Double Action Aniseed Liquid (300 ml bottles; batch number: 128471) were manufactured to Good Manufacturing Practice (GMP) standards by Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS, UK.

Duration of Treatment:

In the Validation Phase, approximately 3 weeks (from screening to post-study follow-up visit).

In the Clinical Phase, approximately 4 weeks (from screening to post-study follow-up visit).

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Reference Therapy: Placebo Aniseed Liquid (150 ml bottles; batch number: PMBN12056) was manufactured to GMP standards by Pharmaterials Ltd, Unit B, 5 Bolton Road, Reading, RG2 0NH for Reckitt Benckiser Healthcare (UK) Ltd.

Criteria for Evaluation:

PH and Impedance:

The primary endpoint was the percentage of time that the electrode 5 cm above the squamocolumnar junction (SCJ) was pH < 4 over a period of 2 hours following treatment with Gaviscon® Double Action Aniseed Liquid versus Placebo Aniseed Liquid.

The secondary endpoints were:

pH Change:

- Percentage of time that the electrode 5 cm above the SCJ was pH < 4 over a period of 2 hours following treatment with Gaviscon® Double Action Aniseed Liquid versus the untreated state.
- Percentage of time that the electrode 5 cm above the SCJ was pH < 4 over a period of 4 hours following treatment with Gaviscon® Double Action Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.
- Percentage of time that the electrode 5 cm above the SCJ was pH < 4 over a period of 2 hours following treatment with Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.
- Percentage of time that the electrode 5 cm above the SCJ was pH < 4 over a period of 4 hours following treatment with Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.
- Percentage of time that each electrode was pH $\leq$ 4 at 15, 30, 45, 60, 75 and 90 minutes following ingestion of each test product at electrodes 4 to 11 inclusive.
- Mean percentage of time with pH < 4 at electrodes 1, 2 and 3 during each of the four 1-hour periods for Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.
- Mean percentage of time with pH < 4 at electrodes 1, 2 and 3 during the 4-hour period for Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.
- Mean percentage of time with pH < 4 at the electrodes within the cardia (electrodes 4 to 7) during each of the four 1-hour periods for Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance

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Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.

Reflux Events as Identified with Impedance Monitoring:

- Total number of (i) liquid, (ii) gas and (iii) mixed reflux episodes occurring in the 2- and 4-hour period following ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.
- Total number of (i) acid and (ii) weakly acidic reflux episodes occurring in the 2- and 4-hour period following ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.
- Number of reflux episodes reaching 15 cm above the lower oesophageal sphincter (LOS) during the 2- and 4-hour period following ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.
- Oesophageal bolus exposure to reflux (percentage time with liquid or mixed reflux within the oesophageal lumen) for each test product versus the untreated state during the 2- and 4-hour period following ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.

Safety: Safety was assessed in terms of the proportion of subjects with AEs. Tolerability was evaluated using data obtained from vital signs and laboratory tests.

Statistical Methods: For each of the pH and impedance endpoints, the relevant contrasts between treatments were compared using an analysis of variance (ANOVA) model incorporating all treatments which included fixed effects for treatment, baseline, treatment period (1 or 2), treatment day (2 or 3) and a random effect for subject.

For the primary endpoint, separate models with added interaction terms for the effect of treatment by treatment period and treatment by treatment day were conducted.

All AEs recorded during the study were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs (TEAEs) are summarised and tabulated by treatment, indicating intensity and causal relationship to study treatment. Any serious adverse events (SAEs), AEs with outcome of death and AEs resulting in discontinuation of treatment are listed separately.

The overall incidence of TEAEs (number and percentage of subjects) as well as the number of events are summarised by study treatment and overall for the following: categories of degree of intensity, SAEs, causally related TEAEs and SAEs, TEAEs leading to discontinuation of treatment, life-threatening SAEs and SAEs resulting in death.

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SUMMARY & CONCLUSIONS

PH AND IMPEDANCE RESULTS:

Primary pH and Impedance Analysis

The primary pH and impedance endpoint was the percentage of time that the electrode 5 cm above the SCJ was pH < 4 over a period of 2 hours following treatment with Gaviscon® Double Action Aniseed Liquid versus Placebo Aniseed Liquid.

No statistically significant difference in the percentage of time that pH < 4 over a period of 2 hours at the electrode 5 cm above the SCJ was observed for Gaviscon® Double Action Aniseed Liquid when compared with Placebo Aniseed Liquid for either the ITT or PP populations. For the PP population, a reduction in the time that pH < 4 was observed for Gaviscon® Double Action Aniseed Liquid when compared with Placebo Aniseed Liquid, with a LS mean difference of -2.1%.

Secondary pH and Impedance Analysis

pH Change:

No statistically significant difference in the percentage of time that pH < 4 over a period of 2 hours at the electrode 5 cm above the SCJ was observed for Gaviscon® Double Action Aniseed Liquid when compared with the untreated state for either the ITT or PP populations. For the PP population, a reduction in the percentage of time that pH < 4 was observed for Gaviscon® Double Action Aniseed Liquid when compared with the untreated state, with a LS mean difference of -2.6%.

No statistically significant difference in the percentage of time that pH < 4 over a period of 4 hours at the electrode 5 cm above the SCJ was observed for Gaviscon® Double Action Aniseed Liquid when compared with Placebo Aniseed Liquid or the untreated state for either the ITT or PP populations. A reduction in the percentage of time that pH < 4 was observed for Gaviscon® Double Action Aniseed Liquid when compared with the untreated state for the ITT population (LS mean difference of -1.8%) and the PP population (LS mean difference of -4.4%).

For both the ITT and PP populations, a reduction in the percentage of time that pH < 4 over a period of 2 hours at the electrode 5 cm above the SCJ of approximately 5% was observed for Gaviscon® Advance Aniseed Liquid when compared with either Placebo Aniseed Liquid or the untreated state. None of these differences was statistically significant.

For both the ITT and PP populations, a reduction in the percentage of time that pH < 4 over a period of 4 hours at the electrode 5 cm above the SCJ was observed for Gaviscon® Advance Aniseed Liquid when compared with either Placebo Aniseed Liquid (approximate 2% reduction) or the untreated state (5% reduction). None of these differences was statistically significant.

For almost all combinations of electrode and timepoints, a reduction in the percentage of time that pH < 4 was observed for both Gaviscon® Double Action Aniseed Liquid and Gaviscon® Advance

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Aniseed Liquid when compared with either the Placebo Aniseed Liquid or the untreated state for the ITT population. In the vast majority of cases, these reductions were not statistically significant nor was there any obvious trend as to which electrode/timepoint these reductions were observed.

For both Gaviscon® Double Action Aniseed Liquid and Gaviscon® Advance Aniseed Liquid, there was a trend for a reduction in the mean percentage of time that pH < 4 compared to both Placebo Aniseed Liquid and the untreated state during the 0 to 1-hour period and compared to untreated state during the 1 to 2-hour period for the ITT population, although none of these reductions achieved statistical significance. The greatest reductions of approximately 11% for Gaviscon® Double Action Aniseed Liquid and approximately 9% for Gaviscon® Advance Aniseed Liquid were observed during the 0 to 1-hour period.

No statistically significant difference in the mean percentage of time that pH < 4 at electrodes 1, 2 and 3 during the 4-hour period was observed for either Gaviscon® Double Action Aniseed Liquid or Gaviscon® Advance Aniseed Liquid when compared with either Placebo Aniseed Liquid or the untreated state for the ITT population. There was a trend for a reduction in the mean percentage of time that pH < 4 for both Gaviscon® Double Action Aniseed Liquid (approximately 4%) and for Gaviscon® Advance Aniseed Liquid (approximately 3%) compared with the untreated state.

No statistically significant difference in the mean percentage of time that pH < 4 at electrodes 4 to 7 during four 1-hour periods was observed for either Gaviscon® Double Action Aniseed Liquid or Gaviscon® Advance Aniseed Liquid when compared with either Placebo Aniseed Liquid or the untreated state for the ITT population. There was a trend for a reduction in the mean percentage of time that pH < 4 during the 0 to 1-hour and 1 to 2-hour periods for both Gaviscon® Double Action Aniseed Liquid and Gaviscon® Advance Aniseed Liquid compared to both Placebo Aniseed Liquid and the untreated state. The greatest reductions of approximately 14% for Gaviscon® Double Action Aniseed Liquid and approximately 16% for Gaviscon® Advance Aniseed Liquid were observed during the 0 to 1-hour period.

Reflux Events as Identified with Impedance Monitoring:

No statistically significant differences in the number of (i) liquid, (ii) gas and (iii) mixed reflux episodes occurring during the 2- and 4-hour periods was observed for either Gaviscon® Double Action Aniseed Liquid or Gaviscon® Advance Liquid when compared with either Placebo Aniseed Liquid or the untreated state for either the ITT of the PP population. There was a trend for a slight reduction in the number of liquid reflux episodes.

No statistically significant reduction in the total number of acid reflux episodes occurring during the 2- and 4-hour periods was observed for either Gaviscon® Double Action Aniseed Liquid or Gaviscon® Advance Aniseed Liquid when compared with Placebo Aniseed Liquid or the untreated state for either the ITT or PP populations. There was a trend for a slight reduction in the number of acid reflux episodes.

A statistically significant difference in the total number of weakly acidic reflux episodes occurring during the 2-hour period, but not during the 4-hour period, was observed for Gaviscon® Advance

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Aniseed Liquid when compared with the untreated state, but not when compared with Placebo Aniseed Liquid for both the ITT and PP populations.

No statistically significant reduction in the number of reflux episodes reaching 15 cm above the LOS during the 2- and 4-hour periods was observed for either Gaviscon® Double Action Aniseed Liquid or Gaviscon® Advance Liquid when compared with either Placebo Aniseed Liquid or the untreated state for either the ITT or PP populations.

No statistically significant reduction in the oesophageal bolus exposure to reflux during the 2- and 4-hour periods was observed for either Gaviscon® Double Action Aniseed Liquid or Gaviscon® Advance Liquid when compared with either Placebo Aniseed Liquid or the untreated state for either the ITT or PP populations.

SAFETY RESULTS:

No deaths, SAEs or withdrawals due to TEAEs were reported.

Overall, 13 TEAEs were reported in 7 (46.7%) subjects (6 TEAEs in 5 [33.3%] subjects following administration of Gaviscon® Double Action Aniseed Liquid, 2 TEAEs in 2 [14.3%] subjects following administration of Gaviscon® Advance Aniseed Liquid, and 5 TEAEs in 5 [33.3%] subjects following administration of Placebo Aniseed Liquid).

The majority of TEAEs (10 TEAEs) were mild in intensity and only 4 TEAEs (nasal discomfort, rhinorrhoea, medical device discomfort and oropharyngeal pain) were considered related (definite or probable) to the study treatment. The events of nasal discomfort, rhinorrhoea, medical device discomfort and oropharyngeal pain were all considered ADEs.

CONCLUSION:

Based on the results from this study, Gaviscon® Double Action Aniseed Liquid did not statistically significantly reduce the percentage of time that pH < 4 over a period of 2 hours at the electrode 5 cm above the SCJ compared with Placebo Aniseed Liquid.

Gaviscon® Double Action Aniseed Liquid (20 ml), Gaviscon® Advance Aniseed Liquid (10 ml) and the study procedures were well tolerated by all of the subjects.

The method upon which this protocol was based was experimental and the first usage of this specific type of pH probe. Thus reproducibility and robustness were still unknowns, as was variability.

Date of the report: 18 July 2014

4 TABLE OF CONTENTS

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

4.2 List of Abbreviations

Abbreviation	Abbreviation in Full
ADE	Adverse device event
AE	Adverse event
ALT	Alanine transaminase
ANOVA	Analysis of variance
AR	Adverse reaction
AST	Aspartate transaminase
BUN	Blood urea nitrogen
CI	Confidence interval
CPU	Clinical pharmacology unit
CRF	Case Report Form
CV%	Coefficient of variation
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HiRM	High Resolution Manometry
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

Abbreviation	Abbreviation in Full
IMP	Investigational Medicinal Product
IMSU	Investigational Material Supply Unit
ITT	Intention to treat
LOS	Lower oesophageal sphincter
LS mean	Least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
PP	Per protocol
PT	Preferred term
QA	Quality assurance
SADE	Serious adverse device event
SAE	Serious adverse event
SAP	Statistical analysis plan
SCJ	Squamocolumnar junction
SD	Standard deviation
SDV	Source Data Verification
SE	Standard error
SOC	System organ class
SOP	Standard Operating Procedure
TEAE	Treatment-emergent adverse event
UK	United Kingdom (of Great Britain and Northern Ireland)

5 ETHICS

5.1 Independent Ethics Committee (IEC)

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

The study protocol, together with subject information and consent documents were reviewed and approved on 04 Sep 2012 by the National Research Ethics Service Committee East Midlands - Northampton. The protocol amendments, together with updated subject information and consent documents were reviewed and approved on 06 Nov 2012 (Substantial Protocol Amendment No. 1), 13 Mar 2013 (Substantial Protocol Amendment No. 2) and 17 May 2013 (Substantial Protocol Amendment No. 3).

The protocol was submitted for consideration by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) and written approval from the MHRA was obtained on 20 Jul 2012, before clinical activities commenced. A Temporary Halt was put in place on 24 Apr 2013. An End of Trial decision was made on 04 Jun 2013 and the IEC was notified on 11 Jun 2013 (see Section 10.2 for details).

5.2 Ethical Conduct of the Study

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

Additional information on minor protocol deviations is included in a Note to File and the protocol deviations log, provided in Appendix 16.2.2. Following a review requested by the MHRA, ICON identified a total of 240 protocol deviations which were reported to RB. RB concluded that the majority (232) of the protocol deviations did not have significant impact on either the scientific value of the study or the safety of the subjects participating in the study. However, RB determined that there had been a significant impact on the safety of 8 subjects where there was no evidence of GP letters being sent to their GPs prior to screening (discovered by RB during a routine co-monitoring visit on 15 Jul 2013). RB reported this to the MHRA as being evidence of a serious breach of GCP. ICON performed a follow up and informed all subjects' GPs. There were no concerns raised by the GPs with regard to their patients' participation in the clinical study and as such ICON and RB determined that no safety issues related to patient safety had arisen.

5.3 Subject Information and Consent

Copies of a representative subject information sheet and a blank informed consent form 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 informed consent form, and to ask questions. If they understood and agreed with the information and instructions provided, they were asked to sign the informed consent form. The Investigator also signed the form.

The subject was given a copy of the information sheet and the signed informed consent form. No protocol-related procedures were performed prior to the subject signing the informed consent form.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Appendix 16.1.4 contains a table listing the names and affiliations of the individuals whose participation materially affected the conduct of the study, together with their roles. The Curriculum Vitae of the Principal Investigators (PIs) are also included in the appendix.

Dr Simon Singer, BSc MB, ChB MRCS (from 01 Mar 2012 until 13 Mar 2013), Dr Peter Dewland, BSc, MA, MBBS, FFPM, DCPSA (from 13 Mar 2013 until 17 Apr 2013) and Dr Pui Man Leung, MBChB, MRCP (UK), MFPM, DPM (from 17 Apr 2013 until 21 May 2013) were the PIs for this study. Dr Peter Dewland is the signatory for the clinical study report (see substantial protocol amendment No. 2 in Appendix 16.1.1). The PI signature page is presented in Appendix 16.1.5.

The clinical pathology and bioanalytical laboratories of ICON Development Solutions were used for this study. Statistical analysis and reporting was undertaken by ICON Development Solutions.

ICON Development Solutions was responsible for the project management, clinic (including ethics committee submission and pharmacy), CRF-design, data management, programming, statistical analysis and quality assurance. ICON Clinical Research was responsible for medical writing.

7 INTRODUCTION

The symptoms of reflux disease are among the most common gastroenterological complaints in the Western world[1]. Whilst there are regional differences, it has been suggested that in Western populations 25% had monthly symptoms, 12% had symptoms at least weekly and 5% had heartburn daily[2]. Post-prandially, it has been shown that intragastric pH is higher than oesophageal pH[3], yet this post-prandial period is when patients report the majority of reflux symptoms[4].

Recently, it was discovered a highly acidic layer on the top of the stomach contents exists. This phenomenon has been described as the “acid pocket”[3,5,6] and it is this acid that is thought to reflux in to the oesophagus during the post-prandial period[4,5].

RB has undertaken this study to further understand the effect of Gaviscon® Double Action and Gaviscon® Advance on the acid pocket[3,5,6]. In this study, comparisons were made between the action of Gaviscon® Double Action, Gaviscon® Advance, and placebo liquid versus the untreated state. This study used a novel 11 electrode pH catheter to measure pH[5], coupled to an impedance catheter to simultaneously detect reflux events. The catheters were fastened together and then inserted nasogastrically with the aid of endoscopy. The catheter was attached to the squamocolumnar junction (SCJ) using haemostatic clips. Measurements were taken at various positions through the oesophagus and stomach following ingestion of a high fat meal.

The Food Standards Agency[7] class a high fat meal as one containing more than 30% total fat. National Health Services[8] guidelines recommend that males should eat no more than 30 g of saturated fat per day and females no more than 20 g of saturated fat per day. NHS guidelines also quantify high levels of saturated fat as more than 5 g of saturated fat per 100 g and low levels of saturated fat as 1.5 g or less per 100 g. In this study the high fat meal which was provided contained 30% total fat. An alternative option was provided for vegetarians but also contained the same level of total fat.

The results of this study were also to provide a basis for sample size calculation for future studies.

Each subject received 2 active products, a liquid placebo and was also assessed in the untreated state in this randomised crossover study.

As this was a new technique, a Validation Phase was performed prior to the Clinical Phase of the study, to assess reproducibility and acceptability of the technique.

Subjects in the Validation Phase of the study had 3 fluoroscopic assessments performed in order to confirm that the catheters maintained a consistent position during procedures. Fluoroscopic assessments with as many radiation dose-reducing features as feasible were performed. Full details of information relating to the level of radiation and associated risk to the subject were provided in the subject information and consent forms.

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 hydrogen carbonate/potassium hydrogen carbonate, and calcium carbonate) or any of the excipients (e.g. hydroxybenzoates [parabens]). Other adverse reactions include:

1. Sodium hydrogen carbonate/potassium hydrogen carbonate – increased plasma sodium or potassium 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.

The upper gastrointestinal endoscopy procedure, electrode insertion, positioning and clipping may be associated with risks including: bleeding, perforation of the oesophagus, stomach or duodenum, and reactions to any drugs administered as part of the procedure, such as local anaesthetics. The use of endoscopy for placement of the pH and impedance catheter was essential to enable accurate placement. Clipping to the SCJ was required to ensure movement of the catheter was limited and therefore that the data collected were accurate. The procedure was performed by a consultant gastroenterologist at either the Manchester Royal Infirmary or the Spire Manchester Hospital.

Subjects were not expected to derive any benefit from participation in the study, however through their participation in this study they helped RB to better understand the effect of Gaviscon® on the acid pocket and to assess the efficiency of this research technique; this in turn might potentially lead to more effective targeted treatment for heartburn.

The study was conducted in accordance with the Declaration of Helsinki, as referenced in EU Directive 2001/20/EC. It complied with ICH GCP and applicable regulatory requirements.

8 STUDY OBJECTIVES

The objectives of this study were to assess the formation of the acid pocket, following a high fat test meal and associated reflux episodes in subjects receiving no treatment and when dosed with Gaviscon® Advance Aniseed Liquid, Gaviscon® Double Action Aniseed Liquid or Placebo Aniseed Liquid.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan – Description

The study protocol and amendments are included as Appendix 16.1.1. The Case Report Form (CRF) is included as Appendix 16.1.2.

Prior to commencement of the Clinical Phase, a Validation Phase was performed to assess reproducibility of the method. In the Validation Phase, subjects were assessed in the untreated state on 2 occasions. This involved subjects undergoing catheter insertion followed by a 4-hour 15-minute data recording period. The catheter remained in place overnight and subjects remained in the clinical pharmacology unit (CPU). The following morning, data recording commenced as per the previous day.

Fluoroscopic studies were included in the Validation Phase of the study in order to demonstrate whether the ingestion of food caused the pH catheter's tethering to be dislodged and hence its migration over the course of the 2 days.

The Clinical Phase of the study was a single-centre, randomised, partially blind, 4-way crossover, placebo-controlled study to investigate the acid pocket via pH and impedance measurements. Subjects were assessed on 4 occasions over 2 visits, each visit with 2 overnight stays. During the treatment periods, subjects were assessed under each condition (i.e., treated with Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid or Placebo Aniseed Liquid, or were assessed in the untreated state), the sequence of treatment was allocated according to the randomisation schedule.

There was a minimum 5-day and a maximum 7-day wash-out period prior to the crossover treatment arm.

Follow-up was performed 3 to 7 days after the second dosing day in Treatment Period 2.

As this was a pilot study, no formal sample size calculation was performed because of the experimental nature of the study. Eight subjects were to be assessed in the Validation Phase. Sixteen subjects were considered to be sufficient to meet the objectives of the Clinical Phase of the study; therefore sufficient subjects were recruited and randomised to aim to have 24 subjects overall complete the study (8 subjects in the Validation Phase and 16 subjects in the Clinical Phase). Up to 2 subjects were assessed per day. Subjects who completed the Validation Phase were not permitted to participate in the Clinical Phase of the study.

The duration of each subject's participation in the Validation Phase of the study was approximately 3 weeks (from the screening visit to post-study follow-up visit). The duration of each subject's participation in the Clinical Phase of the study was approximately 4 weeks (from the screening visit to post-study follow-up visit).

The schedule of assessments is provided in Section 9.5.1 (Table 9-1 [Validation Phase], Table 9-2 [Clinical Phase: Treatment Period 1], and Table 9-3 [Clinical Phase: Treatment Period 2]).

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

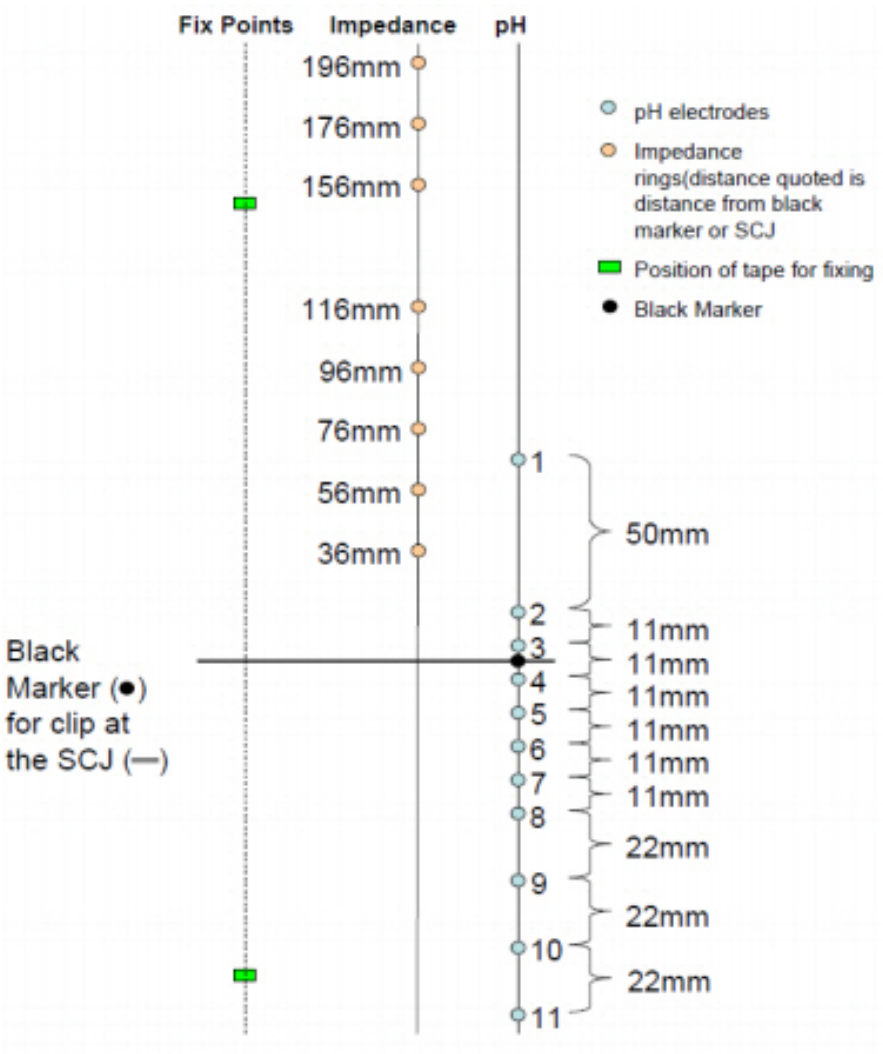
Gaviscon® Advance and Gaviscon® Double Action (Reckitt Benckiser Healthcare [UK] Ltd) are alginate-based formulations that rapidly form physical barriers on top of stomach contents in the form of floating gels, or rafts[9,10]. Gaviscon® Advance 10 ml has a minimal acid neutralising capacity of 6.0 mEq, whilst Gaviscon® Double Action 20 ml has an increased acid neutralising capacity of 18.1 mEq[9,10]. Kwiatek et al. demonstrated that Gaviscon® Double Action can eliminate, or displace, the acid pocket in symptomatic patients with gastro-oesophageal reflux disease 40 minutes after consuming a high fat meal[11].

This study used a novel multi-channel pH catheter[5] coupled to a ZAN-BS-01 non-perfused, single-use impedance probe to allow the continuous recording of pH at 11 sites (7 in the SCJ and cardia, 4 in the oesophagus) and measurement of reflux episodes in the oesophagus.

The study also assessed the acid pocket in the untreated and post-dose state with alginate products and a placebo to allow an insight into the effect of alginate products on the acid pocket and post-prandial reflux episodes.

A schematic of the pH and impedance probes is provided in Figure 9–1.

Figure 9–1 pH and Impedance Probe Specification



Abbreviations: SCJ = squamocolumnar junction

9.3 Selection of Study Population

Subjects were recruited from the ICON Development Solutions' volunteer database.

9.3.1 Inclusion Criteria

To be eligible for inclusion into this study, each subject had to fulfil the following criteria:

1) Male or female subjects aged ≥ 18 years, ≤ 50 years.
2) Subjects who used over-the-counter medication to treat for heartburn, typically at least twice a month for the previous 3 months.

3) Those whose cigarette consumption was < 6 per day and who were willing to abstain from smoking whilst at the CPU.
4) Willingness to consume the refluxogenic meal.
5) Otherwise healthy subjects, in the opinion of the Investigator.
6) Those who were willing to volunteer and provided written informed consent.

9.3.2 Exclusion Criteria

A subject was excluded from the study if they met any of the following criteria:

1) Those with a history of gastro-oesophageal reflux disease or reflux symptoms typically requiring self-medication with over-the-counter or prescription medication more than twice a week on an ongoing basis.
2) Those who had a history or active gastrointestinal disease (gastroduodenal ulcer, gastrointestinal haemorrhage, mechanical obstruction or perforation) within the last year.
3) Those who showed clinically significant allergic, pulmonary, neurological, renal, hepatic, cardiovascular, psychiatric, metabolic, endocrine, or haematological disease.
4) Those who were observed at screening to have a hiatus hernia with a diameter which exceeded 3 cm.
5) Those who had a history of basal skull fracture or who had undergone trans-sphenoidal surgery.
6) Those who had been hospitalised within the previous 3 months for major surgery or medical illness.
7) Those who had had a clinically significant illness within the previous 4 weeks.
8) Those who had taken any prescription medication or non-prescription medication (other than hormonal contraceptives) within 7 days, prior to the screening visit, which the Investigator considered might interfere with the study.
9) Those who had taken H_2 antagonists or motility stimulants in the 2 weeks prior to enrolment in the study and during the study.
10) Those who had taken proton pump inhibitors 4 weeks prior to enrolment into the study and during the study.
11) Any previous history of allergy or known intolerance to any of the study drugs or the formulation constituents.
12) Those who had a current or recent (1 year) history of alcohol abuse or abuse of any legal or illegal drugs, substances, solvents.
13) Those who consumed abnormal quantities of coffee, tea or cola (e.g. more than 6 cups) according to the Investigator's judgement.
14) Those who had taken part in any clinical study within the previous 3 months, or had taken part in a total of 4 or more studies in the last 12 months.

15) Those who were unable to communicate well with the Investigator (i.e. language problem, poor mental development or impaired cerebral function) in the opinion of the Investigator.
16) Those who had evidence of columnar lined oesophagus or any other significant abnormality in the opinion of the endoscopist and Investigator (as determined during the endoscopy procedure to place the catheter).
17) Woman of childbearing potential, who were pregnant or lactating, seeking pregnancy or failing to take adequate contraceptive precautions. Adequate contraceptive precautions included oral or injectable contraceptives, approved hormonal implants or topical patches, intrauterine devices; barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; true abstinence (true abstinence: when this was in line with the preferred and usual lifestyle of the subject. Periodic abstinence e.g., calendar, ovulation, symptothermal, post-ovulation methods and withdrawal were not acceptable methods of contraception. Should the subject become sexually active whilst participating in the study, she and her partner agreed to use a double barrier method or condoms/diaphragms with spermicidal foam/gel/film/cream/ suppository). Subjects were to be informed verbally that a female condom and male condom should not have been used together as friction between the 2 can result in either product failing. A woman of childbearing potential was defined as any female who was less than 2 years postmenopausal or who had not undergone a hysterectomy or surgical sterilisation, e.g. bilateral tubal ligation, bilateral ovariectomy (oophorectomy).
18) Those previously randomised into this study or those enrolled in the Validation Phase.
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 could withdraw a subject from the study at any time. Reasons for removing a subject from the study included, but were not limited to:

- Adverse events (AEs) that in the judgement of the Investigator could cause severe or permanent harm (significant clinical deterioration was considered an AE).
- Violation of the study protocol.
- In the Investigator's judgement, it was in the subject's best interest.
- Subject declined further study participation.

The primary reason for withdrawal was to be documented as one of the following: AEs; lost to follow-up; protocol violation; death or other. The Investigator was to make reasonable attempts to contact subjects who were lost to follow-up; a minimum of 2 documented telephone calls or a letter was considered reasonable.

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

- Vital signs (as for screening).
- Physical examination.
- Laboratory Investigations (as for screening with the exception that viral serology and urine drug screen were not necessary at follow-up).
- Review of concomitant medication and AEs.

9.4 Treatments

9.4.1 Treatments Administered

The following blinded medication was supplied:

Gaviscon® Double Action Aniseed Liquid in 300 ml bottles (PL 00063/0543) (Treatment A). Gaviscon® Advance Aniseed Liquid in 300 ml bottles (PL 00063/0097) (Treatment B). Placebo Aniseed Liquid in 150 ml bottles (Treatment C).

Supplies were provided to the ICON Pharmacy as bulk. Samples were dispensed, in amber syringes and labelled A or B or C, to study nurses to ensure that blind was maintained. The person administering the product was aware of the volume administered and hence was aware of which product was Gaviscon® Advance Aniseed Liquid. However, data collection in this study was automated and therefore it was not possible for an unblinded member of staff to influence the outcome of the study. The PI did not see the IMP prior to or during dosing and therefore remained blinded throughout the study.

9.4.2 Identity of Investigational Medicinal Product(s)

Gaviscon® Double Action Aniseed Liquid (300 ml; batch number: 128471) and Gaviscon® Advance Aniseed Liquid (300 ml; batch number: 223085) were manufactured to Good Manufacturing Practice (GMP) standards by Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS, UK.

The Placebo Aniseed Liquid (150 ml; batch number: PMBN12056) was manufactured to GMP standards by Pharmaterials Ltd, Unit B, 5 Bolton Road, Reading, RG2 0NH, UK for Reckitt Benckiser Healthcare (UK) Ltd.

All drug supplies were packed and labelled to GMP standards by the Investigational Material Supply Unit (IMSU), Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull HU8 7DS, UK. The Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid and Placebo Aniseed Liquid were supplied as double blind. Investigational medicinal product (IMP) was shipped directly from the Reckitt Benckiser Healthcare (UK) Ltd IMSU to ICON.

9.4.3 Method of Assigning Subjects to Treatment Groups

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

On entry into the Validation Phase, subjects were allocated a unique subject number in numerical sequence. A randomisation schedule for the Clinical Phase was produced by the RB statistician and provided to IMSU. Treatments were allocated so that subjects received Gaviscon® Double Action Aniseed Liquid and placebo within the same residential period. This was to account for potential minor variations in location of the probes due to the clipping procedure.

Subjects in the Clinical Phase of the study were randomised to one of the following 8 sequences:

Treatment Sequence	Treatment			
	Period 1		Period 2	
	Day 2	Day 3	Day 2	Day 3
ACBD	A	C	B	D
ACDB	A	C	D	B
CABD	C	A	B	D
CADB	C	A	D	B
BDAC	B	D	A	C
BDCA	B	D	C	A
DBAC	D	B	A	C
DBCA	D	B	C	A

Treatment A: Gaviscon® Double Action Aniseed Liquid (20 ml)
Treatment B: Gaviscon® Advance Aniseed Liquid (10 ml)
Treatment C: Placebo Aniseed Liquid (20 ml)
Treatment D: Untreated state

9.4.4 Selection of Doses in the Study

Subjects received one single oral dose of 10 ml suspension of Gaviscon® Advance Aniseed Liquid, 20 ml of Gaviscon® Double Action Aniseed Liquid or 20 ml of placebo or remained untreated as defined in the randomisation schedule. Dosing occurred on Day 2 and Day 3 of Treatment Period 1 and on Day 2 and Day 3 of Treatment Period 2. Dosing took place under the supervision of ICON staff.

9.4.5 Selection and Timing of Dose for Each Subject

On the morning of Day 2 of each treatment period of the Clinical Phase, fasted subjects had the pH catheter inserted under endoscopic guidance. A minimum of 30 minutes after catheter insertion, baseline pH monitoring commenced for 30 minutes to enable the pH readings to stabilise and a baseline dataset to be produced. Following implementation of non-substantial protocol amendment No. 5, dated 27 Mar 2013, up to 5 minutes of additional recording was permitted. Subjects were then dosed with either Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid or Placebo Aniseed Liquid (as defined in the randomisation schedule) and pH was monitored for 4 hours. Subjects were required to fast from approximately 22:00 on Day 1. The fasting period lasted approximately 12 to 14 hours (including sleep time). There were operational issues in this study resulting in significant deviations in the timing of data collection (see Section 10.2 for details).

9.4.6 Blinding

Blinding of the study was maintained as follows: subjects were administered either 10 ml or 20 ml study treatment or placebo as indicated by the randomisation schedule. Subjects were not informed of which medication was administered as 10 ml or 20 ml. The person administering the product was aware of the volume administered and hence was aware of which product was Gaviscon® Advance Aniseed Liquid. However, data collection in this study was automated and therefore it was not possible for an unblinded member of staff to influence the outcome of the study. The PI did not see the IMP prior to or during dosing and therefore remained blinded throughout the study.

On entry into the Validation Phase, subjects were allocated a unique subject number in numerical sequence. A separate randomisation schedule was provided by the statistician for the Clinical Phase, those subjects in this phase were issued drug in the sequence defined in the randomisation schedule.

Treatments were allocated so that subjects received Gaviscon® Double Action Aniseed Liquid and Placebo Aniseed Liquid within the same residential period. This was to account for potential minor variations in location of the probes due to the clipping procedure.

The IMP was labelled in accordance with EudraLex - Volume 4 GMP guidelines, Annex 13 - Manufacture of IMP, parts 26 to 33 (labelling) and in accordance with EU Directive 2003/94/EC as amended and including any other applicable national/state legislation.

The RB IMSU held the master code for the randomisation schedule and supplied the Investigator (via the ICON Pharmacy department) with the randomisation code for each subject as sealed envelopes. The code was only to be broken for an individual subject in an emergency such as a serious adverse event (SAE) that required knowledge of what study treatment was taken in order that the SAE could be treated appropriately.

The study monitor checked the randomisation codes on a regular basis at monitoring visits, to ensure the above procedures were being followed at the study site. All codes, whether sealed or opened, were returned to RB at the end of the study.

9.4.7 Prior and Concomitant Therapy

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

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

The use of the following treatments was not permitted:

Subjects were asked to withhold any medication that affected gastric acid secretion prior to and during monitoring (see also Section 9.3.2).

- H_2 antagonists or motility stimulants 2 weeks prior to enrolment in the study and during the study.
- Proton pump inhibitors 4 weeks prior to enrolment into the study and during the study.

If concomitant medication was taken the Investigator decided whether the subject should remain in the study or be withdrawn.

In addition, no drinking or eating, including caffeine-containing food and drinks were allowed other than what was provided by ICON during the Validation Phase and Clinical Phase. No alcohol was allowed 48 hours prior to each visit and the treatment visits. In addition, smoking was not permitted during each visit, nicotine replacement patches were not permitted during the study. Female subjects taking hormonal contraceptives were asked to continue.

9.4.8 Treatment Compliance

Study treatment was taken by the subject under supervision of appropriately trained ICON staff who conducted a mouth inspection to ensure compliance with dosing. Any subjects who did not take the study treatment as required were to be withdrawn from the study.

9.5 Study Variables and Methods of Assessment

9.5.1 Measurements Assessed and Schedule

The schedule of assessments for the Validation Phase is presented in Table 9-1.

Table 9-1 Schedule of Assessments: Validation Phase

Study Period	Screening (up to 28 days prior to admission to the CPU)	Admission to the CPU Treatment Period 1: Day 1	Treatment Period 1: Day 2	Treatment Period 1: Day 3	Follow-up
Informed consent	X				
Demography	X				
Medical history	X				
Concomitant medication	X	X	X		
Vital signs	X	X		X	X
Physical examination	X				X
Alcohol and drugs of abuse test	X	X			
Pregnancy test (women only)	X	X			
Laboratory analysis	X				X
Eligibility decision/confirmation	X		X		
HiRM assessment	X				
Insertion of pH and impedance catheters			X		
Fluoroscopy assessment			X	X	
pH and impedance recordings			X	X	
Refluxogenic meal			X	X	
Removal of pH and impedance catheters				X	
Adverse events recorded		X	X	X	X

Abbreviations: CPU = clinical pharmacology unit; HiRM = High Resolution Manometry

The schedule of assessments for the Clinical Phase (Treatment Period 1) is presented in Table 9-2.

Table 9-2 Schedule of Assessments: Clinical Phase (Treatment Period 1)

Study Period	Screening (up to 28 days prior to admission to the CPU)	Admission to the CPU Treatment Period 1: Day 1	Treatment Period 1: Day 2	Treatment Period 1: Day 3	Wash-out period (minimum of 5 days following previous visit)
Informed consent	X				
Demography	X				
Medical history	X				
Concomitant medication	X	X	X		
Vital signs	X	X		X	
Physical examination	X				
Alcohol and drugs of abuse test	X	X			
Pregnancy test (women only)	X	X			
Laboratory analysis	X				
Eligibility decision/confirmation	X		X		
HiRM assessment	X				
Insertion of pH and impedance catheters			X		
pH and impedance recordings			X	X	
Refluxogenic meal			X	X	
Dosing			X	X	
Removal of pH and impedance catheters				X	
Adverse events recorded		X	X	X	X

Abbreviations: CPU = clinical pharmacology unit; HiRM = High Resolution Manometry

Following a minimum of a 5-day wash-out period, subjects returned to the CPU for Treatment Period 2.

The schedule of assessments for the Clinical Phase (Treatment Period 2) is presented in Table 9-3.

Table 9-3 Schedule of Assessments: Clinical Phase (Treatment Period 2)

Study Period	Admission to the CPU Treatment Period 2: Day 1	Treatment Period 2: Day 2	Treatment Period 2: Day 3	Follow-up (3 to 7 days following previous visit)
Informed consent				
Demography				
Medical history				
Concomitant medication	X	X		X
Vital signs	X		X	X
Physical examination				X
Alcohol and drugs of abuse test	X			
Pregnancy test (women only)	X			
Laboratory analysis				X
Eligibility decision/confirmation	X			
Insertion of pH and impedance catheters		X		
pH and impedance recordings		X	X	
Refluxogenic meal		X	X	
Dosing		X	X	
Removal of pH and impedance catheters			X	
Adverse events recorded	X	X	X	X

Abbreviations: CPU = clinical pharmacology unit

The pH and impedance and safety variables, and their methods of assessment, are described in Sections 9.5.3 and 9.5.4, respectively.

9.5.2 Baseline Assessments

9.5.2.1 Overview of Baseline Assessments

The following demographic assessments were determined:

- Sex.
- Race (categorised as: Caucasian, Asian, Afro-Caribbean and Other).
- Date of birth.
- Height (cm).

- Weight (kg).
- Body mass index (kg/m^2).
- Smoking/alcohol/drugs of abuse history/use.
- Medical history and current status:
    - Primary diagnosis.
    - Duration of disease.
    - Medical history and current status.
- Medication and therapy history:
    - Current medication usage.
    - Therapy taken in the previous 28 days was recorded (as per the exclusion requirements in Section 9.3.2, subjects who had taken proton pump inhibitors in the previous 4 weeks were excluded).

The following baseline assessments were performed:

- Vital Signs:
    - Blood pressure (after sitting for 5 minutes with both feet flat on the floor; mmHg).
    - Heart rate (recorded using the blood pressure monitor, bpm).
    - Oral temperature (ºC).
- Physical examination:
    - Standard physical examination.
- Pregnancy testing:
    - Women of childbearing potential underwent urine pregnancy testing.

Subjects who were otherwise eligible visited the Gastrointestinal Investigation Unit of Manchester Royal Infirmary. High resolution manometry (HiRM) was used to assess for the presence or absence of hiatus hernia. Xylocaine spray was available for use if required for the comfort of the subject. The data produced from the HiRM were sent to a RB appointed consultant for review and analysis. The presence or absence of a hiatus hernia was recorded in the subject's CRF. For those found to have a hiatus hernia, size was documented. Subjects were excluded from the study if the hiatus hernia exceeded 3 cm in size.

Safety-related baseline assessments are described in Section 9.5.4.

9.5.2.2 Methods of Baseline Assessment

Standard methods at the study site(s) were used for evaluating subject baseline assessments. Assessments described in Section 9.5.2.1 were conducted at the ICON CPU.

9.5.3 PH and Impedance Variables

9.5.3.1 Overview of pH and Impedance Variables

Oesophageal and intragastric pH monitoring was performed using a high definition 11 electrode pH catheter (custom made by Sandhill Scientific, Inc) and recorded using the Insight device from Sandhill. A new pH catheter was used per subject to record pH 4 times. Each pH catheter was used on 2 occasions for the same subject and clipped at the SCJ using a single clip on each occasion. In between uses, the catheter was cleaned as per the ICON instruction manual using disinfectant wipes.

The pH catheter was calibrated prior to each insertion procedure. The probe was first immersed in pH 4 buffer solution for 3 to 4 minutes, rinsed with water then immersed in pH 7 buffer solution for 3 to 4 minutes. Calibration data were then recorded by completing the following steps: The probe was immersed in pH 7 buffer for 4 minutes and subsequently recorded for 1 minute. The probe was then rinsed and immersed in the pH 4 buffer for 3 minutes, followed by 1 minute of recording. It was then removed and rinsed again and placed in pH 1 for 3 minutes followed by 1 minute of recording. Once rinsed, the probe was placed in the appropriate container to be taken to the Gastroscopy Unit where placement was performed. At the end of the study, the pH catheter was removed and this step (pH 7, followed by pH 4, followed by pH 1) repeated to see how much drift has occurred.

Impedance monitoring was performed using a ZAN-BS-01, non-perfused single-use catheter.

Following a 30-minute period of baseline recording, subjects were provided with a standardised high fat meal.

Clinical Phase

During the Clinical Phase, 15 minutes after completion of the meal, subjects were dosed with Gaviscon® Double Action Aniseed Liquid (20 ml), Gaviscon® Advance Aniseed Liquid (10 ml), Placebo Aniseed Liquid (20 ml) or remained untreated as defined in the randomisation schedule.

Validation Phase

For subjects in the Validation Phase or randomised to an untreated group in the Clinical Phase, changes in oesophageal and intragastric pH were continuously measured over a 4-hour 15-minute period using the pH catheter. For subjects who received one of the 3 test products (as defined in the randomisation schedule), changes in oesophageal and intragastric pH were continuously measured immediately after dosing over a 4-hour period using the pH catheter. Data were stored on a compact flash card and were downloaded onto a CPU computer.

For the Validation Phase, at the end of recording, subjects were then escorted to Manchester Royal Infirmary Radiology Department, to have a fluoroscopic procedure performed, to confirm that the catheter had not moved significantly during the study. On completion of the data monitoring period (Day 3 of each treatment period), the catheters were disconnected from the recording device and removed.

The Investigator compared the reports of the fluoroscopic studies performed before and after pH monitoring and noted any significant changes in the subject's CRF.

The pH and impedance endpoints assessed during the study are provided in Section 9.5.10.

9.5.3.2 Methods of pH and Impedance Assessment

9.5.3.2.1 Catheter Insertion

On Day 2 (of each treatment period), following confirmation of negative test results for the alcohol, drugs of abuse and pregnancy tests, subjects were asked whether they had experienced any symptoms or complaints and were instructed to inform the Investigator during the treatment visit if they suffered any AEs or used any concomitant medication.

Subjects were escorted the short walking distance to the endoscopy suite at the appropriate hospital, by ICON nursing staff, where the pH and impedance catheter was inserted nasogastrically and positioned by a consultant gastroenterologist under endoscopic guidance.

Xylocaine throat spray was available for use if required for comfort.

A loop, which was pre-attached to both the nasogastric pH and impedance catheters, was fixed distal to the SCJ using standard haemostatic metal clips (HX-600-090, Olympus or similar) deployed by an endoscopic clip-fixing device (HX-5LR-1, Olympus or similar). The pH probe was placed so that 3 electrodes recorded pH proximal to the SCJ and 8 electrodes recorded pH distal to the SCJ. Catheters were positioned so that electrode 1 was 5 cm above the SCJ (i.e., in the middle of the lower oesophageal sphincter [LOS]) - electrodes 2 and 3 sat within the LOS.

Following the procedure, the endoscope was removed. The subjects in the Validation Phase then had a fluoroscopic assessment of the upper abdomen performed to demonstrate the position of the catheter. This involved the same procedure as a traditional dynamic X-ray but with the addition of a fluorescent screen between the subject and the instrument. Upon completion of the fluoroscopic assessment, subjects returned to the CPU accompanied by ICON nursing staff.

Prior to commencement of baseline data collection, subjects were allowed to rest for 30 minutes, in a sitting position (up to 5 minutes of additional recording was permitted). This period enabled readings to stabilise. During collection of data, subjects were required to remain seated at approximately 60 degrees. This position was standardised throughout and was therefore the same for all recording periods. After returning to the CPU, baseline readings were performed continuously over a period of 30 minutes (up to 5 minutes of additional recording was permitted).

Following the 30-minute (up to 5 minutes of additional recording was permitted [see protocol amendment, dated 27 Mar 2013, Appendix 16.1.1]) period of baseline data recording, a marker was placed on the recording trace to identify the end of the baseline period. For subjects in the Validation Phase of the study, data recording was halted whilst subjects consumed a high fat meal, and data recording resumed immediately after completion of the meal and continued for 4 hours 15 minutes. For subjects in the Clinical Phase of the study, data continued to be recorded (see protocol amendment, dated 10 Jan 2013, Appendix 16.1.1). Subjects were provided with a standardised high fat meal of a medium McDonalds Quarter Pounder with cheese meal (including fries) which contained 5.17 g/100 g of saturated fat and 820 calories. A pre-defined amount of food was provided to all subjects. To account for differences in subject size and sex, meals were weighed before and after eating, subjects were instructed to complete the meal, or if not possible, to eat until full.

Following completion of the meal, a marker was placed on the tracing to indicate the start of the post-meal recording period. pH and impedance data recording (continued throughout the consumption of the meal and then [see protocol amendment, dated 10 Jan 2013, Appendix 16.1.1]) for a period of 4 hours 15 minutes during the Validation Phase and for 4 hours during the Clinical Phase.

Fifteen minutes after completion of the meal, subjects in the Clinical Phase were dosed with Gaviscon® Double Action Aniseed Liquid (20 ml), Gaviscon® Advance Aniseed Liquid (10 ml), Placebo Aniseed Liquid (20 ml) or remained untreated as defined in the randomisation schedule.

9.5.4 Safety Variables

9.5.4.1 Overview of Safety Variables

Safety was assessed on the basis of the following variables:

- AEs.
- Clinical laboratory investigations.
- Vital signs.
- Physical examinations.

9.5.4.2 Methods of Safety Assessment

Methods of safety assessment are discussed for AEs (Section 9.5.5), clinical laboratory investigations (Section 9.5.6), vital signs (Section 9.5.7) and physical examinations (Section 9.5.8).

9.5.5 Adverse Events

During the Validation Phase no study treatment was administered, however adverse device events (ADEs) were still recorded in order to monitor any untoward medical occurrence associated with catheter insertion and clipping.

An AE was defined as any untoward medical occurrence in a patient or clinical study subject administered a medicinal product or medical device and which did not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

An adverse reaction (AR) to an IMP was defined as all untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting Investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualified as ARs. The expression reasonable causal relationship meant to convey in general that there was evidence or argument to suggest causal relationship.

ADEs were defined as any untoward and unintended response to a medical device. This definition included any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device, the operation, or any malfunction of the investigational medical device, or any event that was a result of a user error.

Device deficiencies included malfunctions, misuse or user errors, labelling errors that did or could have led to an AE or ADE irrespective of whether the device was used or not.

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling.

SAEs were defined as any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect. Life-threatening in the definition of an SAE or serious AR referred to an event in which the subject was at risk of death at the time of the event; it did not refer to an event which hypothetically might have caused death if it were more severe.

Serious ADE (SADE) was defined as an ADE that resulted in any of the consequences characteristic of an SAE or that might have led to death or a serious deterioration in the health of a subject or any other person if suitable action had not been taken. The definition of SADE included incidents and near incidents.

Any untoward medical events that occurred after informed consent, but prior to administration of study treatment were recorded in the subject's medical history and were not reported as an AE. All AEs/ADEs that occurred after the subject had received study treatment were recorded in the subject's CRF. AEs/ADEs were reported spontaneously by the subject or in response to questioning or observation by the Investigator or were a significant laboratory abnormality.

The PI or designee asked the subject: "Are you experiencing any symptoms or complaints?" at the baseline visit and "Have you had any symptoms or complaints since the last visit?" during the study.

AEs/ADEs were recorded according to the criteria given in Table 9-4. Relationship to study treatment was determined by the Investigator.

Assessments of the relationship of AEs/ADEs to study treatment were made by the Investigator.

Table 9-4 Rating Systems Used to Determine Adverse Event/Adverse Device Event Intensity and Relationship to IMP

Variable	Category	Definition
Intensity		Intensity was determined by the Investigator. For symptomatic AEs/ADEs the following definitions were applied, but medical experience and judgement were also to be used in the assessment of intensity.
	Mild	The AE/ADE did not limit usual activities; the subject may have experienced slight discomfort.
	Moderate	The AE/ADE resulted in some limitation of usual activities; the subject may have experienced significant discomfort.
	Severe	The AE/ADE resulted in an inability to carry out usual activities; the subject may have experienced intolerable discomfort or pain.
Relationship to study treatment or device	Definite	An AE/ADE that followed an anticipated response to the study treatment; and that was confirmed by both improvement upon stopping the study treatment (dechallenge), and reappearance of the reaction on repeated exposure (rechallenge). Strong evidence existed that the investigational device caused the AE. There was a temporal relationship between the event onset and administration of the investigational device. There was strong mechanistic evidence that the event was caused by the investigational device. The subject's clinical state and concomitant therapies had been ruled out as a cause.
	Probable	An AE/ADE that followed a reasonable temporal sequence from administration of the study treatment, that was an anticipated response to the study treatment; and that could not be reasonably explained by the known characteristics of the subject's clinical state or concomitant therapy. A temporal relationship existed between the event onset and administration of investigational device, and appeared with some degree of certainty to be related based on known mechanism of action of the device. It cannot be readily explained by the subject's clinical state or concomitant therapies.

Table 9-4 Rating Systems used to Determine Adverse Event/Adverse Device Event Intensity and Relationship to IMP

Variable	Category	Definition
Relationship to study treatment or device	Possible	An AE/ADE that followed a reasonable temporal sequence from administration of the study treatments; that may be an anticipated response to the study treatment; but that could have been produced by the subject's clinical state or concomitant therapy. A temporal relationship existed between the event onset and administration of investigational device. Although the ADE appeared unlikely to be related to the investigational device, it cannot be ruled out with certainty; and or the event cannot be readily explained by the subject's clinical state or concomitant therapies.
	Unlikely	An AE/ADE that did not follow an anticipated response to the study treatment or device; which may be attributable to other than the study treatment or device, and that was more likely to have been produced by the subject's clinical state or concomitant therapy.
Relationship to study treatment or device	None	An AE/ADE that was known beyond all reasonable doubt to be caused by the subject's state or concomitant therapy. Evidence existed that the AE/ADE definitely had a cause other than the investigational device (e.g. pre-existing condition or underlying disease, intercurrent illness, or concomitant medication) and did not meet any other criteria listed.

The procedures for reporting AEs/ADEs and SAEs/SADEs are described in Sections 13.1.3 to 13.1.5 of the protocol and procedures for subjects who experienced onset of AEs after completion of the study are detailed in Section 13.1.6 of the protocol (Appendix 16.1.1).

All SAEs/SADEs, and all AEs/ADEs which caused premature withdrawal of the subject from the study, that had not resolved by the end of the study, were followed up by the Investigator until resolution or until the Investigator believed there was no further change. This could have involved the subject making additional visits to the CPU. All other AEs (including clinically significant laboratory abnormalities) were followed up wherever possible to resolution or until the Investigator believed there was no further change, whichever was the earlier.

9.5.6 Clinical Laboratory Investigations

Samples for haematology, biochemistry and urinalysis assessments were collected at screening and follow-up. Alcohol, drugs of abuse tests and pregnancy tests were performed at screening and on Day 1 of each treatment period.

The following haematology, biochemistry and urinalysis parameters were assessed:

Haematology

- Haemoglobin (g/L).
- Red blood cell count (10^{12}/L).
- White blood cells (10^{9}/L).
- Platelets (10^{9}/L).
- Differential white cell count (10^{9}/L), neutrophils, lymphocytes, monocytes, basophils and eosinophils.

Biochemistry

- Blood urea nitrogen (mmol/L).
- Creatinine (µmol/L).
- Alanine transaminase (ALT) (IU/L or U/L).
- Aspartate transaminase (AST) (IU/L or U/L).

Urinalysis

- Blood (positive or negative).
- Protein (positive or negative).
- Urine pregnancy test for females of childbearing potential.
- Drugs of abuse (positive or negative for: opiates, amphetamine, cannabinoids, cocaine, barbiturates, benzodiazepines, methadone).

Blood samples were collected and labelled in tubes provided by the ICON Clinical Pathology laboratory. Urine samples were collected and labelled in containers, provided by the CPU, at the screening as well as treatment visits. ICON's standard labelling was used.

The laboratory conducting the analysis in this study was accredited by the United Kingdom Accreditation Service and provided documented evidence of suitable accreditation for the laboratory to conduct testing. The Investigator reviewed the results and commented, on the laboratory results sheet, on all abnormal values, identifying those that were clinically significantly abnormal. The Investigator signed and dated the laboratory results sheet, to indicate that the review had taken place.

9.5.7 Vital Signs

Standard methods at the CPU were used for evaluating vital signs. Vital signs (systolic blood pressure, diastolic blood pressure, heart rate and oral temperature) were measured at screening, on admission to the CPU, on Day 3 and follow-up.

9.5.8 Physical Examinations

A standard physical examination (general appearance, ears, nose and throat, neck and thyroid, eyes, heart, lungs, abdomen, extremities, dermatological and neurological) was performed at screening and follow-up.

9.5.9 Appropriateness of Measurements

Although assessment of pH is a standard method for the measurement of antacid effects, this study used a novel catheter containing 11 pH electrodes. More details of the catheter are provided in Appendix 1 of the study protocol (Appendix 16.1.1).

However, due to the high number of minor protocol deviations occurring during the clinical phase, RB decided to hold an additional data review meeting (following database lock and after the study had been unblinded) which included 2 key experts in the area of Gastroenterology to assess the appropriateness of measurements taken (see additional RB data analysis report).

9.5.10 PH and Impedance Variables

PH and Impedance was assessed on the basis of the following variables:

Primary pH and impedance variable:

- The primary endpoint was the percentage of time that the electrode 5 cm above the SCJ was pH < 4 over a period of 2 hours following treatment with Gaviscon® Double Action Aniseed Liquid versus Placebo Aniseed Liquid.

Secondary pH and impedance variables:

pH change:

- Percentage of time that the electrode 5 cm above the SCJ was pH < 4 over a period of 2 hours following treatment with Gaviscon® Double Action Aniseed Liquid versus the untreated state.
- Percentage of time that the electrode 5 cm above the SCJ was pH < 4 over a period of 4 hours following treatment with Gaviscon® Double Action Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.
- Percentage of time that the electrode 5 cm above the SCJ was pH < 4 over a period of 2 hours following treatment with Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.
- Percentage of time that the electrode 5 cm above the SCJ was pH < 4 over a period of 4 hours following treatment with Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.
- Percentage of time that each electrode was pH ≤ 4 at 15, 30, 45, 60, 75 and 90 minutes following ingestion of each test product at electrodes 4 to 11 inclusive.
- Mean percentage of time with pH < 4 at electrodes 1, 2 and 3 during each of the four 1-hour periods for Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.
- Mean percentage of time with pH < 4 at electrodes 1, 2 and 3 during the 4-hour period for Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.
- Mean percentage of time with pH < 4 at the electrodes within the cardia (electrodes 4 to 7) during each of the four 1-hour periods for Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.

Reflux events as identified with impedance monitoring:

- Total number of (i) liquid, (ii) gas and (iii) mixed reflux episodes occurring in the 2- and 4-hour period following ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.

- Total number of (i) acid and (ii) weakly acidic reflux episodes occurring in the 2- and 4-hour period following ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.

- Number of reflux episodes reaching 15 cm above the LOS during the 2- and 4-hour period following ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.

- Oesophageal bolus exposure to reflux (percentage time with liquid or mixed reflux within the oesophageal lumen) for each test product versus the untreated state during the 2- and 4-hour period following ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the untreated state.

9.5.11 Drug Concentration Measurements

Drug concentrations were not measured in this study.

9.6 Data Quality Assurance

The Investigator was responsible for the quality of the data recorded in the CRF. The data recorded were to be a complete and accurate account of the subject's record collected during the study. The Investigator and study monitor identified any data that were recorded directly on the CRF such that the CRF was considered the source document (i.e. no prior written or electronic record of the data). The study monitor documented this in the signed Source Data Verification (SDV) Plan.

The Investigator reviewed all entries for completeness and correctness. When changes or corrections were made on any CRF, the Investigator or authorised persons drew a single line through the error then initialled and dated the correction, as well as stating the reason for the error, except when due to a transcription error. The original entry was not to be obscured.

The Investigator completed and signed the CRFs in a timely fashion after completion of each subject and made them available to the study monitor for full inspection. In addition, any data queries prepared after the original CRF had been completed were answered promptly. Before acceptance, the study monitor reviewed the CRFs for completeness and adherence to the protocol.

On-site monitoring also included SDV. SDV is the procedure whereby the data contained in the CRFs are compared with the primary source data (e.g. patient notes, original recordings from automated instruments, X-ray films, electrocardiogram tracings, and laboratory results) contained in the subject records held at the investigational site, and thereby verified as accurate.

Data management was performed by ICON Development Solutions in accordance with internal Standard Operating Procedures (SOPs). The ICON Development Solutions data management system in SAS® (Version 9.1.3) was used to database study data necessary for the preparation of the final clinical study report[12]. A study-specific database specification document was produced and the study database set-up validated and approved ready for data entry by the director of data management. A validation plan was also produced that detailed what electronic checks were performed. Data were entered using double data entry, followed by electronic compare and validation. SAS programs were used to manipulate the data into the correct format for summarising and listing in Rich Text File (rtf) tables and listings.

ICON Development Solutions' activities were audited on both a study-specific and system basis. A risk assessment was conducted for this study to focus quality assurance (QA) activity appropriately. A study-specific QA audit program was developed for this study and involved the observation of study procedures and data collection, and the confirmation of accuracy of the final report to raw data. For all audits, comparison to national or international regulatory standards, SOPs and the study protocol was involved.

Audits were documented in a report, discussed with managers and actions closely followed up. Work not conducted at ICON Development Solutions that was subcontracted by ICON was not audited by the QA department, unless explicitly arranged in the contract.

The clinical study report was subject to a GCP compliance audit, conducted by ICON QA. The audit certificates are provided in Appendix 16.1.8.

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

9.7.1 Statistical and Analytical Plans

Details of the statistical analyses are described in the final statistical analysis plan (SAP), which was approved before database lock on 23 Aug 2013. Inconsistencies were found between the database and the deviation log (see Appendix 16.2, Section 16.2.2). The database was opened on 09 Oct 2013 to add the additional comments and comments pages containing the missing protocol deviations, and was re-locked on 14 Oct 2013. A copy of the final SAP is available in Appendix 16.1.9. Changes in the planned analyses between the study protocol and the SAP are described in Section 9.8.2.

9.7.1.1 General

All statistical analyses were performed using SAS® (Version 9.1.3). Unless otherwise specified, descriptive data summaries of continuous outcomes included number of subjects with observations (n), mean, standard deviation (SD), median, minimum, maximum and coefficient of variation (CV%). CV% was not presented for change from baseline data. Categorical outcomes are summarised by number and percent of subjects.

All hypothesis tests were performed using the 5% significance level unless otherwise specified. As this was an exploratory study, no adjustments for multiple comparisons were made.

All clinical data collected in CRFs are listed including data not presented in tables. As appropriate, missing values were marked and explained in individual data tables.

Missing data were not imputed and all analyses were based on observed cases. No subgroup analysis was planned.

9.7.1.2 Study Populations

All subjects population: all subjects recruited on to the study were included in the all subjects population for presentation of information on subject disposition, withdrawals and protocol deviations.

Safety population: all subjects who were recruited on to the study and took part in the Clinical Phase or were subjected to any invasive study procedure were included in the safety population. This population was used for safety analyses and demographics.

Intention to treat (ITT) population: all subjects who were recruited on to the study and took part in the Clinical Phase and had any pH data were included in the ITT population.

Per protocol (PP) population: all subjects who were recruited on to the study, met the requirements of the ITT population, had adequate treatment compliance (where appropriate) and no major protocol deviations were included in the PP population. Exclusions from this population were decided during a blind data review meeting prior to database lock. This population was used for additional analysis of pH and impedance endpoints.

Unless otherwise specified, listings were produced for all subjects, including those from the Validation Phase.

9.7.1.3 Baseline, Screening and Compliance with Study Procedures

The following demographic data are listed and summarised descriptively:

- Age (in years, at time of signing informed consent).
- Sex.
- Race (categorised as: Caucasian, Asian, Afro-Caribbean and Other).
- Height (cm).
- Weight (kg).
- Body mass index (kg/m^2).

Past and current medical history was coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 15.0 and listed for the safety population[13].

Summaries of analysis populations, subject disposition and the number of subjects on study at each visit are provided. These data summaries are presented by study phase and contain the following information:

- Number of subjects randomised.
- Number and percent of subjects who received each treatment.
- Number and percent of subjects who completed the treatment, number and percent of subjects who completed the study.

- Number and percent of subjects who discontinued early and reason for early discontinuation.
- Number and percent of subjects in the all subjects, safety and PP analysis populations.
- Number and percent of subjects at each visit.

Excluded subjects are documented, together with the reason for exclusion.

All major protocol deviations that had an effect on the analysis populations are listed by subject, if applicable.

9.7.1.4 Analysis of pH and Impedance Data

9.7.1.4.1 Analysis of pH and Reflux Data

Subject pH levels at each electrode are available in SAS datasets. The calculated percentage of time endpoints described are listed. Results from the impedance monitoring (worksheet only) are listed.

The pH and impedance endpoints described in Section 9.5.10 are listed and summarised descriptively.

All hypothesis tests were performed using the 5% significance level. As this was an exploratory study, no adjustments were made for multiple comparisons.

Analyses of pH and reflux (impedance) data were performed using the ITT population and, if necessary, the PP population.

As a result of the high number of negative readings being observed upon review of pH measurements, ICON requested Synmed and Sandhill Scientific to conduct a review of pH data recorded during the Validation and Clinical Phases of the study. This was completed by Chris Blyth (Managing Director, Synmed Ltd) and Tom Stuebe (VP, Technology Development, Sandhill Scientific, Inc.).

The main issues noted during the review were temperature compensation not being applied (user error), power loss (due to the computer being turned off in error) and calibration data not corresponding exactly to pH values recorded at the start of the recording (pH values had not stabilized during the initial calibration).

Tom Stuebe performed repairs to the affected pH data files. These are outlined in the Note to File in Appendix 16.1.1.

The pH data repairs resulted in changes in the numbers of acid and weakly acid reflux episodes in a small number of subjects and are also summarised in a Note to File in Appendix 16.1.1.

9.7.1.5 Statistical Analysis of pH and Impedance Endpoints

9.7.1.5.1 Primary pH and Impedance Analysis

For the primary endpoint, the contrast between treatments was compared using an analysis of variance (ANOVA) model, incorporating all treatments and including fixed effects for baseline (the parameter calculated over the last 30 minutes of the defined baseline period), treatment, treatment period (1 or 2) and treatment day (2 or 3) and a random effect for subject. The difference between Gaviscon® Double Action Aniseed Liquid and Placebo Aniseed Liquid was estimated from this model using least squares means (LS means), and is presented along with the 95% confidence interval (CI) for this estimate.

9.7.1.5.2 Secondary pH and Impedance Analysis

For each secondary endpoint, the relevant contrasts between treatments were compared using an ANOVA model incorporating all treatments and including fixed effects for baseline (the parameter calculated over the last 30 minutes of the defined baseline period), treatment, treatment period (1 or 2), treatment day (2 or 3) and a random effect for subject. The difference between Gaviscon® Double Action Aniseed Liquid or Gaviscon® Advance Aniseed Liquid and Placebo Aniseed Liquid or the untreated state was estimated from this model using LS means, and presented along with the 95% CI for the estimate.

9.7.1.5.3 Exploratory pH and Impedance Analyses

As an exploratory analysis, 2 separate models were fitted as for the primary analysis with added interaction terms for, firstly, treatment by treatment period and, secondly, treatment by treatment day. The estimates for the Gaviscon® Double Action Aniseed Liquid versus Placebo Aniseed Liquid were presented overall and by treatment period (or treatment day) and the p-values for each model term also presented. This analysis was performed using both populations.

Results from further exploratory analyses of the data are not reported within this clinical study report.

9.7.1.6 Analysis of Safety Data

Unless otherwise specified, repeated measurements and unscheduled assessments are included in the data listings but are not included in data summaries.

9.7.1.6.1 Adverse Events

All AEs and ADEs recorded on the CRF during the study were coded to system organ class (SOC) and preferred terms (PT) using MedDRA, Version 15.0.

All AEs were classified as treatment-emergent (TEAE) if the AE was not present prior to administration of study treatment in the first study period of the Clinical Phase and started at or after the time of the first administration of study treatment, or if the AE presented prior to first administration of study treatment, continued, and increased in intensity after administration of study treatment.

TEAEs were allocated to the last treatment received (Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid or Placebo Aniseed Liquid), or else were classified as an ADE.

AEs occurring whilst the subject had been randomised to the untreated state were classified as either emergent to the previous treatment or, if prior to Day 3 of Period 1, as an ADE.

TEAEs are listed by treatment. These listings detail the MedDRA SOC and PT, CRF description, onset and resolution dates and times, duration of AE, time of onset relative to last dose of study treatment, intensity, outcome, serious or not serious including serious criteria, relationship to study treatment and any action taken.

TEAEs are summarised and tabulated by treatment, giving intensity and causal relationship to study treatment. Any SAEs, AEs with outcome of death and AEs that resulted in discontinuation of treatment were to be listed separately.

The overall incidence of TEAEs (number and percentage of subjects) as well as the number of events are summarised by study treatment and overall, categories of degree of intensity, SAEs, causally related TEAEs and SAEs, TEAEs leading to discontinuation of treatment, life-threatening SAEs and SAEs resulting in death.

TEAEs are summarised and tabulated at both the subject (number [%] of subjects) and event (number of events) level:

- By treatment, SOC and PT.

- By treatment, SOC, PT and maximum reported intensity.
- By treatment, SOC, PT and causal relationship to study drug.

For the incidence at the subject level by SOC and PT, if a subject experienced more than one event within the same SOC and PT during a treatment period, only one occurrence was included in the incidence for that treatment.

For the incidence at the subject level by SOC, PT and intensity, if a subject experienced more than one event within the same SOC and PT, only the most severe occurrence was included in the incidence.

AEs reported during the Validation Phase, AEs that were not treatment-emergent, and ADEs are listed.

9.7.1.6.2 Clinical Laboratory Assessments

Clinical laboratory values (haematology, biochemistry and urinalysis) are listed for each subject by study phase. Each pre-study screening baseline laboratory value was classified as low, normal, or high, based on the reference range. All low and high values are listed separately, together with associated repeats, giving an assessment of clinical significance. Any clinical laboratory comments are also included in the data listings.

Alcohol, drugs of abuse, virology and urine pregnancy test results are also listed.

9.7.1.6.3 Vital Signs

Vital signs data are listed by study phase and subject at each timepoint. Out of range vital signs values are flagged in the data listings.

For the Clinical Phase, at each post-dose measurement of vital signs, summary statistics for the absolute vital sign value are presented by treatment and overall.

9.7.1.6.4 Physical Examination

Abnormalities in physical examination findings are listed by subject and visit.

9.7.1.6.5 Concomitant Medication

Pre-study and concomitant medications were classified according to the World Health Organisation Drug Dictionary (Version Mar2012) Anatomical Therapeutic Chemical code levels 2 to 4 and summarised overall.

9.7.2 Determination of Sample Size

As this was a pilot study, no formal sample size calculation was performed due to the experimental nature of the study. Eight subjects were considered to be sufficient for the Validation Phase. Sixteen subjects were considered to be sufficient to meet the objectives of the Clinical Phase of the study. Therefore approximately 32 subjects were to be recruited and randomised to aim to have 16 complete. Up to 2 subjects were assessed per day. This was a pilot study intended to provide estimates of effect size and variance for use in later studies.

9.8 Changes in the Conduct of the Study or Planned Analysis

9.8.1 Changes in the Conduct of the Study

Three substantial and 5 non-substantial protocol amendments were issued during the course of the study. No amendments were implemented prior to documented ethics approval being received. The study protocol and amendments are included as Appendix 16.1.1.

Substantial Protocol Amendment No. 1 (dated 19 Oct 2012)

The protocol amendment was implemented to incorporate changes to the protocol template within the RB SOP (D0365585 Protocol and CRFs for Investigational Studies), to add additional investigational sites, to update the PL number of product and to correct a number of minor typographical errors in the final study protocol (dated 01 Jun 2012).

The following changes were made:

- Section 5.2 (Investigational Sites): The Spire Manchester Hospital and BMI Alexandra Hospital were added as sites where the HiRM, pH and impedance catheter insertion and clipping could be performed.
- Section 10.2 (Exclusion criterion No. 17): The definition of adequate contraceptive precautions was added to the exclusion criterion.
- Section 11.2.2 (Schedule of Assessments): The schedule of assessments was updated to indicate that pH and impedance recordings were performed on Day 3 as well.
- Section 11.5.1 (Catheter Insertion): The text was adjusted to make provision for the additional hospitals where the endoscopic procedures could be performed.
- Section 11.9 (Study-specific Supplies): The text was adjusted to make provision for the additional hospitals where the endoscopic procedures could be performed.

- Section 12.4 (Packaging): The text was corrected to indicate that sufficient drug supplies were packaged for 32 subjects (16 subjects and 16 replacements).

- Section 13.1.2 (Information to be Collected on Adverse Events/Adverse Device Events): Text was added to clarify that any untoward medical events that occurred after informed consent but prior to IMP administration was to be recorded in the subject's medical history and not reported as an AE.

- Section 13.2 (Overdose/Medication Errors): The procedures around overdose and medication errors were clarified.

- Section 13.3 (Pregnancy): It was clarified that pregnancy should be reported to RB as an AE.

- Product Licence Number Clarification: It was clarified that the Gaviscon® Advance Aniseed Liquid provided to ICON Development Solutions for this study was PL00063/0097.

Substantial Protocol Amendment No. 2 (dated 01 Feb 2013)

The protocol amendment was implemented to include the change of PI, provide flexibility in which clips were used during the study, the addition of the use of xylocaine spray during the HiRM, replacement of the diagram in Appendix 1 and to correct a number of minor typographical errors in the final study protocol (dated 01 Jun 2012).

The following changes were made:

- Section 5.2 (Investigational Sites): The PI for the study was changed to Dr Peter Dewland.

- Section 11.5.1 (Catheter Insertion): It was clarified that the standard haemostatic metal clips to be used during the study could be either HX-600-090, Olympus, or similar and that the endoscopic clip-fixing device could be either HX-5LR-1, Olympus, or similar.

- Section 11.3.2 (Assessment of Hiatus Hernia using HiRM): It was added that xylocaine spray was available for use if required for the comfort of subjects.

- Section 14.2 (Data to be Analysed): It was clarified that data from subjects in the Validation Phase of the study were not being analysed according to the study endpoints and the typographical error (inclusion of the words 'Validation Phase') was corrected.

- Section 14.5.4.1 (Subjects who are Withdrawn from the Study): It was clarified that data from subjects in the Validation Phase of the study were not included in the safety population and the typographical error (inclusion of the words 'Validation Phase') was corrected.

- Appendix 1: The diagram was replaced with a version drawn to scale to clarify (and aid) taping of the catheter.

Substantial Protocol Amendment No. 3 (dated 17 Apr 2013)

The following change was made:

- Section 5.2 (Investigational Sites): The PI for the study was changed to Dr Pui Leung.

Non-substantial Protocol Amendment No. 1 (dated 03 Aug 2012)

The protocol amendment was implemented to clarify a minor typographical error in the final study protocol (dated 01 Jun 2012).

The following changes were made:

- Section 6 (Introduction): It was clarified that subjects in the Validation Phase of the study will undergo 3 fluoroscopic assessments.

Non-substantial Protocol Amendment No. 2 (dated 25 Sep 2012)

This protocol amendment was initially implemented to cover some of the topics described for the substantial amendment (dated 19 Oct 2012) described above.

Non-substantial Protocol Amendment No. 3 (dated 14 Dec 2012)

The protocol amendment was implemented to clarify minor typographical errors in the final study protocol (dated 01 Jun 2012).

The following changes were made:

- Section 12.6 (Accountability of IMP): It was clarified that the study treatment should be stored below 25°C and that the sponsor was to be notified if the temperature fell outside of the specified range of 15°C to 25°C.

Non-substantial Protocol Amendment No. 4 (dated 10 Jan 2013)

The protocol amendment was implemented to clarify details surrounding the recording of data during the refluxogenic meal as described in the final study protocol (dated 01 Jun 2012).

The following changes were made:

- Section 11.5.3 (Refluxogenic Meal): It was clarified that the recording of data continued in order to gain an understanding of pH and impedance readings during meal consumption. The study endpoints were not changed, however, this data would be available if required for an ad hoc analysis at the end of the study.

Non-substantial Protocol Amendment No. 5 (dated 27 Mar 2013)

The protocol amendment was implemented to include the change in RB medical officer and to clarify details surrounding the recording of data during the refluxogenic meal as described in the final study protocol (dated 01 Jun 2012).

The following changes were made:

- Section 5.1 (Reckitt Benckiser Details): The medical officer for RB was changed to Dr Richard Littlewood.
- Section 9.5.2 (Clinical Phase): It was clarified that up to 5 minutes of additional recording would be permitted.
- Section 11.5.2 (Baseline Assessments): It was clarified that up to 5 minutes of additional recording would be permitted.
- Section 11.5.3 (Refluxogenic Meal): It was clarified that up to 5 minutes of additional recording would be permitted.

- Section 11.6.1 (Clinical Assessments): It was clarified that up to 5 minutes of additional recording would be permitted.

- Section 14.4 (pH and Reflux Analysis): It was clarified that for all parameters, a baseline value would be calculated prior to each treatment, and would be the equivalent parameter calculated over the last 30 minutes of the defined baseline period. It was also clarified that all hypothesis tests would be performed using the 5% significance level.

- Section 14.4.3 (Statistical Methods for pH and impedance Analysis): It was clarified that "for baseline" refers to the parameter calculated over the last 30 minutes of the defined baseline period.

9.8.2 Changes in the Planned Statistical Analysis of the Study

There were no changes to the conduct of the study as described in the protocol (Version 5, 17 April 2013). The ITT population described in the final SAP (Version 1.3, 23 August 2013) is additional to the populations planned in the protocol and the Data Complete population has been decided as not required due to the amount of missing data.

10 STUDY SUBJECTS

The locations of all tables, figures, and listings pertinent to Section 10 are provided in Table 10-1.

Table 10-1 Location of Tables and Listings for Subject Disposition and Protocol Deviation Data

Data	Location	
	Tables and Figures	Listings
Disposition of Subjects	Table 14.1.1	Appendix 16.2.1.1
Visit Dates	-	Appendix 16.2.1.2
Protocol Deviations	-	Appendix 16.2.2.1
Number of Subjects at Each Visit	Table 14.1.3	Appendix 16.2.1.2
Eligibility Criteria	-	Appendix 16.2.4.2
Consent Information	-	Appendix 16.2.5.1
Screening Outcome	-	Appendix 16.2.5.2
Randomisation Number Allocation	-	Appendix 16.2.5.8

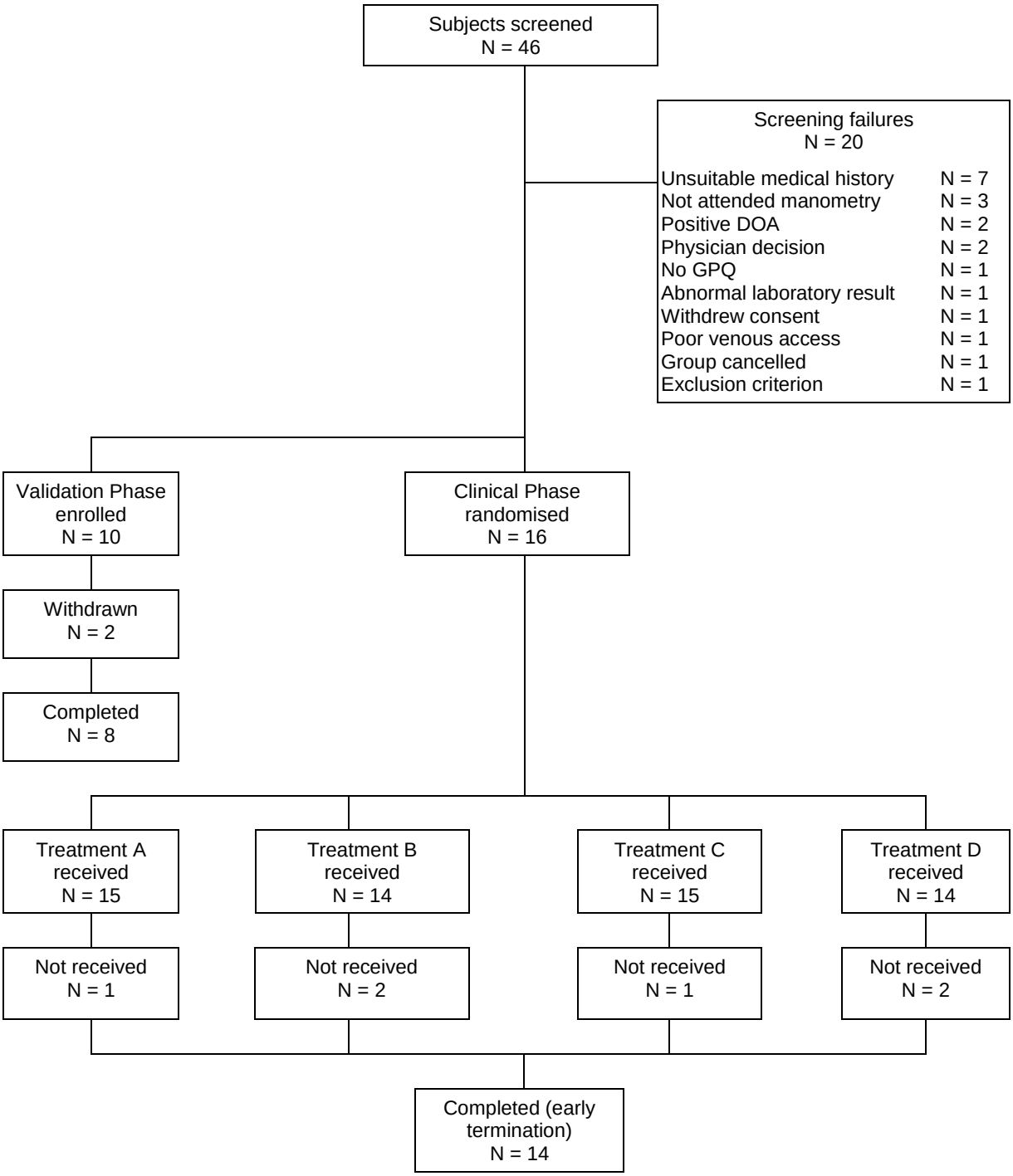
10.1 Disposition of Subjects

A listing of the consent information and screening outcome of all subjects is presented in Appendix 16.2.5, Listing 16.2.5.1 and Listing 16.2.5.2, respectively. A listing of all subjects discontinued from the study after enrolment is presented in Appendix 16.2.1, Listing 16.2.1.1. A listing of visit dates for all subjects is presented in Appendix 16.2.1, Listing 16.2.1.2. A summary of the number of subjects at each visit is presented in Section 14, Table 14.1.3.

Ten subjects were enrolled into the Validation Phase of the study, and 8 (80.0%) subjects completed the Validation Phase. Sixteen subjects were randomised onto the Clinical Phase of the study, and 14 (87.5%) subjects completed the Clinical Phase per protocol. Subject C012 was unable to tolerate the tube insertion and was withdrawn from the study prior to dosing. One subject (Subject C011) completed Treatment Period 1, but was withdrawn from the study due to a positive drugs of abuse test on admission to Treatment Period 2 (Day 1) (see Section 11.2.3). The study was terminated early due to quality issues being identified across a number of RB studies and the IEC informed on 11 Jun 2013.

Disposition of subjects is presented in Figure 10–1.

Figure 10–1 Disposition of Subjects



Source: Section 14, Table 14.1.1, Appendix 16.2.5, Listing 16.2.5.2
Abbreviations: DOA = drugs of abuse; GPQ = general practitioner's questionnaire; N = number of subjects
Treatment A: Gaviscon® Double Action Aniseed Liquid (20 ml)
Treatment B: Gaviscon® Advance Aniseed Liquid (10 ml)
Treatment C: Placebo Aniseed Liquid (20 ml)
Treatment D: Untreated state

10.2 Protocol Deviations

A listing of individual subjects who deviated from the protocol, and were excluded from study populations, is presented in Appendix 16.2.2, Listing 16.2.2.1. Two protocol deviations were noted that resulted in subjects being excluded from study populations. Subject C011 was excluded from the PP population as the subject failed exclusion criterion number 19. Subject C012 was excluded from the ITT and PP populations as the subject was withdrawn from the study following an AE and received no study treatment (see Section 11.1).

Additional information on minor protocol deviations is included in a Note to File and the protocol deviations log, provided in Appendix 16.2.2. Following a review requested by the MHRA, ICON identified a total of 240 protocol deviations which were reported to RB. RB concluded that the majority (232) of the protocol deviations did not have significant impact on either the scientific value of the study or the safety of the subjects participating in the study. However, RB determined that there had been a significant impact on the safety of 8 subjects where there was no evidence of GP letters being sent to their GPs prior to screening (discovered by RB during a routine co-monitoring visit on 15 Jul 2013). RB reported this to the MHRA as being evidence of a serious breach of GCP. ICON performed a follow up and informed all subjects' GPs. There were no concerns raised by the GPs with regard to their patients' participation in the clinical study and as such ICON and RB determined that no safety issues related to patient safety had arisen.

11 PH AND IMPEDANCE EVALUATION

The locations of all tables, figures, and listings pertinent to Section 11 are provided in Table 11-1.

Table 11-1 Location of Tables and Listings for pH and Impedance Data

Topic	Location	
	Tables and Figures	Listings
Data Sets Analysed	Table 14.1.2	Appendix 16.2.3.1
Subjects at Each Visit	Table 14.1.3	Appendix 16.2.1.2
Demographic and Baseline Characteristics	Table 14.1.4	Appendix 16.2.4.1
Medical History	-	Appendix 16.2.4.3
Urine Pregnancy Test	-	Appendix 16.2.4.4
Smoking Status	-	Appendix 16.2.4.5
Hiatus Hernia Assessment	-	Appendix 16.2.4.6
Alcohol Breath Test and Drugs of Abuse Test	-	Appendix 16.2.4.7
Pre-study Medication	-	Appendix 16.2.4.8
Concomitant Medication	-	Appendix 16.2.4.9
Study Treatment Dosing Record	-	Appendix 16.2.5.3
Meal Time and Fasting	-	Appendix 16.2.5.4
Catheter Insertion and Removal	-	Appendix 16.2.5.5
Fluoroscopy	-	Appendix 16.2.5.6
pH and impedance Start and Stop Times	-	Appendix 16.2.5.7
Individual pH Endpoints	-	Appendix 16.2.6.3
Individual Missing pH Response Data	-	Appendix 16.2.6.4
Summary of Primary and Secondary Endpoints (ITT population)	Table 14.2.1.1	-
Summary of Primary and Secondary Endpoints (PP population)	Table 14.2.1.2	-
Statistical Analysis of Primary Endpoint	Table 14.2.2.1	-
Exploratory Analysis 1 of Primary Endpoint	Table 14.2.2.2	-
Exploratory Analysis 2 of Primary Endpoint	Table 14.2.2.3	-
Statistical Analysis of % of Time that Electrode is pH < 4 Over 2 Hours	Table 14.2.2.4	-
Statistical Analysis of % of Time that Electrode is pH < 4 Over 4 Hours	Table 14.2.2.5	-
Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Times	Table 14.2.2.6	-
Statistical Analysis of Mean % of Time with pH < 4 at Electrodes 1, 2 and 3 during four 1-Hour Periods	Table 14.2.2.7	-
Statistical Analysis of Mean % of Time with pH < 4 at Electrodes 1, 2 and 3 Over 4 Hours	Table 14.2.2.8	-
Statistical Analysis of Mean % of Time with pH < 4 at Electrodes 4 to 7 during four 1-Hour Periods	Table 14.2.2.9	-
Individual Reflux Response Data	-	Appendix 16.2.6.2

Table 11-1 Location of Tables and Listings for pH and Impedance Data (Continued)

Topic	Location	
	Tables and Figures	Listings
Individual Reflux Endpoints	-	Appendix 16.2.6.5
Statistical Analysis of Number of Liquid, Gas and Mixed Reflux Episodes Occurring in the 2- and 4-Hour Periods	Table 14.2.2.10	Appendix 16.1.9.9
Statistical Analysis of Number of Acid and Weakly Acidic Reflux Episodes Occurring in the 2- and 4-Hour Periods	Table 14.2.2.11	Appendix 16.1.9.10
Statistical Analysis of Number of Reflux Episodes Reaching 15 cm Above the LOS during the 2- and 4-Hour Periods	Table 14.2.2.12	Appendix 16.1.9.11
Statistical Analysis of Oesophageal Bolus Exposure to Reflux during the 2- and 4-Hour Periods	Table 14.2.2.13	Appendix 16.1.9.12

11.1 Data Sets Analysed

Appendix 16.2.3, Listing 16.2.3.1 contains a tabular listing of all subjects excluded from the analyses. One (6.3%) subject was excluded from the ITT population and 1 (6.3%) subject was excluded from the ITT and PP populations (Section 14, Table 14.1.2).

The strategy for the inclusion/exclusion criteria for each of the datasets analysed was included in the SAP for the study and finalised following discussions of evaluability held before the database had been locked and prior to the blind being broken.

As a result of the high number of negative readings being observed upon review of pH measurements, ICON requested Synmed and Sandhill Scientific to conduct a review of pH data recorded during the Validation and Clinical Phases of the study. This was completed by Chris Blyth (Managing Director, Synmed Ltd) and Tom Stuebe (VP, Technology Development, Sandhill Scientific, Inc.).

The main issues noted during the review were temperature compensation not being applied (user error), power loss (due to the computer being turned off in error) and calibration data not corresponding exactly to pH values recorded at the start of the recording (pH values had not stabilized during the initial calibration).

Tom Stuebe performed repairs to the affected pH data files. These are outlined in the Note to File in Appendix 16.1.1.

The pH data repairs resulted in changes in the numbers of acid and weakly acid reflux episodes in a small number of subjects and are also summarised in a Note to File in Appendix 16.1.1 for more information.

The number of subjects in each of the study populations is shown in Table 11-2.

Table 11-2 Study Populations

Criterion	Overall N (%)
Number of subjects randomised	16
Number of subjects in all subjects population	16 (100.0)
Number of subjects in safety population	16 (100.0)
Number of subjects in ITT population	15 (93.8)
Number of subjects in PP population	14 (87.5)

Source: Section 14, Table 14.1.2
Abbreviations: ITT = intention to treat; N = number of subjects; PP = per protocol

11.2 Demographic and Other Baseline Assessments

11.2.1 Demographics

Subject demographics and other baseline characteristics are listed by subject in Appendix 16.2.4, Listing 16.2.4.1 and summarised in Section 14, Table 14.1.4.

Eleven (68.8%) subjects were male and 5 (31.3%) subjects were female, with a mean age of 33.5 years (SD=8.63 years). The range in age for subjects was 20 to 47 years. All but 2 subjects were Caucasian; the race of the remaining subjects was Afro-Caribbean and Asian, respectively (Section 14, Table 14.1.4).

11.2.2 Medical History

Medical history was reported in 4 (40.0%) subjects in the Validation Phase and by 11 (68.8%) subjects in the Clinical Phase of the study (Appendix 16.2.4, Listing 16.2.4.3). Hiatus hernia assessment results are listed by subject in Appendix 16.2.4, Listing 16.2.4.6.

11.2.3 Pre-study Medication

Pre-study medication is listed by subject in Appendix 16.2.4, Listing 16.2.4.8.

Three (30.0%) subjects had used pre-study medication prior to the start of the Validation Phase of the study. All 3 (30.0%) subjects were female, who took hormonal contraceptives.

Six (37.5%) subjects had used pre-study medication prior to the start of the Clinical Phase of the study. Three (18.8%) subjects were female, who took hormonal contraceptives. One (6.3%) subject used a topical application for eczema and 3 (18.8%) subjects used paracetamol.

No subjects had positive drugs of abuse or alcohol breath tests at screening (Appendix 16.2.4, Listing 16.2.4.7). One subject (Subject C011) had a positive drugs of abuse test (cocaine) on admission to Treatment Period 2 (Day 1).

11.2.4 Concomitant Medication

Concomitant medication is listed by subject in Appendix 16.2.4, Listing 16.2.4.9.

One (10.0%) subject used concomitant medication during the Validation Phase of the study. Subject V003 used 1000 mg of paracetamol for headache.

Six (37.5%) subjects used concomitant medication during the Clinical Phase of the study:

- Subject C007 used 1000 mg of paracetamol for headache during Treatment Period 1. The subject used 1000 mg of paracetamol (on 2 occasions), codeine (unknown dose) and 400 mg of ibuprofen for headache during Treatment Period 2.
- Subject C008 used 500 mg of paracetamol for headache during Treatment Period 1.
- Subject C009 used 1000 mg of paracetamol on 2 occasions for headache during Treatment Periods 1 and 2.
- Subject C011 took 2 tablets of T5 fat burners for weight loss after withdrawal due to a protocol deviation.
- Subject C014 used 1000 mg of paracetamol for headache during Treatment Period 1.
- Subject C015 used 1000 mg of paracetamol for worsening headache and used 400 mg of ibuprofen for lower backache during Treatment Period 2.

11.3 Measurements of Treatment Compliance

Compliance was not an issue in this study as study treatment was taken by subjects under supervision of appropriately trained staff who conducted a mouth inspection to ensure compliance with dosing. The study treatment dosing record is presented in Appendix 16.2.5, Listing 16.2.5.3 and discussed in Section 12.1.

11.4 PH and Impedance Results and Tabulations of Individual Subject Data

11.4.1 Analysis of pH and Impedance

PH and Impedance analysis data are presented in Appendix 16.2, Listing 16.2.5.5 (catheter insertion and removal record), Listing 16.2.5.6 (fluoroscopy) and Listing 16.2.5.7 (pH and impedance start and stop times). Individual missing pH response data are listed in Appendix 16.2.6, Listing 16.2.6.4. Individual pH endpoints are listed in Appendix 16.2.6, Listing 16.2.6.3 and summarised for the ITT population in Section 14, Table 14.2.1.1 and for the PP population in Section 14, Table 14.2.1.2.

Summaries and statistical assessments of the pH endpoints are presented in Section 14, Table 14.2.2.1 (primary endpoint), Table 14.2.2.2 (exploratory analysis 1 of primary endpoint), Table 14.2.2.3 (exploratory analysis 2 of primary endpoint), Table 14.2.2.4 (% of time that electrode is pH < 4 over 2 hours), Table 14.2.2.5 (% of time that electrode is pH < 4 over 4 hours), Table 14.2.2.6 (% of time that electrode is pH < 4 over various times), Table 14.2.2.7 (mean % of time with pH < 4 at electrodes 1, 2, and 3 during 4 x 1 hour periods), Table 14.2.2.8 (mean % of time with pH < 4 at electrodes 1, 2, and 3 over 4 hours), and Table 14.2.2.9 (mean % of time with pH < 4 at electrodes 4 to 7 during 4 x 1 hour periods).

Individual reflux response data are listed in Appendix 16.2.6, Listing 16.2.6.2. Individual reflux endpoints are listed in Appendix 16.2.6, Listing 16.2.6.5.

Statistical assessments of the reflux endpoints are presented in Section 14, Table 14.2.2.10 (number of liquid, gas and mixed reflux episodes occurring in the 2- and 4-hour periods), Table 14.2.2.11 (number of acid and weakly acidic reflux episodes occurring in the 2- and 4-hour periods), Table 14.2.2.12 (number of reflux episodes reaching 15 cm above the LOS during the 2- and 4-hour periods), and Table 14.2.2.13 (oesophageal bolus exposure to reflux during the 2- and 4-hour periods).

11.4.1.1 Primary pH and Impedance Analysis - Percentage of Time that the Electrode 5 cm above the SCJ was pH < 4 over a Period of 2 Hours Following Treatment with Gaviscon® Double Action Aniseed Liquid versus Placebo Aniseed Liquid

The primary pH and impedance endpoint was the percentage of time that the electrode 5 cm above the SCJ was pH < 4 over a period of 2 hours following treatment with Gaviscon® Double Action Aniseed Liquid versus Placebo Aniseed Liquid.

The primary pH and impedance endpoint is summarised by treatment for the ITT population in Section 14, Table 14.2.1.1 and for the PP population in Section 14, Table 14.2.1.2.

The statistical assessment of percentage of time that pH < 4 over a period of 2 hours by treatment and study population for the electrode 5 cm above the SCJ is summarised in Table 14.2.2.1 and presented in Table 11-3.

No statistically significant difference in the percentage of time that pH < 4 over a period of 2 hours at the electrode 5 cm above the SCJ was observed for Gaviscon® Double Action Aniseed Liquid when compared with Placebo Aniseed Liquid for either the ITT or PP populations. For the PP population, a reduction in the time that pH < 4 was observed for Gaviscon® Double Action Aniseed Liquid when compared with Placebo Aniseed Liquid, with a LS mean difference of -2.1%.

Table 11-3 Statistical Assessment of Percentage of Time that pH < 4 over a Period of 2 Hours by Treatment and Study Population for the Electrode 5 cm above the SCJ for Gaviscon® Double Action Aniseed Liquid versus Placebo Aniseed Liquid

Pop	Comparison		Number of Subject		LS mean (SE)		Test - Reference	
	Test	Ref	Test	Ref	Test	Ref	LS mean Difference (95% CI)	p-value
ITT	A	C	15	15	9.7 (3.50)	8.6 (3.50)	1.1 (-8.9, 11.1)	0.821
PP	A	C	14	14	6.5 (3.25)	8.6 (3.25)	-2.1 (-11.5, 7.2)	0.646

Source: Section 14, Table 14.2.2.1

Abbreviations: CI = confidence interval; ITT = intention to treat; LS = least squares; Pop = population; PP = per protocol; Ref = reference; SE = standard error

Note: LS means were obtained from a mixed model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

Treatment A: Gaviscon® Double Action Aniseed Liquid (20 ml)

Treatment C: Placebo Aniseed Liquid (20 ml)

11.4.1.1.1 Exploratory Analysis 1 of Primary Endpoint - Treatment by Treatment Period Interaction

As an exploratory analysis, a separate model was fitted as for the primary analysis with added interaction terms for treatment by treatment period interaction. The estimates for the Gaviscon® Double Action Aniseed Liquid versus Placebo Aniseed Liquid were presented overall and by treatment period and the p-values for each model term also presented. This analysis was performed using both populations.

The exploratory analysis 1 of percentage of time that pH < 4 over a period of 2 hours by treatment and study population for the electrode 5 cm above the SCJ is summarised for treatment by treatment period interaction in Table 14.2.2.2 and presented in Table 11-4.

No statistically significant difference in the percentage of time that pH < 4 over a period of 2 hours at the electrode 5 cm above the SCJ was observed for Gaviscon® Double Action Aniseed Liquid when compared with Placebo Aniseed Liquid during either Treatment Period 1 or 2 for either the ITT or PP populations. For the ITT population, a reduction in the percentage of time that pH < 4 was observed for Gaviscon® Double Action Aniseed Liquid when compared with Placebo Aniseed Liquid during Treatment Period 2, with a LS mean difference of -1.2%. For the PP population, reductions in the percentage of time that pH < 4 were observed for Gaviscon® Double Action Aniseed Liquid when compared with Placebo Aniseed Liquid during both Treatment Period 1, 2, and overall with LS mean differences of -3.1%, -1.4% and -2.3%, respectively.

Table 11-4 Statistical Assessment of Percentage of Time that pH < 4 over a Period of 2 Hours by Treatment and Study Population for the Electrode 5 cm above the SCJ for Treatment by Treatment Period Interaction for Gaviscon® Double Action Aniseed Liquid versus Placebo Aniseed Liquid

Pop	N		TP	LS mean (SE)		Test - Reference		Model p-values			
	Test (A)	Ref (C)		Test	Ref	LS mean Difference (95% CI)	p-value	T	P	D	TPI
ITT	8	8	1	11.2 (4.91)	8.1 (4.82)	3.2 (-10.8, 17.1)	0.650	-	-	-	-
	7	7	2	7.8 (5.15)	9.0 (5.15)	-1.2 (-15.8, 13.4)	0.870	-	-	-	-
	15	15	O	9.5 (3.53)	8.5 (3.54)	1.0 (-9.1, 11.1)	0.845	0.626	0.724	0.097	0.554
PP	7	7	1	4.9 (4.74)	8.0 (4.62)	-3.1 (-16.6, 10.3)	0.642	-	-	-	-
	7	7	2	7.9 (4.62)	9.3 (4.62)	-1.4 (-14.6, 11.7)	0.827	-	-	-	-
	14	14	O	6.4 (3.28)	8.7 (3.29)	-2.3 (-11.7, 7.2)	0.629	0.597	0.385	0.183	0.584

Source: Section 14, Table 14.2.2.2

Abbreviations: CI = confidence interval; D = day; ITT = intention to treat; LS = least squares; N = number of subjects; O = overall; P = period; Pop = population; PP = per protocol; Ref = reference; SE = standard error; T = treatment; TP = treatment period; TPI = treatment by period interaction

Note: LS means were obtained from a mixed model with treatment, baseline, treatment period, treatment period x treatment interaction and treatment day as fixed effects and a random effect for subject.

Treatment A: Gaviscon® Double Action Aniseed Liquid (20 ml)

Treatment C: Placebo Aniseed Liquid (20 ml)

11.4.1.1.2 Exploratory Analysis 2 of Primary Endpoint - Treatment by Treatment Day Interaction

As an exploratory analysis, a separate model was fitted as for the primary analysis with added interaction terms for treatment by treatment day interaction. The estimates for the Gaviscon® Double Action Aniseed Liquid versus Placebo Aniseed Liquid were presented overall and by treatment day and the p-values for each model term also presented. This analysis was performed using both populations.

The exploratory analysis 2 of percentage of time that pH < 4 over a period of 2 hours by treatment and study population for the electrode 5 cm above the SCJ is summarised for treatment by treatment day interaction in Table 14.2.2.3 and presented in Table 11-5.

No statistically significant difference in the percentage of time that pH < 4 over a period of 2 hours at the electrode 5 cm above the SCJ was observed for Gaviscon® Double Action Aniseed Liquid when compared with Placebo Aniseed Liquid during either Day 2 or Day 3 for either the ITT or PP populations. For the PP population, a reduction in the percentage of time that pH < 4 was observed for Gaviscon® Double Action Aniseed Liquid when compared with Placebo Aniseed Liquid on Day 2, with a LS mean difference of -4.8%, and overall (Day 2 and Day 3) of -2.3%.

Table 11-5 Statistical Assessment of Percentage of Time that pH < 4 over a Period of 2 Hours by Treatment and Study Population for the Electrode 5 cm above the SCJ for Treatment by Treatment Day Interaction for Gaviscon® Double Action Aniseed Liquid versus Placebo Aniseed Liquid

Pop	N		TD	LS mean (SE)		Test - Reference		Model p-values			
	Test (A)	Ref (C)		Test	Ref	LS mean Difference (95% CI)	p-value	T	P	D	TDI
ITT	7	8	2	14.1 (5.34)	11.4 (4.89)	2.8 (-11.9, 17.5)	0.705	-	-	-	-
	8	7	3	5.5 (4.88)	5.6 (5.23)	-0.1 (-14.5, 14.2)	0.985	-	-	-	-
	15	15	O	9.8 (3.60)	8.5 (3.59)	1.3 (-9.0, 11.6)	0.797	0.593	0.735	0.100	0.903
PP	6	8	2	6.8 (5.17)	11.6 (4.37)	-4.8 (-18.6, 8.9)	0.485	-	-	-	-
	8	6	3	5.7 (4.36)	5.5 (5.05)	0.2 (-13.2, 13.6)	0.975	-	-	-	-
	14	14	O	6.2 (3.36)	8.5 (3.35)	-2.3 (-11.9, 7.3)	0.632	0.623	0.392	0.188	0.843

Source: Section 14, Table 14.2.2.3

Abbreviations: CI = confidence interval; D = day; ITT = intention to treat; LS = least squares; N = number of subjects; O = overall; P = period; Pop = population; PP = per protocol; Ref = reference; SE = standard error; T = treatment; TD = treatment day; TDI = treatment by day interaction

Note: LS means were obtained from a mixed model with treatment, baseline, treatment period, treatment day x treatment interaction and treatment day as fixed effects and a random effect for subject.

Treatment A: Gaviscon® Double Action Aniseed Liquid (20 ml)

Treatment C: Placebo Aniseed Liquid (20 ml)

11.4.1.2 Secondary pH and Impedance Analyses

11.4.1.2.1 Percentage of Time that the Electrode 5 cm above the SCJ was pH < 4 over a Period of 2 Hours Following Treatment with Gaviscon® Double Action Aniseed Liquid versus the Untreated State

The secondary pH and impedance endpoint is summarised by treatment for the ITT population in Section 14, Table 14.2.1.1 and for the PP population in Section 14, Table 14.2.1.2.

The statistical assessment of percentage of time that pH < 4 over a period of 2 hours by treatment and study population for the electrode 5 cm above the SCJ is summarised in Table 14.2.2.4 and presented in Table 11-6.

No statistically significant difference in the percentage of time that pH < 4 over a period of 2 hours at the electrode 5 cm above the SCJ was observed for Gaviscon® Double Action Aniseed Liquid when compared with the untreated state for either the ITT or PP populations. For the PP population, a reduction in the percentage of time that pH < 4 was observed for Gaviscon® Double Action Aniseed Liquid when compared with the untreated state, with a LS mean difference of -2.6%.

Table 11-6 Statistical Assessment of Percentage of Time that pH < 4 over a Period of 2 Hours by Treatment and Study Population for the Electrode 5 cm above the SCJ for Gaviscon® Double Action Aniseed Liquid versus the Untreated State

Pop	Comparison		Number of Subject		LS mean (SE)		Test - Reference	
	Test	Ref	Test	Ref	Test	Ref	LS mean Difference (95% CI)	p-value
ITT	A	D	15	14	9.7 (3.50)	8.8 (3.62)	0.9 (-9.3, 11.0)	0.862
PP	A	D	14	14	6.5 (3.25)	9.0 (3.24)	-2.6 (-11.8, 6.7)	0.582

Source: Section 14, Table 14.2.2.4

Abbreviations: CI = confidence interval; ITT = intention to treat; LS = least squares; Pop = population; PP = per protocol; Ref = reference; SE = standard error

Note: LS means were obtained from a mixed model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

Treatment A: Gaviscon® Double Action Aniseed Liquid (20 ml)

Treatment D: Untreated state

11.4.1.2.2 Percentage of Time that the Electrode 5 cm above the SCJ was pH < 4 over a Period of 4 Hours Following Treatment with Gaviscon® Double Action Aniseed Liquid versus Placebo Aniseed Liquid and the Untreated State

The secondary pH and impedance endpoint is summarised by treatment for the ITT population in Section 14, Table 14.2.1.1 and for the PP population in Section 14, Table 14.2.1.2.

The statistical assessment of percentage of time that pH < 4 over a period of 4 hours by treatment and study population for the electrode 5 cm above the SCJ is summarised in Table 14.2.2.5 and presented in Table 11-7.

No statistically significant difference in the percentage of time that pH < 4 over a period of 4 hours at the electrode 5 cm above the SCJ was observed for Gaviscon® Double Action Aniseed Liquid when compared with Placebo Aniseed Liquid or the untreated state for either the ITT or PP populations. A reduction in the percentage of time that pH < 4 was observed for Gaviscon® Double Action Aniseed Liquid when compared with the untreated state for the ITT population (LS mean difference of -1.8%) and the PP population (LS mean difference of -4.4%).

Table 11-7 Statistical Assessment of Percentage of Time that pH < 4 over a Period of 4 Hours by Treatment and Study Population for the Electrode 5 cm above the SCJ for Gaviscon® Double Action Aniseed Liquid versus Placebo Aniseed Liquid and the Untreated State

Pop	Comparison		Number of Subject		LS mean (SE)		Test - Reference	
	Test	Ref	Test	Ref	Test	Ref	LS mean Difference (95% CI)	p-value
ITT	A	C	15	15	7.8 (3.40)	6.6 (3.40)	1.2 (-8.5, 10.9)	0.803
	A	D	15	14	7.8 (3.40)	9.6 (3.52)	-1.8 (-11.7, 8.1)	0.716
PP	A	C	14	14	5.4 (3.33)	6.6 (3.33)	-1.2 (-10.7, 8.4)	0.808
	A	D	14	14	5.4 (3.33)	9.8 (3.33)	-4.4 (-13.9, 5.1)	0.357

Source: Section 14, Table 14.2.2.5

Abbreviations: CI = confidence interval; ITT = intention to treat; LS = least squares; Pop = population; PP = per protocol; Ref = reference; SE = standard error

Note: LS means were obtained from a mixed model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

Treatment A: Gaviscon® Double Action Aniseed Liquid (20 ml)

Treatment C: Placebo Aniseed Liquid (20 ml)

Treatment D: Untreated state

11.4.1.2.3 Percentage of Time that the Electrode 5 cm above the SCJ was pH < 4 over a Period of 2 Hours Following Treatment with Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the Untreated State

The secondary pH and impedance endpoint is summarised by treatment for the ITT population in Section 14, Table 14.2.1.1 and for the PP population in Section 14, Table 14.2.1.2.

The statistical assessment of percentage of time that pH < 4 over a period of 2 hours by treatment and study population for the electrode 5 cm above the SCJ is summarised in Table 14.2.2.4 and presented in Table 11-8.

For both populations, a reduction in the percentage of time that pH < 4 over a period of 2 hours at the electrode 5 cm above the SCJ of approximately 5% was observed for Gaviscon® Advance Aniseed Liquid when compared with either Placebo Aniseed Liquid or the untreated state. None of these differences was statistically significant.

Table 11-8 Statistical Assessment of Percentage of Time that pH < 4 over a Period of 2 Hours by Treatment and Study Population for the Electrode 5 cm above the SCJ for Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the Untreated State

Pop	Comparison		Number of Subject		LS mean (SE)		Test - Reference	
	Test	Ref	Test	Ref	Test	Ref	LS mean Difference (95% CI)	p-value
ITT	B	C	14	15	3.5 (3.62)	8.6 (3.50)	-5.1 (-15.3, 5.1)	0.320
	B	D	14	14	3.5 (3.62)	8.8 (3.62)	-5.3 (-15.7, 5.0)	0.305
PP	B	C	14	14	3.4 (3.24)	8.6 (3.25)	-5.2 (-14.5, 4.0)	0.262
	B	D	14	14	3.4 (3.24)	9.0 (3.24)	-5.7 (-14.9, 3.6)	0.226

Source: Section 14, Table 14.2.2.4

Abbreviations: CI = confidence interval; ITT = intention to treat; LS = least squares; Pop = population; PP = per protocol; Ref = reference; SE = standard error

Note: LS means were obtained from a mixed model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

Treatment B: Gaviscon® Advance Aniseed Liquid (10 ml)

Treatment C: Placebo Aniseed Liquid (20 ml)

Treatment D: Untreated state

11.4.1.2.4 Percentage of Time that the Electrode 5 cm above the SCJ was pH < 4 over a Period of 4 Hours Following Treatment with Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the Untreated State

The secondary pH and impedance endpoint is summarised by treatment for the ITT population in Section 14, Table 14.2.1.1 and for the PP population in Section 14, Table 14.2.1.2.

The statistical assessment of percentage of time that pH < 4 over a period of 4 hours by treatment and study population for the electrode 5 cm above the SCJ is summarised in Table 14.2.2.5 and presented in Table 11-9.

For both populations, a reduction in the percentage of time that pH < 4 over a period of 4 hours at the electrode 5 cm above the SCJ was observed for Gaviscon® Advance Aniseed Liquid when compared with either Placebo Aniseed Liquid (approximate 2% reduction) or the untreated state (5% reduction). None of these differences was statistically significant.

Table 11-9 Statistical Assessment of Percentage of Time that pH < 4 over a Period of 4 Hours by Treatment and Study Population for the Electrode 5 cm above the SCJ for Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the Untreated State

Pop	Comparison		Number of Subject		LS mean (SE)		Test - Reference	
	Test	Ref	Test	Ref	Test	Ref	LS mean Difference (95% CI)	p-value
ITT	B	C	14	15	4.6 (3.52)	6.6 (3.40)	-2.0 (-11.9, 7.9)	0.683
	B	D	14	14	4.6 (3.52)	9.6 (3.52)	-5.0 (-15.1, 5.0)	0.319
PP	B	C	14	14	4.5 (3.33)	6.6 (3.33)	-2.0 (-11.6, 7.5)	0.672
	B	D	14	14	4.5 (3.33)	9.8 (3.33)	-5.3 (-14.8, 4.2)	0.270

Source: Section 14, Table 14.2.2.5

Abbreviations: CI = confidence interval; ITT = intention to treat; LS = least squares; Pop = population; PP = per protocol; Ref = reference; SE = standard error

Note: LS means were obtained from a mixed model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

Treatment B: Gaviscon® Advance Aniseed Liquid (10 ml)

Treatment C: Placebo Aniseed Liquid (20 ml)

Treatment D: Untreated state

11.4.1.2.5 Percentage of Time that each Electrode was pH ≤ 4 at 15, 30, 45, 60, 75 and 90 Minutes Following Ingestion of each Test Product at Electrodes 4 to 11 Inclusive

The secondary pH and impedance endpoint is summarised by treatment for the ITT population in Section 14, Table 14.2.1.1 and for the PP population in Section 14, Table 14.2.1.2.

Statistical assessments of percentage of time that each electrode (4 to 11 inclusive) was pH $\leq$ 4 at 15, 30, 45, 60, 75 and 90 minutes following ingestion of each test product are presented for the ITT population in Section 14, Table 14.2.2.6.

For almost all combinations of electrode and timepoints, a reduction in the percentage of time that pH < 4 was observed for both Gaviscon® Double Action Aniseed Liquid and Gaviscon® Advance Aniseed Liquid when compared with either the Placebo Aniseed Liquid or the untreated state for the ITT population. In the vast majority of cases, these reductions were not statistically significant nor was there any obvious trend as to which electrode/timepoint these reductions were observed.

Similar findings were observed for the PP population (Section 14, Table 14.2.2.6).

11.4.1.2.6 Mean Percentage of Time with pH < 4 at Electrodes 1, 2 and 3 during each of the Four 1-hour Periods for Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the Untreated State

The secondary pH and impedance endpoint is summarised by treatment for the ITT population in Section 14, Table 14.2.1.1 and for the PP population in Section 14, Table 14.2.1.2.

Statistical assessments of the mean percentage of time that pH < 4 at electrodes 1, 2 and 3 during four 1-hour periods following ingestion of each test product are presented for the ITT population in Section 14, Table 14.2.2.7 and summarised in Table 11-10.

For both Gaviscon® Double Action Aniseed Liquid and Gaviscon® Advance Aniseed Liquid, there was a trend for a reduction in the mean percentage of time that pH < 4 compared to both Placebo Aniseed Liquid and the untreated state during the 0 to 1-hour period and compared to untreated state during the 1 to 2-hour period for the ITT population, although none of these reductions achieved statistical significance. The greatest reductions of approximately 11% for Gaviscon® Double Action Aniseed Liquid and approximately 9% for Gaviscon® Advance Aniseed Liquid were observed during the 0 to 1-hour period.

Similar findings were observed for the per protocol population (Section 14, Table 14.2.2.7).

Table 11-10 Statistical Assessments of Mean Percentage of Time that pH < 4 at Electrodes 1, 2 and 3 during Four 1-hour Periods Following Ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid, Placebo Aniseed Liquid and the Untreated State (ITT Population, N = 15)

E	Time (hour)	Comparison		Number of Subject		LS mean (SE)		Test - Reference	
		Test	Ref	Test	Ref	Test	Ref	LS mean Difference (95% CI)	p-value
1 - 3	0 - 1	A	C	15	15	14.0 (5.13)	16.3 (5.14)	-2.2 (-16.1, 11.6)	0.745
		A	D	15	14	14.0 (5.13)	24.5 (5.32)	-10.5 (-24.7, 3.7)	0.143
		B	C	14	15	15.6 (5.37)	16.3 (5.14)	-0.7 (-15.0, 13.7)	0.926
		B	D	14	14	15.6 (5.37)	24.5 (5.32)	-8.9 (-23.3, 5.5)	0.217
	1 - 2	A	C	15	15	21.5 (5.47)	18.7 (5.48)	2.9 (-12.0, 17.7)	0.694
		A	D	15	14	21.5 (5.47)	24.4 (5.68)	-2.9 (-18.1, 12.4)	0.703
		B	C	14	15	23.3 (5.72)	18.7 (5.48)	4.6 (-10.8, 20.0)	0.544
		B	D	14	14	23.3 (5.72)	24.4 (5.68)	-1.1 (-16.6, 14.3)	0.881
	2 - 3	A	C	15	15	22.8 (5.47)	12.5 (5.47)	10.3 (-5.3, 25.9)	0.188
		A	D	15	14	22.8 (5.47)	22.5 (5.67)	0.3 (-15.7, 16.2)	0.973
		B	C	14	15	23.6 (5.71)	12.5 (5.47)	11.2 (-4.9, 27.3)	0.168
		B	D	14	14	23.6 (5.71)	22.5 (5.67)	1.1 (-15.2, 17.4)	0.891
	3 - 4	A	C	15	15	17.9 (4.94)	8.8 (4.95)	9.1 (-4.8, 23.0)	0.192
		A	D	15	14	17.9 (4.94)	21.0 (5.12)	-3.1 (-17.3, 11.1)	0.658
		B	C	14	15	16.4 (5.16)	8.8 (4.95)	7.6 (-6.7, 21.9)	0.289
		B	D	14	14	16.4 (5.16)	21.0 (5.12)	-4.6 (-19.1, 9.8)	0.519

Source: Section 14, Table 14.2.2.7

Abbreviations: CI = confidence interval; E = electrodes; ITT = intention to treat; LS = least squares; Ref = reference; SE = standard error

Note: LS means were obtained from a mixed model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

Treatment A: Gaviscon® Double Action Aniseed Liquid (20 ml)

Treatment B: Gaviscon® Advance Aniseed Liquid (10 ml)

Treatment C: Placebo Aniseed Liquid (20 ml)

Treatment D: Untreated state

11.4.1.2.7 Mean Percentage of Time with pH < 4 at Electrodes 1, 2 and 3 during the 4-hour Period for Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the Untreated State

The secondary pH and impedance endpoint is summarised by treatment for the ITT population in Section 14, Table 14.2.1.1 and for the PP population in Section 14, Table 14.2.1.2.

Statistical assessments of the mean percentage of time that pH < 4 at electrodes 1, 2 and 3 during the 4-hour period following ingestion of each test product are presented for the ITT population in Section 14, Table 14.2.2.8 and summarised in Table 11-11.

No statistically significant difference in the mean percentage of time that pH < 4 at electrodes 1, 2 and 3 during the 4-hour period was observed for either Gaviscon® Double Action Aniseed Liquid or Gaviscon® Advance Aniseed Liquid when compared with either Placebo Aniseed Liquid or the untreated state for the ITT population. There was a trend for a reduction in the mean percentage of time that pH < 4 for both Gaviscon® Double Action Aniseed Liquid (approximately 4%) and for Gaviscon® Advance Aniseed Liquid (approximately 3%) compared with the untreated state.

Similar findings were observed for the PP population (Section 14, Table 14.2.2.8).

Table 11-11 Statistical Assessments of Mean Percentage of Time that pH < 4 at Electrodes 1, 2 and 3 during the 4-hour Period Following Ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid, Placebo Aniseed Liquid and the Untreated State (ITT Population, N = 15)

E	Time (hour)	Comparison		Number of Subject		LS mean (SE)		Test - Reference	
		Test	Ref	Test	Ref	Test	Ref	LS mean Difference (95% CI)	p-value
1 - 3	0 - 4	A	C	15	15	19.1 (4.95)	14.1 (4.96)	5.0 (-8.9, 18.9)	0.469
		A	D	15	14	19.1 (4.95)	23.0 (5.14)	-3.9 (-18.1, 10.3)	0.577
		B	C	14	15	19.6 (5.18)	14.1 (4.96)	5.5 (-8.8, 19.8)	0.440
		B	D	14	14	19.6 (5.18)	23.0 (5.14)	-3.4 (-17.8, 11.0)	0.633

Source: Section 14, Table 14.2.2.8

Abbreviations: CI = confidence interval; E = electrodes; ITT = intention to treat; LS = least squares; Ref = reference; SE = standard error

Note: LS means were obtained from a mixed model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

Treatment A: Gaviscon® Double Action Aniseed Liquid (20 ml)

Treatment B: Gaviscon® Advance Aniseed Liquid (10 ml)

Treatment C: Placebo Aniseed Liquid (20 ml)

Treatment D: Untreated state

11.4.1.2.8 Mean Percentage of Time with pH < 4 at the Electrodes within the Cardia (Electrodes 4 to 7) during each of the Four 1-hour Periods for Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the Untreated State

The secondary pH and impedance endpoint is summarised by treatment for the ITT population in Section 14, Table 14.2.1.1 and for the PP population in Section 14, Table 14.2.1.2.

Statistical assessments of the mean percentage of time that pH < 4 at electrodes 4 to 7 during four 1-hour periods following ingestion of each test product are presented for the ITT population in Section 14, Table 14.2.2.9 and summarised in Table 11-12.

No statistically significant difference in the mean percentage of time that pH < 4 at electrodes 4 to 7 was observed for either Gaviscon® Double Action Aniseed Liquid or Gaviscon® Advance Aniseed Liquid when compared with either Placebo Aniseed Liquid or the untreated state for the ITT population. There was a trend for a reduction in the mean percentage of time that pH < 4 during the 0 to 1-hour and 1 to 2-hour periods for both Gaviscon® Double Action Aniseed Liquid and Gaviscon® Advance Aniseed Liquid compared to both Placebo Aniseed Liquid and the untreated state. The greatest reductions of approximately 14% for Gaviscon® Double Action Aniseed Liquid and approximately 16% for Gaviscon® Advance Aniseed Liquid were observed during the 0 to 1-hour period.

This trend was not observed for the PP population (Section 14, Table 14.2.2.9).

Table 11-12 Statistical Assessments of Mean Percentage of Time that pH < 4 at Electrodes 4 to 7 during Four 1-hour Periods Following Ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid, Placebo Aniseed Liquid and the Untreated State (ITT Population, N = 15)

E	Time (hour)	Comparison		Number of Subject		LS mean (SE)		Test - Reference	
		Test	Ref	Test	Ref	Test	Ref	LS mean Difference (95% CI)	p-value
4 - 7	0 - 1	A	C	15	15	25.9 (8.46)	39.4 (8.49)	-13.5 (-32.6, 5.6)	0.161
		A	D	15	14	25.9 (8.46)	33.5 (8.76)	-7.6 (-27.4, 12.1)	0.438
		B	C	14	15	23.2 (8.72)	39.4 (8.49)	-16.2 (-35.9, 3.5)	0.104
		B	D	14	14	23.2 (8.72)	33.5 (8.76)	-10.3 (-30.2, 9.5)	0.299
	1 - 2	A	C	15	15	41.2 (8.81)	54.7 (8.84)	-13.5 (-34.2, 7.2)	0.196
		A	D	15	14	41.2 (8.81)	43.2 (9.14)	-2.1 (-23.5, 19.3)	0.845
		B	C	14	15	45.5 (9.09)	54.7 (8.84)	-9.2 (-30.5, 12.2)	0.391
		B	D	14	14	45.5 (9.09)	43.2 (9.14)	2.2 (-19.3, 23.8)	0.834
	2 - 3	A	C	15	15	49.3 (7.52)	52.6 (7.55)	-3.3 (-24.2, 17.6)	0.750
		A	D	15	14	49.3 (7.52)	45.4 (7.84)	4.0 (-17.4, 25.4)	0.710
		B	C	14	15	51.4 (7.81)	52.6 (7.55)	-1.3 (-22.6, 20.1)	0.906
		B	D	14	14	51.4 (7.81)	45.4 (7.84)	6.0 (-15.7, 27.7)	0.578
	3 - 4	A	C	15	15	52.3 (7.20)	45.0 (7.22)	7.3 (-13.2, 27.7)	0.480
		A	D	15	14	52.3 (7.20)	49.9 (7.49)	2.4 (-18.5, 23.3)	0.819
		B	C	14	15	50.7 (7.46)	45.0 (7.22)	5.6 (-15.3, 26.5)	0.591
		B	D	14	14	50.7 (7.46)	49.9 (7.49)	0.8 (-20.5, 22.0)	0.942

Source: Section 14, Table 14.2.2.9

Abbreviations: CI = confidence interval; E = electrodes; ITT = intention to treat; LS = least squares; Ref = reference; SE = standard error

Note: LS means were obtained from a mixed model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

Treatment A: Gaviscon® Double Action Aniseed Liquid (20 ml)

Treatment B: Gaviscon® Advance Aniseed Liquid (10 ml)

Treatment C: Placebo Aniseed Liquid (20 ml)

Treatment D: Untreated state

11.4.1.2.9 Total Number of (i) Liquid, (ii) Gas and (iii) Mixed Reflux Episodes Occurring During the 2- and 4-Hour Period Following Ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid Versus Placebo Aniseed Liquid and the Untreated State

The secondary pH and impedance endpoint is summarised by treatment for the ITT population in Section 14, Table 14.2.1.1 and for the PP population in Section 14, Table 14.2.1.2.

Statistical assessments of total number of (i) liquid, (ii) gas and (iii) mixed reflux episodes occurring during the 2- and 4-hour periods following ingestion of each test product are presented for the ITT population in Section 14, Table 14.2.2.10 and summarised in Table 11-13.

No statistically significant differences in the number of (i) liquid, (ii) gas and (iii) mixed reflux episodes occurring during the 2- and 4-hour periods was observed for either Gaviscon® Double Action Aniseed Liquid or Gaviscon® Advance Liquid when compared with either Placebo Aniseed Liquid or the untreated state for either the ITT of the PP population. There was a trend for a slight reduction in the number of liquid reflux episodes (Section 14, Table 14.2.2.10).

Table 11-13 Statistical Assessments of Total Number of (i) Liquid, (ii) Gas and (iii) Mixed Reflux Episodes Occurring during the 2- and 4-hour Periods Following Ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid, Placebo Aniseed Liquid and the Untreated State (ITT Population, N = 15)

Reflux Episode	Time (hour)	Comparison		Number of Subject		LS mean (SE)		Test - Reference	
		Test	Ref	Test	Ref	Test	Ref	LS mean Difference (95% CI)	p-value
Liquid	2	A	C	14	14	2.5 (0.90)	3.5 (0.93)	-1.0 (-3.1, 1.2)	0.378
		A	D	14	13	2.5 (0.90)	2.8 (0.92)	-0.3 (-2.4, 1.9)	0.810
		B	C	13	14	2.9 (0.93)	3.5 (0.93)	-0.5 (-2.8, 1.7)	0.620
		B	D	13	13	2.9 (0.93)	2.8 (0.92)	0.1 (-2.0, 2.3)	0.893
	4	A	C	14	14	3.4 (1.25)	5.0 (1.28)	-1.5 (-4.2, 1.2)	0.259
		A	D	14	13	3.4 (1.25)	4.1 (1.28)	-0.6 (-3.3, 2.1)	0.643
		B	C	13	14	4.5 (1.29)	5.0 (1.28)	-0.5 (-3.3, 2.3)	0.708
		B	D	13	13	4.5 (1.29)	4.1 (1.28)	0.4 (-2.3, 3.1)	0.775
Gas	2	A	C	14	14	0.6 (0.20)	0.6 (0.21)	-0.1 (-0.6, 0.4)	0.728
		A	D	14	13	0.6 (0.20)	0.3 (0.21)	0.2 (-0.3, 0.8)	0.344
		B	C	13	14	0.4 (0.21)	0.6 (0.21)	-0.2 (-0.8, 0.3)	0.366
		B	D	13	13	0.4 (0.21)	0.3 (0.21)	0.1 (-0.4, 0.6)	0.721
	4	A	C	14	14	1.5 (0.38)	1.2 (0.39)	0.3 (-0.7, 1.2)	0.563
		A	D	14	13	1.5 (0.38)	0.6 (0.39)	0.8 (-0.1, 1.8)	0.094
		B	C	13	14	1.2 (0.39)	1.2 (0.39)	0.1 (-0.9, 1.0)	0.900
		B	D	13	13	1.2 (0.39)	0.6 (0.39)	0.6 (-0.4, 1.6)	0.221

Table 11-13 Statistical Assessments of Total Number of (i) Liquid, (ii) Gas and (iii) Mixed Reflux Episodes Occurring during the 2- and 4-hour Periods Following Ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid, Placebo Aniseed Liquid and the Untreated State (ITT Population, N = 15)

Reflux Episode	Time (hour)	Comparison		Number of Subject		LS mean (SE)		Test - Reference	
		Test	Ref	Test	Ref	Test	Ref	LS mean Difference (95% CI)	p-value
Mixed	2	A	C	14	14	1.5 (0.62)	2.0 (0.65)	-0.5 (-2.1, 1.1)	0.513
		A	D	14	13	1.5 (0.62)	1.7 (0.69)	-0.2 (-1.9, 1.5)	0.815
		B	C	13	14	2.4 (0.65)	2.0 (0.65)	0.4 (-1.3, 2.0)	0.647
		B	D	13	13	2.4 (0.65)	1.7 (0.69)	0.7 (-1.1, 2.5)	0.424
	4	A	C	14	14	2.5 (0.92)	2.4 (0.96)	0.1 (-2.2, 2.4)	0.949
		A	D	14	13	2.5 (0.92)	3.0 (1.03)	-0.5 (-3.0, 2.0)	0.692
		B	C	13	14	3.6 (0.97)	2.4 (0.96)	1.1 (-1.3, 3.5)	0.341
		B	D	13	13	3.6 (0.97)	3.0 (1.03)	0.6 (-2.0, 3.1)	0.647

Source: Section 14, Table 14.2.2.10

Abbreviations: CI = confidence interval; ITT = intention to treat; LS = least squares; Ref = reference; SE = standard error

Note: LS means were obtained from a mixed model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

Treatment A: Gaviscon® Double Action Aniseed Liquid (20 ml)

Treatment B: Gaviscon® Advance Aniseed Liquid (10 ml)

Treatment C: Placebo Aniseed Liquid (20 ml)

Treatment D: Untreated state

11.4.1.2.10 Total Number of (i) Acid and (ii) Weakly Acidic Reflux Episodes Occurring During the 2- and 4-Hour Period Following Ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid Versus Placebo Aniseed Liquid and the Untreated State

The secondary pH and impedance endpoint is summarised by treatment for the ITT population in Section 14, Table 14.2.1.1 and for the PP population in Section 14, Table 14.2.1.2.

Statistical assessments of total number of (i) acid and (ii) weakly acidic reflux episodes occurring during the 2- and 4-hour periods following ingestion of each test product are presented for the ITT population in Section 14, Table 14.2.2.11 and summarised in Table 11-14.

No statistically significant reduction in the total number of acid reflux episodes occurring during the 2- and 4-hour periods was observed for either Gaviscon® Double Action Aniseed Liquid or Gaviscon® Advance Aniseed Liquid when compared with Placebo Aniseed Liquid or the untreated state for either the ITT or PP populations. There was a trend for a slight reduction in the number of acid reflux episodes.

A statistically significant difference in the total number of weakly acidic reflux episodes occurring during the 2-hour period, but not during the 4-hour period, was observed for Gaviscon® Advance Aniseed Liquid when compared with the untreated state, but not when compared with Placebo Aniseed Liquid for both the ITT and PP populations (Section 14, Table 14.2.2.11).

Table 11-14 Statistical Assessments of Total Number of (i) Acid and (ii) Weakly Acidic Reflux Episodes Occurring during the 2- and 4-hour Periods Following Ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid, Placebo Aniseed Liquid and the Untreated State (ITT Population, N = 15)

Reflux Episodes	Time (hour)	Comparison		Number of Subject		LS mean (SE)		Test - Reference	
		Test	Ref	Test	Ref	Test	Ref	LS mean Difference (95% CI)	p-value
Acid	2	A	C	14	14	1.9 (0.62)	2.5 (0.65)	-0.6 (-2.4, 1.1)	0.478
		A	D	14	13	1.9 (0.62)	2.6 (0.65)	-0.8 (-2.5, 1.0)	0.386
		B	C	13	14	2.4 (0.65)	2.5 (0.65)	-0.1 (-1.9, 1.7)	0.917
		B	D	13	13	2.4 (0.65)	2.6 (0.65)	-0.2 (-2.0, 1.6)	0.794
	4	A	C	14	14	3.0 (1.02)	3.4 (1.06)	-0.4 (-3.2, 2.4)	0.796
		A	D	14	13	3.0 (1.02)	4.1 (1.06)	-1.1 (-3.9, 1.7)	0.440
		B	C	13	14	4.0 (1.07)	3.4 (1.06)	0.6 (-2.3, 3.5)	0.676
		B	D	13	13	4.0 (1.07)	4.1 (1.06)	-0.1 (-3.0, 2.8)	0.935
Weakly Acidic	2	A	C	14	14	2.2 (0.73)	2.7 (0.75)	-0.5 (-2.2, 1.2)	0.541
		A	D	14	13	2.2 (0.73)	1.3 (0.76)	0.9 (-0.8, 2.6)	0.278
		B	C	13	14	3.3 (0.76)	2.7 (0.75)	0.6 (-1.2, 2.3)	0.505
		B	D	13	13	3.3 (0.76)	1.3 (0.76)	2.0 (0.3, 3.8)	0.025
	4	A	C	14	14	3.1 (1.08)	3.7 (1.11)	-0.6 (-2.9, 1.7)	0.616
		A	D	14	13	3.1 (1.08)	2.2 (1.12)	0.9 (-1.4, 3.2)	0.441
		B	C	13	14	4.5 (1.12)	3.7 (1.11)	0.8 (-1.5, 3.2)	0.483
		B	D	13	13	4.5 (1.12)	2.2 (1.12)	2.3 (-0.1, 4.7)	0.059

Source: Section 14, Table 14.2.2.11

Abbreviations: CI = confidence interval; ITT = intention to treat; LS = least squares; Ref = reference; SE = standard error

Note: LS means were obtained from a mixed model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

Treatment A: Gaviscon® Double Action Aniseed Liquid (20 ml)

Treatment B: Gaviscon® Advance Aniseed Liquid (10 ml)

Treatment C: Placebo Aniseed Liquid (20 ml)

Treatment D: Untreated state

11.4.1.2.11 Number of Reflux Episodes Reaching 15 cm Above the LOS During the 2- and 4-Hour Period Following Ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid Versus Placebo Aniseed Liquid and the Untreated State

The secondary pH and impedance endpoint is summarised by treatment for the ITT population in Section 14, Table 14.2.1.1 and for the PP population in Section 14, Table 14.2.1.2.

Statistical assessments of total number of reflux episodes reaching 15 cm above the LOS during the 2- and 4-hour periods following ingestion of each test product are presented for the ITT population in Section 14, Table 14.2.2.12 and summarised in Table 11-15.

No statistically significant reduction in the number of reflux episodes reaching 15 cm above the LOS during the 2- and 4-hour periods was observed for either Gaviscon® Double Action Aniseed Liquid or Gaviscon® Advance Liquid when compared with either Placebo Aniseed Liquid or the untreated state for either the ITT or PP populations (Section 14, Table 14.2.2.12).

Table 11-15 Statistical Assessments of Total Number of Reflux Episodes Reaching 15 cm Above the LOS during the 2- and 4-hour Periods Following Ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid, Placebo Aniseed Liquid and the Untreated State (ITT Population, N = 15)

Time (hour)	Comparison		Number of Subject		LS mean (SE)		Test - Reference	
	Test	Ref	Test	Ref	Test	Ref	LS mean Difference (95% CI)	p-value
2	A	C	14	14	0.9 (0.56)	1.2 (0.57)	-0.2 (-1.2, 0.8)	0.634
	A	D	14	13	0.9 (0.56)	0.8 (0.57)	0.1 (-0.9, 1.1)	0.835
	B	C	13	14	1.2 (0.57)	1.2 (0.57)	0.1 (-1.0, 1.1)	0.902
	B	D	13	13	1.2 (0.57)	0.8 (0.57)	0.4 (-0.6, 1.4)	0.420
4	A	C	14	14	1.0 (0.62)	1.2 (0.64)	-0.2 (-1.3, 0.9)	0.724
	A	D	14	13	1.0 (0.62)	1.1 (0.64)	-0.2 (-1.3, 1.0)	0.777
	B	C	13	14	1.6 (0.64)	1.2 (0.64)	0.4 (-0.7, 1.6)	0.445
	B	D	13	13	1.6 (0.64)	1.1 (0.64)	0.5 (-0.6, 1.6)	0.395

Source: Section 14, Table 14.2.2.12

Abbreviations: CI = confidence interval; ITT = intention to treat; LOS = lower oesophageal sphincter; LS = least squares; Ref = reference; SE = standard error

Note: LS means were obtained from a mixed model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

Treatment A: Gaviscon® Double Action Aniseed Liquid (20 ml)

Treatment B: Gaviscon® Advance Aniseed Liquid (10 ml)

Treatment C: Placebo Aniseed Liquid (20 ml)

Treatment D: Untreated state

11.4.1.2.12 Oesophageal Bolus Exposure to Reflux (Percentage Time with Liquid or Mixed Reflux within the Oesophageal Lumen) for Each Test Product Versus the Untreated State During the 2- and 4-Hour Period Following Ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid versus Placebo Aniseed Liquid and the Untreated State

The secondary pH and impedance endpoint is summarised by treatment for the ITT population in Section 14, Table 14.2.1.1 and for the PP population in Section 14, Table 14.2.1.2.

Statistical assessments of oesophageal bolus exposure to reflux during the 2- and 4-hour periods following ingestion of each test product are presented for the ITT population in Section 14, Table 14.2.2.13 and summarised in Table 11-16.

No statistically significant reduction in the oesophageal bolus exposure to reflux during the 2- and 4-hour periods was observed for either Gaviscon® Double Action Aniseed Liquid or Gaviscon® Advance Liquid when compared with either Placebo Aniseed Liquid or the untreated state for either the ITT or PP populations (Section 14, Table 14.2.2.13).

Table 11-16 Statistical Assessments of Oesophageal Bolus Exposure to Reflux during the 2- and 4-hour Periods Following Ingestion of Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid, Placebo Aniseed Liquid and the Untreated State (ITT Population, N = 15)

Time (hour)	Comparison		Number of Subject		LS mean (SE)		Test - Reference	
	Test	Ref	Test	Ref	Test	Ref	LS mean Difference (95% CI)	p-value
2	A	C	14	14	0.6 (0.19)	1.1 (0.20)	-0.4 (-0.9, 0.0)	0.055
	A	D	14	13	0.6 (0.19)	0.8 (0.20)	-0.2 (-0.7, 0.2)	0.332
	B	C	13	14	1.2 (0.20)	1.1 (0.20)	0.1 (-0.4, 0.6)	0.711
	B	D	13	13	1.2 (0.20)	0.8 (0.20)	0.3 (-0.2, 0.8)	0.193
4	A	C	14	14	0.4 (0.14)	0.7 (0.15)	-0.2 (-0.5, 0.1)	0.143
	A	D	14	13	0.4 (0.14)	0.6 (0.15)	-0.2 (-0.5, 0.1)	0.186
	B	C	13	14	0.8 (0.15)	0.7 (0.15)	0.2 (-0.2, 0.5)	0.329
	B	D	13	13	0.8 (0.15)	0.6 (0.15)	0.2 (-0.2, 0.5)	0.276

Source: Section 14, Table 14.2.2.13

Abbreviations: CI = confidence interval; ITT = intention to treat; LS = least squares; Ref = reference; SE = standard error

Note: LS means were obtained from a mixed model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

Treatment A: Gaviscon® Double Action Aniseed Liquid (20 ml)

Treatment B: Gaviscon® Advance Aniseed Liquid (10 ml)

Treatment C: Placebo Aniseed Liquid (20 ml)

Treatment D: Untreated state

11.4.2 Statistical/Analytical Issues

Detailed documentation of statistical methods, as the final SAP, 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 Withdrawals or Missing Data

Missing data were not imputed. All analyses were based on observed cases. For AEs/ADEs, if the severity or relationship to the AE/ADE was missing, a worst-case scenario was assumed (i.e., it was set to severe or probable/definite relationship).

Completed treatment periods for subjects who withdrew from the study were used in the analyses due to the mixed modelling approach.

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-site study, therefore this section is not applicable.

11.4.2.5 Multiple Comparison/Multiplicity

As this was an exploratory study, no adjustments for the multiple comparisons across endpoints, treatments and timepoints have been made, therefore this section is not applicable.

11.4.2.6 Use of an “pH and Impedance Subset” of Subjects

No pH and impedance subsets of subjects were analysed, 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 Sub-groups

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

11.4.3 Tabulation of Individual Response Data

In addition to tables providing group data for pH and impedance variables, relevant individual subject data are presented in by-subject tabular listings in Appendix 16.2.6.

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

11.4.4 Drug Dose, Drug Concentration and Relationships to Response

11.4.4.1 Drug Dose and Relationships to Response

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

11.4.4.2 Drug Concentration, Pharmacokinetics, and Relationships to Response

Drug concentrations were not measured; therefore this section is not applicable.

11.4.5 Drug-drug and Drug-disease Interactions

Drug-drug or drug-disease interactions were not measured; therefore 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 pH and Impedance Conclusions

The results from the study are summarised below:

Gaviscon® Double Action Aniseed Liquid

- A reduction of approximately 2% in the time that pH < 4 over a period of 2 hours at the electrode 5 cm above the SCJ was observed for Gaviscon® Double Action Aniseed Liquid when compared with Placebo Aniseed Liquid. This reduction was not statistically significant. Neither the first nor second exploratory analyses of the primary endpoint resulted in any statistically significant treatment effect, period effect or day effect and there was no evidence of a treatment by period interaction or treatment by day interaction.

- A reduction of approximately 5% in the time that pH < 4 over a period of 4 hours at the electrode 5 cm above the SCJ was observed for Gaviscon® Double Action Aniseed Liquid when compared with the untreated state. No statistically significant reductions were observed.

- A reduction of approximately 11% in the time that pH < 4 during the first 1-hour period (0 to 1-hour) at the electrode 5 cm above the SCJ was observed for Gaviscon® Double Action Aniseed Liquid when compared with the untreated state. This reduction was not statistically significant.

- A reduction of approximately 4% in the time that pH < 4 at electrodes 1, 2 and 3 during the 4-hour period was observed for Gaviscon® Double Action Aniseed Liquid when compared with the untreated state. This reduction was not statistically significant.

- A reduction of approximately 14% in the time that pH < 4 at electrodes 4 to 7 during the first 1-hour period (0 to 1-hour) was observed for Gaviscon® Double Action Aniseed Liquid when compared with Placebo Aniseed Liquid. A reduction in the percentage of time that pH < 4 at electrodes 4 to 7 during first 1-hour period (0 to 1-hour) was also observed compared to the untreated state (approximately 8%). These reductions were not statistically significant.

Gaviscon® Advance Aniseed Liquid

- A reduction of approximately 5% in the time that pH < 4 over a period of 2 hours at the electrode 5 cm above the SCJ was observed for Gaviscon® Advance Aniseed Liquid when compared with both Placebo Aniseed Liquid and the untreated state. No statistically significant reductions were observed.

- Reduction of approximately 2% and 5% in the time that pH < 4 over a period of 4 hours at the electrode 5 cm above the SCJ was observed for Gaviscon® Advance Aniseed Liquid when compared with Placebo Aniseed Liquid and the untreated state, respectively. No statistically significant reductions were observed.

- A reduction of approximately 9% in the time that pH < 4 during the first 1-hour period (0 to 1-hour) at the electrode 5 cm above the SCJ was observed for Gaviscon® Advance Aniseed Liquid when compared with the untreated state. This reduction was not statistically significant.

- A reduction of approximately 3% in the time that pH < 4 at electrodes 1, 2 and 3 during the 4-hour period was observed for Gaviscon® Advance Aniseed Liquid when compared with the untreated state. This reduction was not statistically significant.

- A reduction of approximately 16% in the time that pH < 4 at electrodes 4 to 7 during the first 1-hour period (0 to 1-hour) was observed for Gaviscon® Advance Aniseed Liquid when compared with Placebo Aniseed Liquid. A reduction in the percentage of time that pH < 4 at electrodes 4 to 7 during first 1-hour period (0 to 1-hour) was also observed compared to the untreated state (approximately 10%). These reductions were not statistically significant.

Reflux Episodes

- A trend for a slight reduction in the number of liquid reflux episodes was observed. No statistically significant difference in the total number of (i) liquid, (ii) gas and (iii) mixed reflux episodes occurring during the 2- and 4-hour periods was observed for Gaviscon® Double Action Aniseed Liquid or Gaviscon® Advance Aniseed Liquid when compared with Placebo Aniseed Liquid or the untreated state.

- A trend for a slight reduction in the number of acid reflux episodes was observed. No statistically significant difference in the total number of acid reflux episodes occurring during the 2- and 4-hour periods was observed for Gaviscon® Double Action Aniseed Liquid or Gaviscon® Advance Aniseed Liquid when compared with Placebo Aniseed Liquid or the untreated state.

- A statistically significant difference in the total number of weakly acidic reflux episodes occurring during the 2-hour period, but not during the 4-hour period, was observed for Gaviscon® Advance Aniseed Liquid, when compared with the untreated state, nor for Gaviscon® Double Action Aniseed Liquid, when compared with the untreated state. No statistically significant difference was observed for Gaviscon® Advance Aniseed Liquid or Gaviscon® Double Action Aniseed Liquid when compared with Placebo Aniseed Liquid.

- No statistically significant difference in the total number of reflux episodes reaching 15 cm above the LOS during the 2- and 4-hour periods was observed for Gaviscon® Double Action Aniseed Liquid or Gaviscon® Advance Aniseed Liquid when compared with Placebo Aniseed Liquid or the untreated state.

- No statistically significant difference in the oesophageal bolus exposure to reflux during the 2- and 4-hour periods was observed for Gaviscon® Double Action Aniseed Liquid or Gaviscon® Advance Aniseed Liquid when compared with Placebo Aniseed Liquid or the untreated state.

12 SAFETY EVALUATION

All subjects who were recruited on to the study and took part in the Clinical Phase or were subjected to any invasive study procedure were included in the safety population.

The locations of all tables, figures, and listings pertinent to Section 12 are provided in Table 12-1.

Table 12-1 Location of Tables and Listings for Safety Data

Topic	Location	
	Tables and Figures	Listings
Study Treatment Dosing Record	-	Appendix 16.2.5.3
Summary of TEAEs	Table 14.3.1.1	Appendix 16.2.7.1
Summary of TEAEs by SOC, PT and Treatment	Table 14.3.1.2	Appendix 16.2.7.1
Summary of TEAEs by SOC, PT, Intensity and Treatment	Table 14.3.1.3	Appendix 16.2.7.1
Summary of TEAEs by SOC, PT, Relationship to Study treatment and Treatment	Table 14.3.1.4	Appendix 16.2.7.1
Listing of Deaths, Other SAEs and Other Significant AEs	Table 14.3.2.1	Appendix 16.2.7.1
Summary of ADEs by Subject	-	Appendix 16.2.7.2
Normal Ranges for Laboratory Data	-	Appendix 16.2.8.1
Clinical Laboratory Data by Category	-	Appendix 16.2.8.2
Abnormal Laboratory Results	-	Appendix 16.2.8.3
Virology	-	Appendix 16.2.8.4
Summary of Vital Signs	Table 14.3.5.1	Appendix 16.2.9.1
Abnormal Physical Examination Findings	-	Appendix 16.2.9.2
Investigator Comments	-	Appendix 16.2.10.1

12.1 Extent of Exposure

Study treatment dosing record is listed by subject in Appendix 16.2.5, Listing 16.2.5.3.

The number of subjects who received study treatment is presented in Table 12-2.

Table 12-2 Extent of Exposure (Safety Population)

Disposition	Overall N (%)
Subjects who received all 4 randomised treatments	14 (87.5)
Subjects who received Gaviscon® Double Action Aniseed Liquid (20 ml)	15 (93.8)
Subjects who received Gaviscon® Advance Aniseed Liquid (10 ml)	14 (87.5)
Subjects who received Placebo Aniseed Liquid (20 ml)	15 (93.8)
Subjects who were assessed in the randomised untreated state	14 (87.5)

Source: Section 14, Table 14.1.1
Abbreviations: N = number of subjects exposed

12.2 Adverse Events

An overview of the locations of tables, figures, and listings reporting AE data is provided in Table 12-1.

All AEs for each subject, including the same event on several occasions are listed in Appendix 16.2.7, Listing 16.2.7.1, giving both PT according to MedDRA, Version 15.0 and the original term used by the Investigator. All ADEs for each subject are listed in Appendix 16.2.7, Listing 16.2.7.2, giving both PTs according to MedDRA, Version 15.0 and the original term used by the Investigator.

The sections that follow describe AEs occurring after the initiation of treatment with IMP. Full tables are included in Section 14.3.

12.2.1 Brief Summary of Adverse Events

Overall, there were no deaths or SAEs during the study and no subjects were withdrawn due to a TEAE. There were 13 TEAEs in 7 (46.7%) subjects (6 TEAEs in 5 [33.3%] subjects following administration of Gaviscon® Double Action Aniseed Liquid, 2 TEAEs in 2 [14.3%] subjects following administration of Gaviscon® Advance Aniseed Liquid, and 5 TEAEs in 5 [33.3%] subjects following administration of Placebo Aniseed Liquid).

A summary of TEAEs is presented in Table 12-3.

Table 12-3 Summary of Treatment-emergent Adverse Events (Safety Population)

AE Category	Treatment			Overall (N=15) n (%) [E]
	A (N=15) n (%) [E]	B (N=14) n (%) [E]	C (N=15) n (%) [E]	
Any TEAEs	5 (33.3) [6]	2 (14.3) [2]	5 (33.3) [5]	7 (46.7) [13]
Intensity in TEAEs				
Mild	4 (26.7) [4]	2 (14.3) [2]	4 (26.7) [4]	7 (46.7) [10]
Moderate	2 (13.3) [2]	0 (0.0) [0]	1 (6.7) [1]	2 (13.3) [3]
Severe	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Causality in TEAEs				
Definite	1 (6.7) [2]	1 (7.1) [1]	0 (0.0) [0]	2 (13.3) [3]
Probable	0 (0.0) [0]	0 (0.0) [0]	1 (6.7) [1]	1 (6.7) [1]
Unlikely	3 (20.0) [3]	1 (7.1) [1]	4 (26.7) [4]	4 (26.7) [8]
None	1 (6.7) [1]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [1]
Any SAEs	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Any TEAEs leading to discontinuation	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

Source: Section 14, Table 14.3.1.1 and Table 14.3.1.4

Abbreviations: E = number of events; n = number of subjects with an event; N = number of subjects; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Treatment A: Gaviscon® Double Action Aniseed Liquid (20 ml)

Treatment B: Gaviscon® Advance Aniseed Liquid (10 ml)

Treatment C: Placebo Aniseed Liquid (20 ml)

Treatment D: Untreated state

12.2.2 Display of Adverse Events

All AEs for each subject, including the same event on several occasions are listed in Appendix 16.2.7, Listing 16.2.7.1, giving both PTs according to MedDRA, Version 15.0 and the original term used by the Investigator. All ADEs for each subject are listed in Appendix 16.2.7, Listing 16.2.7.2, giving both PTs according to MedDRA, Version 15.0 and the original term used by the Investigator.

An overview of the locations of tables, figures, and listings reporting AE data is provided in Table 12-1.

One subject (Subject V002) reported an ADE of retching during the Validation Phase. The tube was removed and the subject discontinued from the study.

12.2.3 Analysis of Adverse Events

12.2.3.1 Analysis of Treatment-emergent Adverse Events

Treatment-emergent AEs by SOC, PT and treatment are summarised in Section 14, Table 14.3.1.2 and presented in Table 12-4.

The only TEAE that was reported in more than 1 subject was headache. All other TEAEs were reported by individual subjects.

Table 12-4 Treatment-emergent Adverse Events Reported by System Organ Class, Preferred Term and Treatment (Safety Population)

System organ class Preferred Term	**Treatment**			**Overall (N=15) n (%) [E]**
	A (N=15) n (%) [E]	**B (N=14) n (%) [E]**	**C (N=15) n (%) [E]**	
Subjects with any TEAEs	5 (33.3) [6]	2 (14.3) [2]	5 (33.3) [5]	7 (46.7) [13]
General disorders and administration site conditions	**1 (6.7) [1]**	**2 (14.3) [2]**	**0 (0.0) [0]**	**2 (13.3) [3]**
Fatigue	1 (6.7) [1]	1 (7.1) [1]	0 (0.0) [0]	1 (6.7) [2]
Medical device discomfort	0 (0.0) [0]	1 (7.1) [1]	0 (0.0) [0]	1 (6.7) [1]
Musculoskeletal and connective tissue disorders	**1 (6.7) [1]**	**0 (0.0) [0]**	**0 (0.0) [0]**	**1 (6.7) [1]**
Back pain	1 (6.7) [1]	0 (0.0) [0]	0 (0.0) [0]	1 (6.7) [1]
Nervous system disorders	**2 (13.3) [2]**	**0 (0.0) [0]**	**4 (26.7) [4]**	**4 (26.7) [6]**
Headache	2 (13.3) [2]	0 (0.0) [0]	4 (26.7) [4]	4 (26.7) [6]
Respiratory, thoracic and mediastinal disorders	**1 (6.7) [2]**	**0 (0.0) [0]**	**1 (6.7) [1]**	**2 (13.3) [3]**
Nasal discomfort	1 (6.7) [1]	0 (0.0) [0]	0 (0.0) [0]	1 (6.7) [1]
Oropharyngeal pain	0 (0.0) [0]	0 (0.0) [0]	1 (6.7) [1]	1 (6.7) [1]
Rhinorrhoea	1 (6.7) [1]	0 (0.0) [0]	0 (0.0) [0]	1 (6.7) [1]

Source: Section 14, Table 14.3.1.2

Abbreviations: E = number of events; n = number of subjects with an event; N = number of subjects; TEAE = treatment-emergent adverse event

Note: Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in those categories.

Treatment A: Gaviscon® Double Action Aniseed Liquid (20 ml)

Treatment B: Gaviscon® Advance Aniseed Liquid (10 ml)

Treatment C: Placebo Aniseed Liquid (20 ml)

Treatment D: Untreated state

12.2.3.2 Analysis of Treatment-emergent Adverse Events by Intensity

Treatment-emergent AEs by SOC, PT, intensity grade and treatment are summarised in Section 14, Table 14.3.1.3.

No severe TEAEs were reported. The majority of TEAEs (10 TEAEs) were mild in intensity and were experienced by 3 (20.0%) subjects (4 TEAEs) following administration of Gaviscon® Double Action Aniseed Liquid, 2 (14.3%) subjects (2 TEAEs) following administration of Gaviscon® Advance Aniseed Liquid and 4 (26.7%) subjects (4 TEAEs) following administration of Placebo Aniseed Liquid. The only moderate TEAEs were headache (1 instance following administration of Gaviscon® Double Action Aniseed Liquid and 1 instance following administration of Placebo Aniseed Liquid) and 1 TEAE of nasal discomfort following administration of Gaviscon® Double Action Aniseed Liquid.

12.2.3.3 Analysis of Treatment-emergent Adverse Events by Relationship

Treatment-emergent AEs by SOC, PT, and relationship to study treatment and treatment are summarised in Section 14, Table 14.3.1.4.

The majority of TEAEs were considered not related to study treatment (unlikely: 8 TEAEs; none: 1 TEAE). Three TEAEs were considered definitely related to study treatment and were experienced by 1 (6.7%) subject (1 TEAE of nasal discomfort and 1 TEAE of rhinorrhoea) following administration of Gaviscon® Double Action Aniseed Liquid and 1 (7.1%) subject (1 TEAE of medical device discomfort) following administration of Gaviscon® Advance Aniseed Liquid. One TEAE was considered probably related to study treatment and was experienced by 1 (6.7%) subject (oropharyngeal pain) following administration of Placebo Aniseed Liquid. The events of nasal discomfort, rhinorrhoea, medical device discomfort and oropharyngeal pain were all considered ADEs (Appendix 16.2.7, Listing 16.2.7.2).

12.3 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

There were no deaths, other SAEs, or other significant AEs in this study (Section 14, Table 14.3.2.1).

12.4 Clinical Laboratory Evaluation

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

Normal ranges for laboratory data are presented in Appendix 16.2.8, Listing 16.2.8.1; individual clinical laboratory data by category are presented in Appendix 16.2.8, Listing 16.2.8.2; abnormal laboratory results by category are presented in Appendix 16.2.8, Listing 16.2.8.3; virology results are presented in Appendix 16.2.8, Listing 16.2.8.4.

12.4.2 Evaluation of Each Laboratory Parameter

The active moiety of the IMP used in this study has been licensed for use in man for many years. Their safety profile is very well established. For the purposes of this study, a clinically significant laboratory abnormal value is based on the clinical judgement of the Investigator.

12.4.2.1 Individual Subject Changes

Abnormal laboratory results by category are presented in Appendix 16.2.8, Listing 16.2.8.3. The majority of subjects had normal haematology and biochemistry values at screening and at follow-up. For some parameters, only a small number of subjects had abnormal haematology and biochemistry values at screening and at follow-up.

During the Validation Phase, abnormal haematology values at screening were noted for eosinophil count (3 [30.0%] subjects), red blood cell count (2 [20.0%] subjects), and monocyte count (1 [10.0%] subject). Abnormal haematology values at follow-up were noted in individual subjects for eosinophil count, neutrophil count, white blood cell count and basophil count. One (10.0%) subject had abnormal biochemistry values (ALT) at screening and 2 (20.0%) subjects had abnormal biochemistry values at follow-up (ALT and creatinine). All of the abnormal haematology and biochemistry findings were considered not clinically significant (Appendix 16.2.8, Listing 16.2.8.3).

During the Clinical Phase, abnormal haematology values at screening were noted for platelet count (3 [18.8%] subjects), and in individual subjects for eosinophil count, neutrophil count, red blood cell count, lymphocyte count and haemoglobin. Abnormal haematology values at follow-up were noted for basophil count (2 [12.5%] subjects) and in individual subjects for platelet count and haemoglobin. Abnormal biochemistry values at screening were noted for ALT (3 [18.8%] subjects), blood urea nitrogen (BUN) (2 [12.5%] subjects), creatinine (2 [12.5%] subjects) and in individual subjects for AST. Abnormal biochemistry values at follow-up were noted for ALT (2 [12.5%] subjects) and in individual subjects for BUN, creatinine and AST. All of the abnormal haematology and biochemistry findings were considered not clinically significant (Appendix 16.2.8, Listing 16.2.8.3).

12.4.2.2 Individual Clinically Significant Abnormalities

Individual clinical laboratory data by category are presented in Appendix 16.2.8, Listing 16.2.8.2; abnormal laboratory results by category are presented in Appendix 16.2.8, Listing 16.2.8.3.

There were no clinically significant changes in haematology and biochemistry values during the study, in the opinion of the Investigator.

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

12.5.1 Vital Signs

Individual vital sign measurements are presented in Appendix 16.2.9, Listing 16.2.9.1. Summary statistics for the safety population by timepoint are presented in Section 14, Table 14.3.5.1. There were no clinically significant changes in vital signs during the study.

12.5.2 Physical Examination

Individual physical examination abnormalities are presented in Appendix 16.2.9, Listing 16.2.9.2. There were no clinically significant abnormalities in physical examination at screening or follow-up.

12.5.3 Pregnancy

No female subjects had a positive pregnancy test at screening or admission to the CPU (Appendix 16.2.4, Listing 16.2.4.4).

12.6 Safety Conclusions

- Administration of Gaviscon® Double Action Aniseed Liquid (20 ml) and Gaviscon® Advance Aniseed Liquid (10 ml) was well tolerated.
- Of the 16 subjects randomised in the Clinical Phase of the study, 14 (87.5%) subjects completed the study per protocol.
- No deaths, SAEs or withdrawals due to TEAEs were reported.
- Overall, 13 TEAEs were reported in 7 (46.7%) subjects (6 TEAEs in 5 [33.3%] subjects following administration of Gaviscon® Double Action Aniseed Liquid, 2 TEAEs in 2 [14.3%] subjects following administration of Gaviscon® Advance Aniseed Liquid, and 5 TEAEs in 5 [33.3%] subjects following administration of Placebo Aniseed Liquid).
- The majority of TEAEs (10 TEAEs) were mild in intensity and only 4 TEAEs were considered related (definite or probable) to the study treatment.
- There were no clinically significant clinical laboratory findings, vital signs or physical examinations during the study.

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

As the study was terminated early, fewer subjects were recruited than intended. However, it should be noted that as this was a pilot study and due to its experimental nature, no formal sample size calculation was performed. Thus an endpoint of statistical significance might not necessarily be expected.

This study design was based on the paper by Clarke et al[5], but there were certain methodological differences which merit discussion.

The pH catheter was used in conjuction with an impedance probe unlike the original paper. The Prolene® tie was positioned in all cases by the Principal Investigator but the loop size of 3 mm is difficult to achive accurately with this material and there may have been some variation which might have allowed the position to vary by a few millimetres. There may have been variation in the accuracy of the catheter positioning using endoscopy as there was more than one operator and these individuals were performing this procedure for the first time.

The Clarke technique involved one endoscopy with 2 hours stabilisation afterwards whereas the equilibrium phase (baseline recording period) in this study was shorter and repeat endoscopies were involved.

Clarke's subjects were allowed to lie semi-recumbent on a couch with the head end at 45°, whilst the subjects in this study were kept at 60°.

The meal that was used was different to the Fish and Chips used by Clarke, as the high fat meal in this study consisted of a medium McDonalds Quarter Pounder with cheese meal (including fries). The relative fat content of these meals is not clearly defined. The use of a very fatty meal may be criticized in that the fat may float on the surface of the stomach contents and actually prevent or reduce acid release as well as possibly buffering it.

Clarke only quotes measurements made for 90 minutes after completion of the meal, not the 4 hours used in this study.

There were some problems with the calibration of the data capture process in terms of pH measurement as this software (and hardware) was new to the clinical unit conducting this study.

Some changes which did not reach statistical significance were seen and, as this was a pilot study which was terminated early, the planned numbers were not studied. As variable physiological functions were investigated, a larger number of subjects may have shown a significant change. The sensitivity of the method is endorsed by the fact that pH changes in the body of the stomach due to the buffering action of Gaviscon® were discernable and shown to be of the order of a maximum of 14% to 16% lowering of the time the pH was <4.

New methods need to be accurate, reproducible, robust and specific. The method upon which this protocol was based was experimental and the first usage of this specific type of pH probe. Thus reproducibility and robustness were still unknowns, as was variability. In summary, this study failed to detect a statistically significant endpoint as specified in the protocol, whilst it did appear sensitive enough to detect pH change in certain areas of the stomach.

13.2 Conclusion

Based on the results from this study, Gaviscon® Double Action Aniseed Liquid did not statistically significantly reduce the percentage of time that pH < 4 over a period of 2 hours at the electrode 5 cm above the SCJ compared with Placebo Aniseed Liquid.

Gaviscon® Double Action Aniseed Liquid (20 ml), Gaviscon® Advance Aniseed Liquid (10 ml) and the study procedures were well tolerated by all of the subjects.

The method upon which this protocol was based was experimental and the first usage of this specific type of pH probe. Thus reproducibility and robustness were still unknowns, as was variability.

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

14.1 Demographic and Subject Characteristics Data Summaries

14.1.1 Summary of Subject Disposition (All Subjects)

Reckitt Benckiser Healthcare (UK) Ltd Study GA1116 (0543/031) Page 1 of 2

Table 14.1.1 Summary of Subject Disposition
All Subjects (N=26)

Disposition	N (%)
Validation Phase	
Subjects enrolled	10
Subjects who completed validation phase	8 (80.0%)
Subjects who terminated validation phase early	2 (20.0%)
Adverse Event	1 (10.0%)
Physician Decision	1 (10.0%)
Clinical Phase	
Subjects randomised	16
Subjects who received all 4 randomised treatments	14 (87.5%)
Subjects who completed study	14 (87.5%)
Subjects who terminated study early	2 (12.5%)
Other:Unable to tolerate ng tube insertion of the two attempts of endoscopy.	1 (6.3%)
Protocol Violation	1 (6.3%)
Subjects who received Gaviscon Double Action Liquid (20 mL)	15 (93.8%)
Subjects who did not receive Gaviscon Double Action Liquid (20 mL)	1 (6.3%)
Subjects who received Gaviscon Advance Liquid (10 mL)	14 (87.5%)
Subjects who did not receive Gaviscon Advance Liquid (10 mL)	2 (12.5%)
Subjects who received Placebo Liquid (20 mL)	15 (93.8%)
Subjects who did not receive Placebo Liquid (20 mL)	1 (6.3%)

Data Source: Listing 16.2.1.1 and 16.2.5.3
Percentages are calculated as 100 x (number of subjects/number of subjects enrolled or randomised into the study phase).
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Reckitt Benckiser Healthcare (UK) Ltd Study GA1116 (0543/031)

Table 14.1.1 Summary of Subject Disposition
All Subjects (N=26)

Disposition	N (%)
Subjects who were assessed in the randomised untreated state	14 (87.5%)
Subjects who were not assessed in the randomised untreated state	2 (12.5%)

Data Source: Listing 16.2.1.1 and 16.2.5.3
Percentages are calculated as 100 x (number of subjects/number of subjects enrolled or randomised into the study phase).
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_01_01.sas 15OCT2013 12:01

14.1.2 Summary of Analysis Populations (All Subjects)

Reckitt Benckiser Healthcare (UK) Ltd Study GA1116 (0543/031) Page 1 of 1

Table 14.1.2 Summary of Analysis Populations
All Subjects (N=26)

Criterion	Overall
Subjects Randomised	16
All Subjects Population	
Subjects Included	16 (100%)
Subjects Excluded	0
Safety Population	
Subjects Included	16 (100%)
Subjects Excluded	0
ITT Population	
Subjects Included	15 (93.8%)
Subjects Excluded	1 (6.3%)
Reasons for Exclusion:	
Withdrawn from study after AE no treatment received	1 (6.3%)
Per Protocol Population	
Subjects Included	14 (87.5%)
Subjects Excluded	2 (12.5%)
Reasons for Exclusion:	
Failed exclusion criteria 19	1 (6.3%)
Withdrawn from study after AE no treatment received	1 (6.3%)

Data Source: Listing 16.2.3.1
This listing is for the Clinical Phase only.
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_01_02.sas 15OCT2013 12:01

14.1.3 Summary of Number of Subjects at Each Visit (All Subjects)

Reckitt Benckiser Healthcare (UK) Ltd Study GA1116 (0543/031) Page 1 of 1

Table 14.1.3 Summary of Number of Subjects at Each Visit
All Subjects (N=26)

Number (%) of Subjects Attending	Overall N=26
VP Screening	10 (100%)
VP Treatment Period 1 Day 1	10 (100%)
VP Treatment Period 1 Day 2	10 (100%)
VP Treatment Period 1 Day 3	8 (80.0%)
VP Follow-up	10 (100%)
CP Screening	16 (100%)
CP Treatment Period 1 Day 1	16 (100%)
CP Treatment Period 1 Day 2	16 (100%)
CP Treatment Period 1 Day 3	15 (93.8%)
CP Treatment Period 2 Day 1	15 (93.8%)
CP Treatment Period 2 Day 2	14 (87.5%)
CP Treatment Period 2 Day 3	14 (87.5%)
CP Follow-up	15 (93.8%)

Data Source: Listing 16.2.1.2
Percentages are calculated as 100 x (number of subjects/number of subjects enrolled or randomised into the study phase).
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_01_03.sas 15OCT2013 12:02

14.1.4 Demographic and Baseline Characteristics (Safety Population)

Reckitt Benckiser Healthcare (UK) Ltd Study GA1116 (0543/031) Page 1 of 2

Table 14.1.4 Demographic and Baseline Characteristics
Safety Population (N=16)

Parameter	Statistic	Overall
Age (Years)	n	16
	Mean	33.5
	SD	8.63
	CV(%)	25.75
	Median	32.0
	Minimum	20
	Maximum	47
Sex		
Male	n (%)	11 (68.8%)
Female	n (%)	5 (31.3%)
Race		
Caucasian	n (%)	14 (87.5%)
Asian	n (%)	1 (6.3%)
Afro-Caribbean	n (%)	1 (6.3%)
Other	n (%)	0
Weight (kg)	n	16
	Mean	87.91
	SD	15.685
	CV(%)	17.84
	Median	87.95
	Minimum	63.0
	Maximum	110.6

Data Source: Listing 16.2.4.1
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_01_04.sas 15OCT2013 12:02

Table 14.1.4 Demographic and Baseline Characteristics
Safety Population (N=16)

Parameter	Statistic	Overall
Height (m)	n	16
	Mean	1.768
	SD	0.0946
	CV(%)	5.35
	Median	1.785
	Minimum	1.58
	Maximum	1.89
BMI (kg/m^2)	n	16
	Mean	28.00
	SD	3.671
	CV(%)	13.11
	Median	29.80
	Minimum	22.2
	Maximum	33.9

Data Source: Listing 16.2.4.1
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_01_04.sas 15OCT2013 12:02

14.2 pH and Reflux Data

14.2.1 pH and Reflux Data Summaries

14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment (ITT Population)

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	Treatment B	Treatment C	Treatment D
pH < 4	5 cm above SCJ	2 hours	n	15	14	15	14
			Mean	12.381	5.549	5.638	6.871
			SD	28.1848	17.0857	11.3715	19.0429
			CV(%)	227.65	307.93	201.69	277.13
			Minimum	0.00	0.00	0.00	0.00
			Median	0.000	0.415	0.670	0.085
			Maximum	100.00	64.63	40.50	71.94
		4 hours	n	15	14	15	14
			Mean	10.833	6.991	3.315	7.388
			SD	26.9588	21.4585	6.5303	22.7179
			CV(%)	248.85	306.93	196.97	307.50
			Minimum	0.00	0.00	0.00	0.00
			Median	0.000	0.525	0.360	0.125
			Maximum	100.00	81.28	21.97	86.04

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

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Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	4	15 mins	n	15	14	15	14
			Mean	17.405	15.614	10.873	21.803
			SD	35.5011	35.5129	25.8873	36.3997
			CV(%)	203.97	227.45	238.08	166.95
			Minimum	0.00	0.00	0.00	0.00
			Median	0.000	0.000	0.440	0.230
			Maximum	100.00	100.00	100.00	100.00
		30 mins	n	15	14	15	14
			Mean	21.419	17.617	18.918	29.846
			SD	37.7302	35.4417	29.8993	37.8663
			CV(%)	176.15	201.18	158.05	126.87
			Minimum	0.00	0.00	0.00	0.00
			Median	0.440	0.000	0.670	10.985
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Study Sponsor: Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS, UK
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Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	4	45 mins	n	15	14	15	14
			Mean	22.495	21.384	22.037	35.624
			SD	38.7855	35.8921	33.6919	39.2964
			CV(%)	172.42	167.85	152.89	110.31
			Minimum	0.00	0.00	0.00	0.00
			Median	0.440	0.295	1.480	17.990
			Maximum	100.00	100.00	100.00	100.00
		60 mins	n	15	14	15	14
			Mean	22.834	24.783	24.764	38.128
			SD	38.8699	37.4377	35.7843	39.4599
			CV(%)	170.23	151.06	144.50	103.49
			Minimum	0.00	0.00	0.00	0.00
			Median	0.330	1.110	3.330	19.790
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

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Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	4	75 mins	n	15	14	15	14
			Mean	23.658	27.546	27.806	40.282
			SD	38.5468	38.7146	36.2154	39.7336
			CV(%)	162.93	140.55	130.24	98.64
			Minimum	0.00	0.00	0.00	0.00
			Median	0.620	2.445	7.640	24.560
			Maximum	100.00	100.00	100.00	100.00
		90 mins	n	15	14	15	14
			Mean	26.159	30.129	29.112	41.007
			SD	37.1340	39.3876	35.7719	41.2072
			CV(%)	141.95	130.73	122.88	100.49
			Minimum	0.00	0.00	0.00	0.00
			Median	9.550	6.260	8.520	21.720
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	5	15 mins	n	15	14	15	14
			Mean	16.938	8.570	33.007	23.808
			SD	34.3790	26.4347	40.7438	37.0242
			CV(%)	202.97	308.46	123.44	155.51
			Minimum	0.00	0.00	0.00	0.00
			Median	0.890	0.000	8.000	2.905
			Maximum	100.00	100.00	99.56	100.00
		30 mins	n	15	14	15	14
			Mean	21.353	12.696	38.667	26.005
			SD	35.3677	28.8487	43.1644	35.5927
			CV(%)	165.64	227.23	111.63	136.87
			Minimum	0.00	0.00	0.00	0.00
			Median	0.670	0.665	9.560	5.165
			Maximum	100.00	100.00	99.78	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	Treatment B	Treatment C	Treatment D
pH < 4	5	45 mins	n	15	14	15	14
			Mean	25.599	16.968	39.635	30.824
			SD	38.0088	31.1794	43.3498	33.9117
			CV(%)	148.48	183.76	109.37	110.02
			Minimum	0.00	0.00	0.00	0.00
			Median	1.630	2.220	7.850	20.060
			Maximum	100.00	100.00	99.85	100.00
		60 mins	n	15	14	15	14
			Mean	29.501	20.009	41.952	34.850
			SD	38.9116	32.8891	43.5010	35.5140
			CV(%)	131.90	164.37	103.69	101.91
			Minimum	0.00	0.00	0.00	0.00
			Median	1.560	3.385	18.170	22.570
			Maximum	100.00	100.00	99.89	99.89

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

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Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	5	75 mins	n	15	14	15	14
			Mean	31.617	23.697	42.259	37.441
			SD	40.2078	34.0053	43.4072	36.5044
			CV(%)	127.17	143.50	102.72	97.50
			Minimum	0.00	0.00	0.00	0.00
			Median	1.600	4.760	22.580	20.355
			Maximum	100.00	100.00	99.91	99.91
		90 mins	n	15	14	15	14
			Mean	33.553	26.406	41.603	39.153
			SD	40.1557	35.3637	42.8145	36.8240
			CV(%)	119.68	133.92	102.91	94.05
			Minimum	0.00	0.00	0.37	0.00
			Median	12.290	4.740	27.010	27.260
			Maximum	100.00	100.00	99.93	99.92

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	Treatment B	Treatment C	Treatment D
pH < 4	6	15 mins	n	15	14	15	14
			Mean	16.649	9.046	24.237	16.536
			SD	35.5790	26.6729	35.7786	35.6567
			CV(%)	213.70	294.84	147.62	215.63
			Minimum	0.00	0.00	0.00	0.00
			Median	0.000	0.000	3.110	1.110
			Maximum	100.00	100.00	100.00	100.00
		30 mins	n	15	14	15	14
			Mean	19.686	11.905	34.400	21.675
			SD	36.9477	29.8559	38.3704	35.2645
			CV(%)	187.68	250.78	111.54	162.70
			Minimum	0.00	0.00	0.00	0.00
			Median	0.670	0.000	16.000	2.885
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	Treatment B	Treatment C	Treatment D
pH < 4	6	45 mins	n	15	14	15	14
			Mean	23.473	13.714	37.317	26.528
			SD	37.4367	31.4014	39.1772	36.2072
			CV(%)	159.49	228.98	104.99	136.49
			Minimum	0.00	0.00	0.00	0.00
			Median	0.440	0.150	21.040	9.255
			Maximum	100.00	100.00	100.00	100.00
		60 mins	n	15	14	15	14
			Mean	26.202	16.958	41.181	30.050
			SD	37.7609	31.8710	39.8137	37.3579
			CV(%)	144.11	187.94	96.68	124.32
			Minimum	0.00	0.00	0.00	0.00
			Median	0.550	2.220	28.170	13.375
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	Treatment B	Treatment C	Treatment D
pH < 4	6	75 mins	n	15	14	15	14
			Mean	27.189	21.488	42.998	32.905
			SD	38.1729	32.5476	40.5257	38.1602
			CV(%)	140.40	151.47	94.25	115.97
			Minimum	0.00	0.00	0.00	0.00
			Median	0.530	4.885	42.310	20.215
			Maximum	100.00	100.00	100.00	100.00
		90 mins	n	15	14	15	14
			Mean	28.696	24.667	45.116	34.726
			SD	38.8762	33.6620	41.1389	37.5615
			CV(%)	135.48	136.47	91.18	108.16
			Minimum	0.00	0.00	0.89	0.00
			Median	1.480	5.145	49.630	20.085
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	7	15 mins	n	15	14	15	14
			Mean	14.900	17.421	17.037	20.651
			SD	34.6987	29.4162	32.9466	27.2290
			CV(%)	232.88	168.85	193.38	131.85
			Minimum	0.00	0.00	0.00	0.00
			Median	0.000	0.660	2.670	12.240
			Maximum	100.00	88.94	98.22	100.00
		30 mins	n	15	14	15	14
			Mean	16.635	17.475	27.837	25.555
			SD	34.5975	32.2139	33.0208	32.0113
			CV(%)	207.98	184.34	118.62	125.26
			Minimum	0.00	0.00	0.00	0.00
			Median	0.440	0.555	20.670	9.890
			Maximum	100.00	94.46	97.78	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	7	45 mins	n	15	14	15	14
			Mean	19.081	18.973	38.195	33.172
			SD	35.2402	32.8384	34.7504	34.5041
			CV(%)	184.69	173.08	90.98	104.02
			Minimum	0.00	0.00	0.34	0.00
			Median	0.590	0.665	44.890	30.200
			Maximum	100.00	96.30	98.52	100.00
		60 mins	n	15	14	15	14
			Mean	20.834	22.794	44.831	35.947
			SD	34.8371	33.5226	35.6915	36.3835
			CV(%)	167.21	147.07	79.61	101.21
			Minimum	0.00	0.00	0.67	0.00
			Median	0.440	4.215	58.670	35.960
			Maximum	100.00	97.23	98.89	99.77

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	7	75 mins	n	15	14	15	14
			Mean	21.385	25.809	49.207	36.849
			SD	35.1180	34.1396	36.3225	36.7033
			CV(%)	164.22	132.28	73.82	99.60
			Minimum	0.00	0.00	1.78	0.00
			Median	0.360	5.860	66.930	30.860
			Maximum	100.00	97.78	99.11	99.82
		90 mins	n	15	14	15	14
			Mean	22.263	28.844	52.100	37.749
			SD	35.3942	34.6991	36.0677	37.0098
			CV(%)	158.98	120.30	69.23	98.04
			Minimum	0.00	0.00	1.56	0.00
			Median	1.040	14.620	66.440	25.980
			Maximum	100.00	98.15	99.26	99.77

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	8	15 mins	n	15	14	15	14
			Mean	15.523	21.044	19.022	24.226
			SD	34.5327	29.4047	36.0515	35.8037
			CV(%)	222.46	139.73	189.53	147.79
			Minimum	0.00	0.00	0.00	0.00
			Median	0.000	5.780	2.220	0.220
			Maximum	100.00	84.89	99.11	100.00
		30 mins	n	15	14	15	14
			Mean	18.588	22.348	29.127	26.154
			SD	35.5608	31.8672	35.6977	36.1080
			CV(%)	191.31	142.60	122.56	138.06
			Minimum	0.00	0.00	0.00	0.00
			Median	0.220	2.890	10.890	6.110
			Maximum	100.00	85.59	99.33	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	8	45 mins	n	15	14	15	14
			Mean	18.705	23.343	38.777	33.699
			SD	36.0942	34.9069	34.8993	37.2392
			CV(%)	192.96	149.54	90.00	110.50
			Minimum	0.00	0.00	0.17	0.00
			Median	0.300	2.000	32.150	21.630
			Maximum	100.00	90.38	99.41	100.00
		60 mins	n	15	14	15	14
			Mean	19.975	26.309	44.437	37.147
			SD	36.5485	36.7055	34.3973	38.7331
			CV(%)	182.97	139.52	77.41	104.27
			Minimum	0.00	0.00	0.12	0.00
			Median	0.220	7.660	41.440	29.875
			Maximum	100.00	92.79	99.56	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	8	75 mins	n	15	14	15	14
			Mean	21.058	30.666	49.031	41.534
			SD	36.9644	37.2195	35.4445	38.5435
			CV(%)	175.54	121.37	72.29	92.80
			Minimum	0.00	0.00	0.10	0.00
			Median	0.180	12.525	52.440	36.740
			Maximum	100.00	94.23	99.64	100.00
		90 mins	n	15	14	15	14
			Mean	22.732	34.824	51.057	44.560
			SD	36.8354	37.5733	36.3422	38.7267
			CV(%)	162.04	107.90	71.18	86.91
			Minimum	0.00	0.00	0.16	0.00
			Median	0.150	25.240	60.370	39.215
			Maximum	100.00	95.19	99.63	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	Treatment B	Treatment C	Treatment D
pH < 4	9	15 mins	n	15	14	15	14
			Mean	15.727	25.323	19.201	29.536
			SD	34.5521	41.1405	34.8950	36.0270
			CV(%)	219.69	162.46	181.74	121.97
			Minimum	0.00	0.00	0.00	0.00
			Median	0.880	0.000	2.670	11.555
			Maximum	100.00	100.00	95.56	100.00
		30 mins	n	15	14	15	14
			Mean	14.679	27.561	24.326	37.056
			SD	34.7285	42.2762	31.6253	39.2557
			CV(%)	236.58	153.39	130.01	105.93
			Minimum	0.00	0.00	0.00	0.00
			Median	0.440	0.000	13.780	25.960
			Maximum	100.00	100.00	97.78	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	9	45 mins	n	15	14	15	14
			Mean	15.131	28.933	31.741	42.248
			SD	34.5573	42.8857	30.3022	39.7442
			CV(%)	228.39	148.22	95.47	94.07
			Minimum	0.00	0.00	2.02	0.00
			Median	1.190	2.370	13.930	40.520
			Maximum	100.00	100.00	98.52	100.00
		60 mins	n	15	14	15	14
			Mean	15.806	31.428	38.009	44.139
			SD	34.3644	42.5136	30.3006	41.1889
			CV(%)	217.41	135.27	79.72	93.32
			Minimum	0.00	0.00	1.46	0.00
			Median	1.330	8.610	29.560	47.535
			Maximum	100.00	100.00	98.89	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	9	75 mins	n	15	14	15	14
			Mean	16.989	35.065	41.398	47.044
			SD	34.3250	41.5457	31.9741	41.6752
			CV(%)	202.05	118.48	77.24	88.59
			Minimum	0.00	0.00	1.15	0.00
			Median	1.240	16.265	37.070	55.670
			Maximum	100.00	100.00	98.84	100.00
		90 mins	n	15	14	15	14
			Mean	18.863	38.570	43.587	50.966
			SD	34.3724	40.6324	33.0614	39.9249
			CV(%)	182.22	105.35	75.85	78.34
			Minimum	0.00	0.00	1.26	0.00
			Median	1.040	22.630	47.560	58.170
			Maximum	100.00	100.00	99.04	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	10	15 mins	n	15	14	15	14
			Mean	16.999	26.761	36.593	45.804
			SD	34.3173	42.5310	42.2690	39.8685
			CV(%)	201.88	158.93	115.51	87.04
			Minimum	0.00	0.00	0.00	0.00
			Median	0.880	2.885	9.330	38.345
			Maximum	100.00	100.00	100.00	100.00
		30 mins	n	15	14	15	14
			Mean	18.217	30.901	44.415	51.335
			SD	33.7238	42.3902	36.5771	39.4674
			CV(%)	185.13	137.18	82.35	76.88
			Minimum	0.00	0.00	5.33	0.00
			Median	5.560	2.000	25.560	56.165
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	10	45 mins	n	15	14	15	14
			Mean	24.103	35.751	50.749	57.575
			SD	33.1135	42.8185	34.8963	38.0227
			CV(%)	137.39	119.77	68.76	66.04
			Minimum	0.00	0.00	11.26	0.00
			Median	10.520	7.480	47.410	65.510
			Maximum	100.00	100.00	100.00	100.00
		60 mins	n	15	14	15	14
			Mean	31.149	40.818	55.601	59.453
			SD	32.4962	40.2867	34.1429	38.1813
			CV(%)	104.32	98.70	61.41	64.22
			Minimum	0.00	0.00	14.00	0.33
			Median	26.220	24.600	60.000	68.135
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	10	75 mins	n	15	14	15	14
			Mean	36.633	45.459	58.351	63.179
			SD	33.0104	40.1371	34.5757	35.7416
			CV(%)	90.11	88.29	59.26	56.57
			Minimum	0.00	0.00	13.07	0.27
			Median	39.700	39.670	67.470	74.060
			Maximum	100.00	100.00	100.00	100.00
		90 mins	n	15	14	15	14
			Mean	40.141	48.232	60.653	67.554
			SD	34.2342	40.3043	34.3054	32.5688
			CV(%)	85.28	83.56	56.56	48.21
			Minimum	0.00	0.30	10.96	0.22
			Median	49.260	49.350	66.300	78.345
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	11	15 mins	n	15	14	15	14
			Mean	38.476	49.801	73.837	66.273
			SD	34.9630	46.8091	35.2830	43.5747
			CV(%)	90.87	93.99	47.78	65.75
			Minimum	0.00	0.00	2.67	0.00
			Median	28.760	35.775	93.780	99.780
			Maximum	100.00	100.00	100.00	100.00
		30 mins	n	15	14	15	14
			Mean	48.950	49.578	74.727	68.313
			SD	37.1718	44.3102	31.6085	40.8759
			CV(%)	75.94	89.37	42.30	59.84
			Minimum	0.00	0.00	2.89	0.00
			Median	49.110	46.175	84.890	99.890
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	11	45 mins	n	15	14	15	14
			Mean	55.328	52.988	74.300	71.170
			SD	34.9830	42.8408	32.5574	38.9140
			CV(%)	63.23	80.85	43.82	54.68
			Minimum	0.00	0.00	2.22	0.00
			Median	63.700	48.345	89.040	99.925
			Maximum	100.00	100.00	100.00	100.00
		60 mins	n	15	14	15	14
			Mean	59.259	56.826	75.223	74.743
			SD	34.3760	42.0626	33.3250	35.0201
			CV(%)	58.01	74.02	44.30	46.85
			Minimum	0.00	0.00	2.56	0.89
			Median	72.110	59.415	91.780	99.945
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

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Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	11	75 mins	n	15	14	15	14
			Mean	63.169	58.623	75.968	77.864
			SD	33.5020	42.2560	33.1939	31.9151
			CV(%)	53.04	72.08	43.69	40.99
			Minimum	0.00	0.27	7.29	0.71
			Median	77.690	67.530	93.420	99.955
			Maximum	100.00	100.00	100.00	100.00
		90 mins	n	15	14	15	14
			Mean	66.714	60.623	76.480	79.934
			SD	31.8240	41.7222	32.3246	30.1428
			CV(%)	47.70	68.82	42.27	37.71
			Minimum	0.15	0.44	6.22	0.59
			Median	81.410	72.940	94.520	99.965
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	Mean of 1 - 3	0 - 1 hour	n	15	14	15	14
			Mean	11.916	18.265	14.003	25.544
			SD	24.4626	27.6556	20.3840	28.6775
			CV(%)	205.29	151.41	145.57	112.27
			Minimum	0.00	0.00	0.41	0.00
			Median	0.190	1.220	1.220	12.390
			Maximum	76.63	88.53	67.96	81.10
		1 - 2 hours	n	15	14	15	14
			Mean	18.835	26.729	15.741	25.775
			SD	27.8058	32.5064	25.3203	32.1618
			CV(%)	147.63	121.62	160.86	124.78
			Minimum	0.00	0.00	0.00	0.00
			Median	0.670	5.925	7.410	7.685
			Maximum	81.22	87.81	90.70	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	Mean of 1 - 3	2 - 3 hours	n	15	14	15	14
			Mean	19.835	27.526	9.525	24.749
			SD	31.4631	33.8205	18.4415	32.4548
			CV(%)	158.62	122.87	193.62	131.14
			Minimum	0.00	0.00	0.00	0.00
			Median	0.300	10.630	2.150	4.130
			Maximum	85.26	100.00	68.67	100.00
		3 - 4 hours	n	15	14	15	14
			Mean	15.228	20.175	5.829	22.654
			SD	24.6199	32.4087	17.0818	32.0498
			CV(%)	161.67	160.64	293.03	141.48
			Minimum	0.00	0.00	0.00	0.00
			Median	0.440	2.200	0.480	5.630
			Maximum	71.37	98.63	66.96	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	Mean of 1 - 3	0 - 4 hours	n	15	14	15	14
			Mean	16.453	23.174	11.291	24.684
			SD	26.2745	30.5367	19.4094	30.7959
			CV(%)	159.70	131.77	171.90	124.76
			Minimum	0.00	0.00	0.11	0.00
			Median	0.700	5.395	2.780	7.910
			Maximum	76.28	93.74	73.57	95.35
	Mean of 4 - 7	0 - 1 hour	n	15	14	15	14
			Mean	24.842	21.136	38.182	34.744
			SD	34.7785	31.9933	34.7733	32.6356
			CV(%)	140.00	151.37	91.07	93.93
			Minimum	0.00	0.00	0.25	0.00
			Median	5.600	9.790	25.940	23.820
			Maximum	100.00	99.31	83.03	99.91

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	Mean of 4 - 7	1 - 2 hours	n	15	14	15	14
			Mean	39.127	44.242	51.621	46.659
			SD	37.3046	40.9950	36.2343	43.6890
			CV(%)	95.34	92.66	70.19	93.63
			Minimum	0.00	0.00	0.75	0.00
			Median	38.500	34.140	62.390	32.905
			Maximum	100.00	100.00	100.00	99.97
		2 - 3 hours	n	15	14	15	14
			Mean	46.853	51.601	48.922	51.228
			SD	35.9379	40.7127	40.5014	43.2847
			CV(%)	76.70	78.90	82.79	84.49
			Minimum	0.00	0.00	0.14	0.00
			Median	59.420	46.085	55.830	47.040
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	Mean of 4 - 7	3 - 4 hours	n	15	14	15	14
			Mean	49.553	51.054	40.947	56.574
			SD	40.9719	42.8519	40.1736	41.9735
			CV(%)	82.68	83.94	98.11	74.19
			Minimum	0.00	0.00	0.00	0.00
			Median	64.640	44.460	41.830	65.000
			Maximum	100.00	100.00	100.00	100.00
Total number of Reflux Episodes	Liquid	2 hours	n	14	13	14	13
			Mean	2.9	2.5	3.3	2.7
			SD	3.38	3.10	4.14	3.25
			CV(%)	115.57	125.89	126.01	120.72
			Minimum	0	0	0	0
			Median	1.5	1.0	1.5	1.0
			Maximum	11	9	15	8

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	Treatment B	Treatment C	Treatment D
Total number of Reflux Episodes	Liquid	4 hours	n	14	13	14	13
			Mean	4.0	3.9	4.9	4.0
			SD	4.76	5.19	5.14	4.64
			CV(%)	118.89	132.23	105.86	115.92
			Minimum	0	0	0	0
			Median	1.5	2.0	3.0	1.0
			Maximum	16	16	18	12
	Gas	2 hours	n	14	13	14	13
			Mean	0.6	0.5	0.6	0.3
			SD	0.85	0.66	0.94	0.63
			CV(%)	149.04	143.05	164.08	204.89
			Minimum	0	0	0	0
			Median	0.0	0.0	0.0	0.0
			Maximum	2	2	3	2

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
Total number of Reflux Episodes	Gas	4 hours	n	14	13	14	13
			Mean	1.5	1.4	1.2	0.6
			SD	1.83	1.39	1.48	0.77
			CV(%)	121.95	100.15	121.63	124.79
			Minimum	0	0	0	0
			Median	1.0	1.0	1.0	0.0
			Maximum	6	4	5	2
	Mixed	2 hours	n	14	13	14	13
			Mean	1.5	2.3	1.8	2.2
			SD	1.56	3.01	2.36	2.12
			CV(%)	103.77	130.46	132.12	98.21
			Minimum	0	0	0	0
			Median	1.0	1.0	1.0	2.0
			Maximum	5	9	7	7

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
Total number of Reflux Episodes	Mixed	4 hours	n	14	13	14	13
			Mean	2.5	3.5	2.1	3.5
			SD	2.50	4.84	2.74	3.20
			CV(%)	100.15	139.85	127.94	90.56
			Minimum	0	0	0	0
			Median	2.0	1.0	1.0	3.0
			Maximum	7	15	9	9
	Acid	2 hours	n	14	13	14	13
			Mean	2.1	1.6	2.6	2.9
			SD	3.44	1.89	3.16	4.05
			CV(%)	160.47	117.29	122.71	138.59
			Minimum	0	0	0	0
			Median	0.0	1.0	1.0	1.0
			Maximum	12	6	8	13

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
Total number of Reflux Episodes	Acid	4 hours	n	14	13	14	13
			Mean	3.4	2.9	3.6	4.5
			SD	5.58	3.38	4.59	5.64
			CV(%)	166.30	115.56	128.41	124.19
			Minimum	0	0	0	0
			Median	0.0	2.0	1.5	2.0
			Maximum	19	11	14	18
	Weakly Acidic	2 hours	n	14	13	14	13
			Mean	2.4	3.2	2.5	1.8
			SD	2.28	3.89	2.93	1.74
			CV(%)	93.78	123.38	117.15	98.32
			Minimum	0	0	0	0
			Median	2.0	3.0	1.0	1.0
			Maximum	7	14	9	5

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	Treatment B	Treatment C	Treatment D
Total number of Reflux Episodes	Weakly Acidic	4 hours	n	14	13	14	13
			Mean	3.4	4.5	3.4	2.9
			SD	3.90	5.62	3.82	3.09
			CV(%)	113.66	126.00	111.34	105.87
			Minimum	0	0	0	0
			Median	2.5	3.0	1.5	2.0
			Maximum	13	19	12	9
	Reaching 15 cm above the LOS	2 hours	n	14	13	14	13
			Mean	1.1	0.9	1.1	0.5
			SD	1.94	1.71	2.79	0.97
			CV(%)	181.07	184.81	260.06	179.66
			Minimum	0	0	0	0
			Median	0.0	0.0	0.0	0.0
			Maximum	7	5	10	3

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
Total number of Reflux Episodes	Reaching 15 cm above the LOS	4 hours	n	14	13	14	13
			Mean	1.1	1.3	1.1	0.8
			SD	2.18	2.25	2.79	1.68
			CV(%)	190.65	172.09	260.06	198.03
			Minimum	0	0	0	0
			Median	0.0	0.0	0.0	0.0
			Maximum	8	7	10	5
Oesophageal Bolus Exposure to Reflux		2 hours	n	14	13	14	13
			Mean	0.8	0.9	0.8	1.1
			SD	0.78	0.93	0.91	1.16
			CV(%)	101.11	99.06	108.63	108.03
			Minimum	0	0	0	0
			Median	0.6	0.5	0.4	0.8
			Maximum	3	3	3	4

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

Table 14.2.1.1 Summary of Primary and Secondary Endpoints, by Treatment
ITT Population (N=15)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
Oesophageal Bolus Exposure to Reflux		4 hours	n	14	13	14	13
			Mean	0.5	0.7	0.5	0.8
			SD	0.59	0.76	0.60	0.73
			CV(%)	112.63	109.26	109.68	93.05
			Minimum	0	0	0	0
			Median	0.5	0.3	0.2	0.5
			Maximum	2	2	2	2

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_01.sas 12FEB2014 11:33

14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment (PP Population)

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	5 cm above SCJ	2 hours	n	14	14	14	14
			Mean	9.349	5.549	5.707	6.871
			SD	26.5891	17.0857	11.7974	19.0429
			CV(%)	284.42	307.93	206.71	277.13
			Minimum	0.00	0.00	0.00	0.00
			Median	0.000	0.415	0.615	0.085
			Maximum	100.00	64.63	40.50	71.94
		4 hours	n	14	14	14	14
			Mean	8.625	6.991	3.312	7.388
			SD	26.5312	21.4585	6.7768	22.7179
			CV(%)	307.61	306.93	204.61	307.50
			Minimum	0.00	0.00	0.00	0.00
			Median	0.000	0.525	0.320	0.125
			Maximum	100.00	81.28	21.97	86.04

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	Treatment B	Treatment C	Treatment D
pH < 4	4	15 mins	n	14	14	14	14
			Mean	11.506	15.614	11.555	21.803
			SD	28.1963	35.5129	26.7245	36.3997
			CV(%)	245.06	227.45	231.28	166.95
			Minimum	0.00	0.00	0.00	0.00
			Median	0.000	0.000	0.220	0.230
			Maximum	100.00	100.00	100.00	100.00
		30 mins	n	14	14	14	14
			Mean	15.806	17.617	16.809	29.846
			SD	32.0023	35.4417	29.8480	37.8663
			CV(%)	202.46	201.18	177.57	126.87
			Minimum	0.00	0.00	0.00	0.00
			Median	0.220	0.000	0.555	10.985
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	4	45 mins	n	14	14	14	14
			Mean	16.959	21.384	18.924	35.624
			SD	33.5402	35.8921	32.6473	39.2964
			CV(%)	197.78	167.85	172.52	110.31
			Minimum	0.00	0.00	0.00	0.00
			Median	0.220	0.295	1.405	17.990
			Maximum	100.00	100.00	100.00	100.00
		60 mins	n	14	14	14	14
			Mean	17.322	24.783	21.231	38.128
			SD	33.7095	37.4377	34.3137	39.4599
			CV(%)	194.60	151.06	161.62	103.49
			Minimum	0.00	0.00	0.00	0.00
			Median	0.165	1.110	3.330	19.790
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	4	75 mins	n	14	14	14	14
			Mean	18.205	27.546	24.122	40.282
			SD	33.4636	38.7146	34.5431	39.7336
			CV(%)	183.82	140.55	143.20	98.64
			Minimum	0.00	0.00	0.00	0.00
			Median	0.310	2.445	6.265	24.560
			Maximum	100.00	100.00	100.00	100.00
		90 mins	n	14	14	14	14
			Mean	20.885	30.129	25.276	41.007
			SD	32.1812	39.3876	33.7700	41.2072
			CV(%)	154.09	130.73	133.60	100.49
			Minimum	0.00	0.00	0.00	0.00
			Median	5.255	6.260	6.335	21.720
			Maximum	94.60	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	Treatment B	Treatment C	Treatment D
pH < 4	5	15 mins	n	14	14	14	14
			Mean	11.005	8.570	34.794	23.808
			SD	26.5370	26.4347	41.6679	37.0242
			CV(%)	241.14	308.46	119.76	155.51
			Minimum	0.00	0.00	0.00	0.00
			Median	0.665	0.000	6.445	2.905
			Maximum	100.00	100.00	99.56	100.00
		30 mins	n	14	14	14	14
			Mean	15.735	12.696	38.381	26.005
			SD	28.9363	28.8487	44.7791	35.5927
			CV(%)	183.90	227.23	116.67	136.87
			Minimum	0.00	0.00	0.00	0.00
			Median	0.670	0.665	6.000	5.165
			Maximum	100.00	100.00	99.78	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	Treatment B	Treatment C	Treatment D
pH < 4	5	45 mins	n	14	14	14	14
			Mean	20.284	16.968	38.054	30.824
			SD	33.1598	31.1794	44.5347	33.9117
			CV(%)	163.48	183.76	117.03	110.02
			Minimum	0.00	0.00	0.00	0.00
			Median	1.035	2.220	5.860	20.060
			Maximum	100.00	100.00	99.85	100.00
		60 mins	n	14	14	14	14
			Mean	24.465	20.009	39.854	34.850
			SD	34.9422	32.8891	44.3482	35.5140
			CV(%)	142.83	164.37	111.28	101.91
			Minimum	0.00	0.00	0.00	0.00
			Median	0.945	3.385	12.140	22.570
			Maximum	100.00	100.00	99.89	99.89

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	5	75 mins	n	14	14	14	14
			Mean	26.733	23.697	39.772	37.441
			SD	36.8188	34.0053	43.9232	36.5044
			CV(%)	137.73	143.50	110.44	97.50
			Minimum	0.00	0.00	0.00	0.00
			Median	1.200	4.760	15.870	20.355
			Maximum	100.00	100.00	99.91	99.91
		90 mins	n	14	14	14	14
			Mean	28.806	26.406	38.797	39.153
			SD	37.0490	35.3637	42.9754	36.8240
			CV(%)	128.61	133.92	110.77	94.05
			Minimum	0.00	0.00	0.37	0.00
			Median	7.070	4.740	17.320	27.260
			Maximum	100.00	100.00	99.93	99.92

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	Treatment B	Treatment C	Treatment D
pH < 4	6	15 mins	n	14	14	14	14
			Mean	10.696	9.046	25.904	16.536
			SD	28.1187	26.6729	36.5192	35.6567
			CV(%)	262.90	294.84	140.98	215.63
			Minimum	0.00	0.00	0.00	0.00
			Median	0.000	0.000	3.555	1.110
			Maximum	100.00	100.00	100.00	100.00
		30 mins	n	14	14	14	14
			Mean	13.949	11.905	34.746	21.675
			SD	30.6353	29.8559	39.7945	35.2645
			CV(%)	219.62	250.78	114.53	162.70
			Minimum	0.00	0.00	0.00	0.00
			Median	0.555	0.000	11.445	2.885
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	Treatment B	Treatment C	Treatment D
pH < 4	6	45 mins	n	14	14	14	14
			Mean	18.007	13.714	36.194	26.528
			SD	32.0414	31.4014	40.4048	36.2072
			CV(%)	177.94	228.98	111.64	136.49
			Minimum	0.00	0.00	0.00	0.00
			Median	0.370	0.150	13.485	9.255
			Maximum	100.00	100.00	100.00	100.00
		60 mins	n	14	14	14	14
			Mean	20.931	16.958	39.496	30.050
			SD	32.9654	31.8710	40.7574	37.3579
			CV(%)	157.50	187.94	103.19	124.32
			Minimum	0.00	0.00	0.00	0.00
			Median	0.440	2.220	25.195	13.375
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	6	75 mins	n	14	14	14	14
			Mean	21.989	21.488	40.939	32.905
			SD	33.6501	32.5476	41.2335	38.1602
			CV(%)	153.03	151.47	100.72	115.97
			Minimum	0.00	0.00	0.00	0.00
			Median	0.485	4.885	32.575	20.215
			Maximum	100.00	100.00	100.00	100.00
		90 mins	n	14	14	14	14
			Mean	23.603	24.667	42.873	34.726
			SD	34.7647	33.6620	41.7291	37.5615
			CV(%)	147.29	136.47	97.33	108.16
			Minimum	0.00	0.00	0.89	0.00
			Median	1.000	5.145	34.445	20.085
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	7	15 mins	n	14	14	14	14
			Mean	8.821	17.421	17.810	20.651
			SD	26.4527	29.4162	34.0490	27.2290
			CV(%)	299.87	168.85	191.18	131.85
			Minimum	0.00	0.00	0.00	0.00
			Median	0.000	0.660	2.000	12.240
			Maximum	100.00	88.94	98.22	100.00
		30 mins	n	14	14	14	14
			Mean	10.680	17.475	26.889	25.555
			SD	26.7634	32.2139	34.0548	32.0113
			CV(%)	250.59	184.34	126.65	125.26
			Minimum	0.00	0.00	0.00	0.00
			Median	0.220	0.555	14.445	9.890
			Maximum	100.00	94.46	97.78	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	7	45 mins	n	14	14	14	14
			Mean	13.301	18.973	36.584	33.172
			SD	28.2442	32.8384	35.4766	34.5041
			CV(%)	212.35	173.08	96.97	104.02
			Minimum	0.00	0.00	0.34	0.00
			Median	0.515	0.665	36.445	30.200
			Maximum	100.00	96.30	98.52	100.00
		60 mins	n	14	14	14	14
			Mean	15.179	22.794	42.993	35.947
			SD	28.1149	33.5226	36.2948	36.3835
			CV(%)	185.22	147.07	84.42	101.21
			Minimum	0.00	0.00	0.67	0.00
			Median	0.385	4.215	52.335	35.960
			Maximum	100.00	97.23	98.89	99.77

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	7	75 mins	n	14	14	14	14
			Mean	15.769	25.809	47.262	36.849
			SD	28.6141	34.1396	36.8739	36.7033
			CV(%)	181.45	132.28	78.02	99.60
			Minimum	0.00	0.00	1.78	0.00
			Median	0.315	5.860	61.865	30.860
			Maximum	100.00	97.78	99.11	99.82
		90 mins	n	14	14	14	14
			Mean	16.711	28.844	50.091	37.749
			SD	29.1730	34.6991	36.5483	37.0098
			CV(%)	174.58	120.30	72.96	98.04
			Minimum	0.00	0.00	1.56	0.00
			Median	0.630	14.620	65.220	25.980
			Maximum	100.00	98.15	99.26	99.77

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	8	15 mins	n	14	14	14	14
			Mean	9.489	21.044	20.381	24.226
			SD	26.3834	29.4047	37.0117	35.8037
			CV(%)	278.03	139.73	181.60	147.79
			Minimum	0.00	0.00	0.00	0.00
			Median	0.000	5.780	2.445	0.220
			Maximum	100.00	84.89	99.11	100.00
		30 mins	n	14	14	14	14
			Mean	12.773	22.348	28.921	26.154
			SD	28.5585	31.8672	37.0361	36.1080
			CV(%)	223.59	142.60	128.06	138.06
			Minimum	0.00	0.00	0.00	0.00
			Median	0.110	2.890	10.890	6.110
			Maximum	100.00	85.59	99.33	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	Treatment B	Treatment C	Treatment D
pH < 4	8	45 mins	n	14	14	14	14
			Mean	12.899	23.343	37.641	33.699
			SD	29.2971	34.9069	35.9282	37.2392
			CV(%)	227.13	149.54	95.45	110.50
			Minimum	0.00	0.00	0.17	0.00
			Median	0.225	2.000	26.520	21.630
			Maximum	100.00	90.38	99.41	100.00
		60 mins	n	14	14	14	14
			Mean	14.259	26.309	42.968	37.147
			SD	30.1786	36.7055	35.2042	38.7331
			CV(%)	211.64	139.52	81.93	104.27
			Minimum	0.00	0.00	0.12	0.00
			Median	0.165	7.660	41.000	29.875
			Maximum	100.00	92.79	99.56	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	Treatment B	Treatment C	Treatment D
pH < 4	8	75 mins	n	14	14	14	14
			Mean	15.419	30.666	47.404	41.534
			SD	30.9493	37.2195	36.1960	38.5435
			CV(%)	200.72	121.37	76.36	92.80
			Minimum	0.00	0.00	0.10	0.00
			Median	0.135	12.525	51.730	36.740
			Maximum	100.00	94.23	99.64	100.00
		90 mins	n	14	14	14	14
			Mean	17.213	34.824	49.704	44.560
			SD	31.1313	37.5733	37.3200	38.7267
			CV(%)	180.86	107.90	75.08	86.91
			Minimum	0.00	0.00	0.16	0.00
			Median	0.110	25.240	59.150	39.215
			Maximum	100.00	95.19	99.63	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	9	15 mins	n	14	14	14	14
			Mean	9.708	25.323	20.509	29.536
			SD	26.4643	41.1405	35.8287	36.0270
			CV(%)	272.61	162.46	174.70	121.97
			Minimum	0.00	0.00	0.00	0.00
			Median	0.440	0.000	2.890	11.555
			Maximum	100.00	100.00	95.56	100.00
		30 mins	n	14	14	14	14
			Mean	8.585	27.561	24.683	37.056
			SD	26.4363	42.2762	32.7878	39.2557
			CV(%)	307.94	153.39	132.84	105.93
			Minimum	0.00	0.00	0.00	0.00
			Median	0.330	0.000	13.110	25.960
			Maximum	100.00	100.00	97.78	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	9	45 mins	n	14	14	14	14
			Mean	9.069	28.933	30.960	42.248
			SD	26.3141	42.8857	31.2891	39.7442
			CV(%)	290.17	148.22	101.06	94.07
			Minimum	0.00	0.00	2.02	0.00
			Median	0.745	2.370	13.780	40.520
			Maximum	100.00	100.00	98.52	100.00
		60 mins	n	14	14	14	14
			Mean	9.792	31.428	36.882	44.139
			SD	26.2207	42.5136	31.1168	41.1889
			CV(%)	267.77	135.27	84.37	93.32
			Minimum	0.00	0.00	1.46	0.00
			Median	1.110	8.610	25.835	47.535
			Maximum	100.00	100.00	98.89	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	9	75 mins	n	14	14	14	14
			Mean	11.059	35.065	40.076	47.044
			SD	26.4747	41.5457	32.7528	41.6752
			CV(%)	239.39	118.48	81.73	88.59
			Minimum	0.00	0.00	1.15	0.00
			Median	0.975	16.265	32.800	55.670
			Maximum	100.00	100.00	98.84	100.00
		90 mins	n	14	14	14	14
			Mean	13.068	38.570	42.743	50.966
			SD	27.0144	40.6324	34.1412	39.9249
			CV(%)	206.72	105.35	79.88	78.34
			Minimum	0.00	0.00	1.26	0.00
			Median	0.890	22.630	35.670	58.170
			Maximum	100.00	100.00	99.04	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	10	15 mins	n	14	14	14	14
			Mean	11.101	26.761	39.175	45.804
			SD	26.5796	42.5310	42.6190	39.8685
			CV(%)	239.43	158.93	108.79	87.04
			Minimum	0.00	0.00	0.00	0.00
			Median	0.660	2.885	15.555	38.345
			Maximum	100.00	100.00	100.00	100.00
		30 mins	n	14	14	14	14
			Mean	12.391	30.901	47.206	51.335
			SD	26.0095	42.3902	36.2615	39.4674
			CV(%)	209.91	137.18	76.81	76.88
			Minimum	0.00	0.00	8.22	0.00
			Median	4.445	2.000	31.225	56.165
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	Treatment B	Treatment C	Treatment D
pH < 4	10	45 mins	n	14	14	14	14
			Mean	18.692	35.751	53.570	57.575
			SD	26.6076	42.8185	34.3933	38.0227
			CV(%)	142.35	119.77	64.20	66.04
			Minimum	0.00	0.00	11.26	0.00
			Median	9.475	7.480	48.890	65.510
			Maximum	100.00	100.00	100.00	100.00
		60 mins	n	14	14	14	14
			Mean	26.239	40.818	57.771	59.453
			SD	27.3457	40.2867	34.3415	38.1813
			CV(%)	104.22	98.70	59.44	64.22
			Minimum	0.00	0.00	14.00	0.33
			Median	25.555	24.600	61.390	68.135
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	10	75 mins	n	14	14	14	14
			Mean	32.114	45.459	60.982	63.179
			SD	29.0433	40.1371	34.2867	35.7416
			CV(%)	90.44	88.29	56.22	56.57
			Minimum	0.00	0.00	13.07	0.27
			Median	35.760	39.670	68.845	74.060
			Maximum	100.00	100.00	100.00	100.00
		90 mins	n	14	14	14	14
			Mean	35.871	48.232	63.699	67.554
			SD	31.1050	40.3043	33.4282	32.5688
			CV(%)	86.71	83.56	52.48	48.21
			Minimum	0.00	0.30	10.96	0.22
			Median	39.260	49.350	70.745	78.345
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	11	15 mins	n	14	14	14	14
			Mean	37.605	49.801	73.810	66.273
			SD	36.1135	46.8091	36.6147	43.5747
			CV(%)	96.03	93.99	49.61	65.75
			Minimum	0.00	0.00	2.67	0.00
			Median	27.490	35.775	96.000	99.780
			Maximum	100.00	100.00	100.00	100.00
		30 mins	n	14	14	14	14
			Mean	47.066	49.578	74.001	68.313
			SD	37.8243	44.3102	32.6717	40.8759
			CV(%)	80.36	89.37	44.15	59.84
			Minimum	0.00	0.00	2.89	0.00
			Median	47.445	46.175	85.780	99.890
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	11	45 mins	n	14	14	14	14
			Mean	53.311	52.988	73.999	71.170
			SD	35.3872	42.8408	33.7647	38.9140
			CV(%)	66.38	80.85	45.63	54.68
			Minimum	0.00	0.00	2.22	0.00
			Median	63.405	48.345	89.115	99.925
			Maximum	100.00	100.00	100.00	100.00
		60 mins	n	14	14	14	14
			Mean	57.229	56.826	74.724	74.743
			SD	34.7287	42.0626	34.5246	35.0201
			CV(%)	60.68	74.02	46.20	46.85
			Minimum	0.00	0.00	2.56	0.89
			Median	72.015	59.415	91.835	99.945
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	11	75 mins	n	14	14	14	14
			Mean	61.244	58.623	75.286	77.864
			SD	33.8941	42.2560	34.3378	31.9151
			CV(%)	55.34	72.08	45.61	40.99
			Minimum	0.00	0.27	7.29	0.71
			Median	74.235	67.530	93.465	99.955
			Maximum	100.00	100.00	100.00	100.00
		90 mins	n	14	14	14	14
			Mean	64.924	60.623	76.049	79.934
			SD	32.2318	41.7222	33.4999	30.1428
			CV(%)	49.65	68.82	44.05	37.71
			Minimum	0.15	0.44	6.22	0.59
			Median	75.715	72.940	94.555	99.965
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	Mean of 1 - 3	0 - 1 hour	n	14	14	14	14
			Mean	7.294	18.265	11.846	25.544
			SD	17.3001	27.6556	19.2967	28.6775
			CV(%)	237.20	151.41	162.89	112.27
			Minimum	0.00	0.00	0.41	0.00
			Median	0.130	1.220	1.130	12.390
			Maximum	62.45	88.53	67.96	81.10
		1 - 2 hours	n	14	14	14	14
			Mean	14.379	26.729	12.828	25.775
			SD	22.6247	32.5064	23.5240	32.1618
			CV(%)	157.34	121.62	183.38	124.78
			Minimum	0.00	0.00	0.00	0.00
			Median	0.430	5.925	7.315	7.685
			Maximum	66.26	87.81	90.70	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	Mean of 1 - 3	2 - 3 hours	n	14	14	14	14
			Mean	15.162	27.526	8.734	24.749
			SD	26.7076	33.8205	18.8722	32.4548
			CV(%)	176.15	122.87	216.07	131.14
			Minimum	0.00	0.00	0.00	0.00
			Median	0.260	10.630	1.315	4.130
			Maximum	76.15	100.00	68.67	100.00
		3 - 4 hours	n	14	14	14	14
			Mean	11.891	20.175	6.199	22.654
			SD	21.7469	32.4087	17.6642	32.0498
			CV(%)	182.88	160.64	284.94	141.48
			Minimum	0.00	0.00	0.00	0.00
			Median	0.255	2.200	0.390	5.630
			Maximum	71.37	98.63	66.96	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	Mean of 1 - 3	0 - 4 hours	n	14	14	14	14
			Mean	12.179	23.174	9.901	24.684
			SD	21.1767	30.5367	19.3519	30.7959
			CV(%)	173.87	131.77	195.45	124.76
			Minimum	0.00	0.00	0.11	0.00
			Median	0.605	5.395	2.760	7.910
			Maximum	59.20	93.74	73.57	95.35
	Mean of 4 - 7	0 - 1 hour	n	14	14	14	14
			Mean	19.474	21.136	35.894	34.744
			SD	28.9315	31.9933	34.8941	32.6356
			CV(%)	148.57	151.37	97.22	93.93
			Minimum	0.00	0.00	0.25	0.00
			Median	3.495	9.790	20.365	23.820
			Maximum	100.00	99.31	83.03	99.91

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	Mean of 4 - 7	1 - 2 hours	n	14	14	14	14
			Mean	34.779	44.242	48.474	46.659
			SD	34.5440	40.9950	35.4099	43.6890
			CV(%)	99.32	92.66	73.05	93.63
			Minimum	0.00	0.00	0.75	0.00
			Median	36.960	34.140	60.210	32.905
			Maximum	99.75	100.00	100.00	99.97
		2 - 3 hours	n	14	14	14	14
			Mean	43.057	51.601	48.422	51.228
			SD	34.0307	40.7127	41.9822	43.2847
			CV(%)	79.04	78.90	86.70	84.49
			Minimum	0.00	0.00	0.14	0.00
			Median	49.960	46.085	55.040	47.040
			Maximum	100.00	100.00	100.00	100.00

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
pH < 4	Mean of 4 - 7	3 - 4 hours	n	14	14	14	14
			Mean	46.600	51.054	42.951	56.574
			SD	40.8289	42.8519	40.9046	41.9735
			CV(%)	87.62	83.94	95.24	74.19
			Minimum	0.00	0.00	0.00	0.00
			Median	55.850	44.460	47.900	65.000
			Maximum	100.00	100.00	100.00	100.00
Total number of Reflux Episodes	Liquid	2 hours	n	13	13	13	13
			Mean	2.8	2.5	2.9	2.7
			SD	3.51	3.10	4.07	3.25
			CV(%)	123.26	125.89	139.29	120.72
			Minimum	0	0	0	0
			Median	1.0	1.0	1.0	1.0
			Maximum	11	9	15	8

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
Total number of Reflux Episodes	Liquid	4 hours	n	13	13	13	13
			Mean	3.9	3.9	4.5	4.0
			SD	4.94	5.19	5.13	4.64
			CV(%)	125.94	132.23	114.88	115.92
			Minimum	0	0	0	0
			Median	1.0	2.0	3.0	1.0
			Maximum	16	16	18	12
	Gas	2 hours	n	13	13	13	13
			Mean	0.6	0.5	0.5	0.3
			SD	0.87	0.66	0.97	0.63
			CV(%)	141.33	143.05	179.66	204.89
			Minimum	0	0	0	0
			Median	0.0	0.0	0.0	0.0
			Maximum	2	2	3	2

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
Total number of Reflux Episodes	Gas	4 hours	n	13	13	13	13
			Mean	1.6	1.4	1.2	0.6
			SD	1.85	1.39	1.54	0.77
			CV(%)	114.53	100.15	124.79	124.79
			Minimum	0	0	0	0
			Median	1.0	1.0	1.0	0.0
			Maximum	6	4	5	2
	Mixed	2 hours	n	13	13	13	13
			Mean	1.5	2.3	1.6	2.2
			SD	1.61	3.01	2.36	2.12
			CV(%)	104.86	130.46	146.36	98.21
			Minimum	0	0	0	0
			Median	1.0	1.0	1.0	2.0
			Maximum	5	9	7	7

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
Total number of Reflux Episodes	Mixed	4 hours	n	13	13	13	13
			Mean	2.5	3.5	1.9	3.5
			SD	2.60	4.84	2.72	3.20
			CV(%)	102.49	139.85	141.55	90.56
			Minimum	0	0	0	0
			Median	2.0	1.0	1.0	3.0
			Maximum	7	15	9	9
	Acid	2 hours	n	13	13	13	13
			Mean	1.9	1.6	2.2	2.9
			SD	3.48	1.89	2.85	4.05
			CV(%)	180.71	117.29	132.47	138.59
			Minimum	0	0	0	0
			Median	0.0	1.0	1.0	1.0
			Maximum	12	6	8	13

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
Total number of Reflux Episodes	Acid	4 hours	n	13	13	13	13
			Mean	3.1	2.9	3.1	4.5
			SD	5.71	3.38	4.37	5.64
			CV(%)	185.50	115.56	141.95	124.19
			Minimum	0	0	0	0
			Median	0.0	2.0	1.0	2.0
			Maximum	19	11	14	18
	Weakly Acidic	2 hours	n	13	13	13	13
			Mean	2.6	3.2	2.4	1.8
			SD	2.26	3.89	3.01	1.74
			CV(%)	86.26	123.38	126.43	98.32
			Minimum	0	0	0	0
			Median	3.0	3.0	1.0	1.0
			Maximum	7	14	9	5

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
Total number of Reflux Episodes	Weakly Acidic	4 hours	n	13	13	13	13
			Mean	3.7	4.5	3.3	2.9
			SD	3.92	5.62	3.95	3.09
			CV(%)	106.27	126.00	119.27	105.87
			Minimum	0	0	0	0
			Median	3.0	3.0	1.0	2.0
			Maximum	13	19	12	9
	Reaching 15 cm above the LOS	2 hours	n	13	13	13	13
			Mean	1.0	0.9	0.4	0.5
			SD	2.00	1.71	1.12	0.97
			CV(%)	200.00	184.81	291.43	179.66
			Minimum	0	0	0	0
			Median	0.0	0.0	0.0	0.0
			Maximum	7	5	4	3

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	Treatment B	Treatment C	Treatment D
Total number of Reflux Episodes	Reaching 15 cm above the LOS	4 hours	n	13	13	13	13
			Mean	1.1	1.3	0.4	0.8
			SD	2.25	2.25	1.12	1.68
			CV(%)	209.23	172.09	291.43	198.03
			Minimum	0	0	0	0
			Median	0.0	0.0	0.0	0.0
			Maximum	8	7	4	5
Oesophageal Bolus Exposure to Reflux		2 hours	n	13	13	13	13
			Mean	0.7	0.9	0.7	1.1
			SD	0.80	0.93	0.86	1.16
			CV(%)	108.96	99.06	116.63	108.03
			Minimum	0	0	0	0
			Median	0.4	0.5	0.3	0.8
			Maximum	3	3	3	4

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Table 14.2.1.2 Summary of Primary and Secondary Endpoints, by Treatment
Per Protocol Population (N=14)

pH of Reflux Event	Electrode/Type Of Reflux Event	Timepoint (post treatment)	Statistic	Treatment A	B	C	D
Oesophageal Bolus Exposure to Reflux		4 hours	n	13	13	13	13
			Mean	0.5	0.7	0.5	0.8
			SD	0.61	0.76	0.59	0.73
			CV(%)	121.11	109.26	119.37	93.05
			Minimum	0	0	0	0
			Median	0.3	0.3	0.2	0.5
			Maximum	2	2	2	2

Data Source: Listing 16.2.6.2, Listing 16.2.6.3, Listing 16.2.6.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated

Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_01_02.sas 12FEB2014 11:29

14.2.2 pH and Reflux Data Analyses

14.2.2.1 Statistical Analysis of Primary Endpoint

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Table 14.2.2.1 Statistical Analysis of Primary Endpoint

	Comparison		Number of Subjects		LS Mean (Standard Error)		Test-Reference	
Population	Test	Reference	Test	Reference	Test	Reference	LS Mean Difference (95% CI)	p-value
ITT	A	C	15	15	9.7 (3.50)	8.6 (3.50)	1.1 (-8.9, 11.1)	0.821
Per Protocol	A	C	14	14	6.5 (3.25)	8.6 (3.25)	-2.1 (-11.5, 7.2)	0.646

Data Source: Appendix 16.1.9.1
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

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14.2.2.2 Exploratory Analysis 1 of Primary Endpoint

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Table 14.2.2.2 Exploratory Analysis 1 of Primary Endpoint

	Number of Subjects			LS Mean (Standard Error)		Test-Reference		Model p-values			
Population	Test (A)	Ref. (C)	Treatment Period	Test	Reference	LS Mean Difference (95% CI)	p-value	Treat -ment	Period	Day	Treatment by Period Interaction
ITT	8	8	Period 1	11.2 (4.91)	8.1 (4.82)	3.2 (-10.8, 17.1)	0.650				
	7	7	Period 2	7.8 (5.15)	9.0 (5.15)	-1.2 (-15.8, 13.4)	0.870				
	15	15	Overall	9.5 (3.53)	8.5 (3.54)	1.0 (-9.1, 11.1)	0.845	0.626	0.724	0.097	0.554
Per Protocol	7	7	Period 1	4.9 (4.74)	8.0 (4.62)	-3.1 (-16.6, 10.3)	0.642				
	7	7	Period 2	7.9 (4.62)	9.3 (4.62)	-1.4 (-14.6, 11.7)	0.827				
	14	14	Overall	6.4 (3.28)	8.7 (3.29)	-2.3 (-11.7, 7.2)	0.629	0.597	0.385	0.183	0.584

Data Source: Appendix 16.1.9.2
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period, treatment period x treament interaction and treatment day as fixed effects and a random effect for subject.

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14.2.2.3 Exploratory Analysis 2 of Primary Endpoint

Table 14.2.2.3 Exploratory Analysis 2 of Primary Endpoint

Population	Number of Subjects: Test (A)	Number of Subjects: Ref. (C)	Treatment Day	LS Mean (Standard Error): Test	LS Mean (Standard Error): Reference	Test-Reference: LS Mean Difference (95% CI)	Test-Reference: p-value	Model p-values: Treatment	Model p-values: Period	Model p-values: Day	Model p-values: Treatment by Day Interaction
ITT	7	8	Day 2	14.1 (5.34)	11.4 (4.89)	2.8 (-11.9, 17.5)	0.705				
	8	7	Day 3	5.5 (4.88)	5.6 (5.23)	-0.1 (-14.5, 14.2)	0.985				
	15	15	Overall	9.8 (3.60)	8.5 (3.59)	1.3 (-9.0, 11.6)	0.797	0.593	0.735	0.100	0.903
Per Protocol	6	8	Day 2	6.8 (5.17)	11.6 (4.37)	-4.8 (-18.6, 8.9)	0.485				
	8	6	Day 3	5.7 (4.36)	5.5 (5.05)	0.2 (-13.2, 13.6)	0.975				
	14	14	Overall	6.2 (3.36)	8.5 (3.35)	-2.3 (-11.9, 7.3)	0.632	0.623	0.392	0.188	0.843

Data Source: Appendix 16.1.9.3
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period, treatment day x treatment interaction and treatment day as fixed effects and a random effect for subject.

HobsonR: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_02_03.sas 11NOV2013 10:03

14.2.2.4 Statistical Analysis of Percentage of Time that Electrode is pH <4 over 2 Hours

Table 14.2.2.4 Statistical Analysis of % of Time that Electrode is pH < 4 Over 2 Hours

	Comparison		Number of Subjects		LS Mean (Standard Error)		Test-Reference	
Population	Test	Reference	Test	Reference	Test	Reference	LS Mean Difference (95% CI)	p-value
ITT	A	D	15	14	9.7 (3.50)	8.8 (3.62)	0.9 (-9.3, 11.0)	0.862
	B	C	14	15	3.5 (3.62)	8.6 (3.50)	-5.1 (-15.3, 5.1)	0.320
	B	D	14	14	3.5 (3.62)	8.8 (3.62)	-5.3 (-15.7, 5.0)	0.305
Per Protocol	A	D	14	14	6.5 (3.25)	9.0 (3.24)	-2.6 (-11.8, 6.7)	0.582
	B	C	14	14	3.4 (3.24)	8.6 (3.25)	-5.2 (-14.5, 4.0)	0.262
	B	D	14	14	3.4 (3.24)	9.0 (3.24)	-5.7 (-14.9, 3.6)	0.226

Data Source: Appendix 16.1.9.1
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

HobsonR: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_02_04.sas 11NOV2013 10:03

14.2.2.5 Statistical Analysis of Percentage of Time that Electrode is pH <4 over 4 Hours

Table 14.2.2.5 Statistical Analysis of % of Time that Electrode is pH < 4 Over 4 Hours

	Comparison		Number of Subjects		LS Mean (Standard Error)		Test-Reference	
Population	Test	Reference	Test	Reference	Test	Reference	LS Mean Difference (95% CI)	p-value
ITT	A	C	15	15	7.8 (3.40)	6.6 (3.40)	1.2 (-8.5, 10.9)	0.803
	A	D	15	14	7.8 (3.40)	9.6 (3.52)	-1.8 (-11.7, 8.1)	0.716
	B	C	14	15	4.6 (3.52)	6.6 (3.40)	-2.0 (-11.9, 7.9)	0.683
	B	D	14	14	4.6 (3.52)	9.6 (3.52)	-5.0 (-15.1, 5.0)	0.319
Per Protocol	A	C	14	14	5.4 (3.33)	6.6 (3.33)	-1.2 (-10.7, 8.4)	0.808
	A	D	14	14	5.4 (3.33)	9.8 (3.33)	-4.4 (-13.9, 5.1)	0.357
	B	C	14	14	4.5 (3.33)	6.6 (3.33)	-2.0 (-11.6, 7.5)	0.672
	B	D	14	14	4.5 (3.33)	9.8 (3.33)	-5.3 (-14.8, 4.2)	0.270

Data Source: Appendix 16.1.9.4
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

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14.2.2.6 Statistical Analysis of Percentage of Time that each Electrode is pH <4 over Various Times

Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
ITT	4	15 mins	A	C	15	15	18.8 (8.69)	11.7 (8.70)	7.1 (-13.9, 28.1)	0.496
			B	C	14	15	16.8 (8.98)	11.7 (8.70)	5.1 (-16.8, 26.9)	0.642
			A	D	15	14	18.8 (8.69)	21.1 (9.05)	-2.3 (-24.3, 19.8)	0.835
			B	D	14	14	16.8 (8.98)	21.1 (9.05)	-4.4 (-26.2, 17.5)	0.689
		30 mins	A	C	15	15	23.6 (9.09)	20.6 (9.10)	3.0 (-18.3, 24.3)	0.778
			B	C	14	15	18.5 (9.38)	20.6 (9.10)	-2.1 (-24.3, 20.1)	0.850
			A	D	15	14	23.6 (9.09)	28.6 (9.45)	-5.0 (-27.4, 17.4)	0.653
			B	D	14	14	18.5 (9.38)	28.6 (9.45)	-10.1 (-32.2, 12.1)	0.363
		45 mins	A	C	15	15	25.1 (9.41)	24.3 (9.42)	0.8 (-21.0, 22.6)	0.942
			B	C	14	15	22.0 (9.71)	24.3 (9.42)	-2.3 (-25.1, 20.5)	0.839
			A	D	15	14	25.1 (9.41)	34.1 (9.79)	-9.0 (-31.9, 14.0)	0.433
			B	D	14	14	22.0 (9.71)	34.1 (9.79)	-12.1 (-34.8, 10.6)	0.287
		60 mins	A	C	15	15	25.7 (9.51)	27.4 (9.52)	-1.6 (-24.1, 20.8)	0.883
			B	C	14	15	24.9 (9.82)	27.4 (9.52)	-2.5 (-25.9, 20.9)	0.831
			A	D	15	14	25.7 (9.51)	35.9 (9.90)	-10.2 (-33.8, 13.4)	0.387
			B	D	14	14	24.9 (9.82)	35.9 (9.90)	-11.0 (-34.4, 12.3)	0.345
		75 mins	A	C	15	15	26.9 (9.46)	30.7 (9.46)	-3.8 (-27.1, 19.4)	0.740
			B	C	14	15	27.2 (9.78)	30.7 (9.46)	-3.5 (-27.7, 20.7)	0.771
			A	D	15	14	26.9 (9.46)	37.4 (9.85)	-10.5 (-34.9, 13.9)	0.389
			B	D	14	14	27.2 (9.78)	37.4 (9.85)	-10.2 (-34.4, 14.0)	0.399

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
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C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

HobsonR: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_02_06.sas 11NOV2013 10:04

Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
ITT	4 (ctd.)	90 mins	A	C	15	15	29.5 (9.37)	32.2 (9.38)	-2.7 (-25.9, 20.5)	0.815
			B	C	14	15	29.6 (9.69)	32.2 (9.38)	-2.6 (-26.7, 21.6)	0.830
			A	D	15	14	29.5 (9.37)	38.0 (9.77)	-8.5 (-32.9, 15.8)	0.482
			B	D	14	14	29.6 (9.69)	38.0 (9.77)	-8.4 (-32.6, 15.7)	0.485
	5	15 mins	A	C	15	15	17.1 (8.91)	32.3 (8.92)	-15.1 (-39.0, 8.7)	0.206
			B	C	14	15	9.9 (9.25)	32.3 (8.92)	-22.4 (-46.9, 2.0)	0.071
			A	D	15	14	17.1 (8.91)	22.9 (9.24)	-5.8 (-30.2, 18.6)	0.634
			B	D	14	14	9.9 (9.25)	22.9 (9.24)	-13.0 (-37.8, 11.7)	0.293
		30 mins	A	C	15	15	21.8 (9.15)	38.4 (9.17)	-16.5 (-39.2, 6.1)	0.148
			B	C	14	15	14.4 (9.48)	38.4 (9.17)	-24.0 (-47.3, -0.7)	0.044
			A	D	15	14	21.8 (9.15)	25.4 (9.47)	-3.6 (-26.8, 19.6)	0.757
			B	D	14	14	14.4 (9.48)	25.4 (9.47)	-11.0 (-34.6, 12.5)	0.349
		45 mins	A	C	15	15	26.3 (9.32)	39.7 (9.34)	-13.4 (-35.0, 8.2)	0.216
			B	C	14	15	18.9 (9.63)	39.7 (9.34)	-20.8 (-43.1, 1.4)	0.066
			A	D	15	14	26.3 (9.32)	30.5 (9.63)	-4.2 (-26.4, 18.0)	0.704
			B	D	14	14	18.9 (9.63)	30.5 (9.63)	-11.6 (-34.1, 10.9)	0.302
		60 mins	A	C	15	15	30.2 (9.54)	42.1 (9.55)	-11.9 (-33.8, 9.9)	0.276
			B	C	14	15	21.8 (9.85)	42.1 (9.55)	-20.3 (-42.9, 2.3)	0.076
			A	D	15	14	30.2 (9.54)	34.5 (9.84)	-4.3 (-26.7, 18.2)	0.702
			B	D	14	14	21.8 (9.85)	34.5 (9.84)	-12.6 (-35.4, 10.1)	0.267

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

HobsonR: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_02_06.sas 11NOV2013 10:04

Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
ITT	5 (ctd.)	75 mins	A	C	15	15	32.3 (9.71)	42.5 (9.73)	-10.2 (-32.0, 11.6)	0.350
			B	C	14	15	25.5 (10.02)	42.5 (9.73)	-17.0 (-39.5, 5.5)	0.134
			A	D	15	14	32.3 (9.71)	37.1 (10.01)	-4.8 (-27.2, 17.7)	0.670
			B	D	14	14	25.5 (10.02)	37.1 (10.01)	-11.6 (-34.2, 11.1)	0.308
		90 mins	A	C	15	15	34.4 (9.69)	42.1 (9.71)	-7.7 (-29.2, 13.8)	0.472
			B	C	14	15	28.2 (10.00)	42.1 (9.71)	-13.9 (-36.1, 8.2)	0.211
			A	D	15	14	34.4 (9.69)	38.8 (9.99)	-4.3 (-26.4, 17.7)	0.692
			B	D	14	14	28.2 (10.00)	38.8 (9.99)	-10.6 (-32.9, 11.8)	0.343
	6	15 mins	A	C	15	15	16.7 (8.56)	22.9 (8.59)	-6.2 (-30.1, 17.8)	0.603
			B	C	14	15	10.2 (8.89)	22.9 (8.59)	-12.7 (-37.1, 11.8)	0.300
			A	D	15	14	16.7 (8.56)	16.1 (8.91)	0.6 (-23.8, 25.0)	0.959
			B	D	14	14	10.2 (8.89)	16.1 (8.91)	-5.9 (-30.7, 19.0)	0.635
		30 mins	A	C	15	15	19.8 (9.07)	33.4 (9.10)	-13.6 (-37.5, 10.3)	0.256
			B	C	14	15	13.5 (9.40)	33.4 (9.10)	-19.9 (-44.3, 4.5)	0.108
			A	D	15	14	19.8 (9.07)	21.6 (9.42)	-1.8 (-26.2, 22.6)	0.883
			B	D	14	14	13.5 (9.40)	21.6 (9.42)	-8.1 (-32.9, 16.7)	0.514
		45 mins	A	C	15	15	23.6 (9.30)	36.7 (9.33)	-13.1 (-36.4, 10.2)	0.261
			B	C	14	15	15.8 (9.63)	36.7 (9.33)	-20.9 (-44.7, 3.0)	0.084
			A	D	15	14	23.6 (9.30)	26.6 (9.65)	-3.0 (-26.8, 20.8)	0.801
			B	D	14	14	15.8 (9.63)	26.6 (9.65)	-10.7 (-34.9, 13.4)	0.374

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

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Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
ITT	6 (ctd.)	60 mins	A	C	15	15	26.3 (9.40)	40.8 (9.43)	-14.5 (-37.4, 8.3)	0.206
			B	C	14	15	19.3 (9.71)	40.8 (9.43)	-21.5 (-44.9, 1.9)	0.071
			A	D	15	14	26.3 (9.40)	29.9 (9.73)	-3.6 (-27.0, 19.7)	0.754
			B	D	14	14	19.3 (9.71)	29.9 (9.73)	-10.6 (-34.3, 13.1)	0.370
		75 mins	A	C	15	15	27.3 (9.47)	42.8 (9.50)	-15.5 (-38.0, 7.0)	0.172
			B	C	14	15	24.1 (9.78)	42.8 (9.50)	-18.7 (-41.8, 4.4)	0.110
			A	D	15	14	27.3 (9.47)	32.6 (9.80)	-5.3 (-28.3, 17.8)	0.645
			B	D	14	14	24.1 (9.78)	32.6 (9.80)	-8.5 (-31.8, 14.9)	0.468
		90 mins	A	C	15	15	28.8 (9.53)	45.3 (9.56)	-16.5 (-38.5, 5.5)	0.138
			B	C	14	15	27.4 (9.82)	45.3 (9.56)	-17.8 (-40.4, 4.7)	0.118
			A	D	15	14	28.8 (9.53)	34.2 (9.85)	-5.5 (-28.0, 17.1)	0.626
			B	D	14	14	27.4 (9.82)	34.2 (9.85)	-6.8 (-29.7, 16.0)	0.548
	7	15 mins	A	C	15	15	15.4 (7.96)	16.7 (7.98)	-1.3 (-21.9, 19.2)	0.895
			B	C	14	15	19.5 (8.25)	16.7 (7.98)	2.8 (-18.3, 23.9)	0.789
			A	D	15	14	15.4 (7.96)	19.6 (8.30)	-4.3 (-25.4, 16.9)	0.686
			B	D	14	14	19.5 (8.25)	19.6 (8.30)	-0.1 (-21.6, 21.4)	0.992
		30 mins	A	C	15	15	16.9 (8.47)	27.5 (8.50)	-10.6 (-33.2, 12.0)	0.348
			B	C	14	15	19.3 (8.79)	27.5 (8.50)	-8.1 (-31.2, 14.9)	0.479
			A	D	15	14	16.9 (8.47)	24.8 (8.84)	-7.9 (-31.1, 15.3)	0.495
			B	D	14	14	19.3 (8.79)	24.8 (8.84)	-5.4 (-29.0, 18.1)	0.643

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

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Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
ITT	7 (ctd.)	45 mins	A	C	15	15	19.4 (8.79)	38.1 (8.82)	-18.7 (-41.2, 3.7)	0.099
			B	C	14	15	21.3 (9.11)	38.1 (8.82)	-16.8 (-39.8, 6.2)	0.147
			A	D	15	14	19.4 (8.79)	32.3 (9.16)	-12.9 (-36.0, 10.2)	0.266
			B	D	14	14	21.3 (9.11)	32.3 (9.16)	-10.9 (-34.4, 12.5)	0.352
		60 mins	A	C	15	15	21.2 (8.92)	45.0 (8.94)	-23.7 (-46.3, -1.2)	0.040
			B	C	14	15	25.4 (9.23)	45.0 (8.94)	-19.6 (-42.6, 3.5)	0.094
			A	D	15	14	21.2 (8.92)	34.6 (9.29)	-13.4 (-36.6, 9.8)	0.248
			B	D	14	14	25.4 (9.23)	34.6 (9.29)	-9.2 (-32.8, 14.3)	0.431
		75 mins	A	C	15	15	21.9 (8.95)	49.5 (8.98)	-27.6 (-50.0, -5.2)	0.017
			B	C	14	15	28.7 (9.26)	49.5 (8.98)	-20.8 (-43.7, 2.1)	0.074
			A	D	15	14	21.9 (8.95)	35.2 (9.32)	-13.3 (-36.3, 9.8)	0.251
			B	D	14	14	28.7 (9.26)	35.2 (9.32)	-6.5 (-29.8, 16.9)	0.579
		90 mins	A	C	15	15	22.9 (8.88)	52.7 (8.91)	-29.8 (-51.8, -7.8)	0.009
			B	C	14	15	32.0 (9.19)	52.7 (8.91)	-20.7 (-43.2, 1.8)	0.070
			A	D	15	14	22.9 (8.88)	35.7 (9.25)	-12.8 (-35.4, 9.8)	0.259
			B	D	14	14	32.0 (9.19)	35.7 (9.25)	-3.7 (-26.7, 19.2)	0.744
	8	15 mins	A	C	15	15	16.3 (8.71)	19.5 (8.75)	-3.2 (-25.1, 18.6)	0.766
			B	C	14	15	23.1 (9.01)	19.5 (8.75)	3.6 (-18.7, 26.0)	0.743
			A	D	15	14	16.3 (8.71)	23.0 (9.06)	-6.7 (-29.1, 15.7)	0.549
			B	D	14	14	23.1 (9.01)	23.0 (9.06)	0.2 (-22.6, 22.9)	0.987

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

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Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
ITT	8 (ctd.)	30 mins	A	C	15	15	19.2 (8.91)	29.7 (8.95)	-10.5 (-32.2, 11.2)	0.332
			B	C	14	15	24.8 (9.21)	29.7 (8.95)	-5.0 (-27.2, 17.3)	0.655
			A	D	15	14	19.2 (8.91)	25.0 (9.26)	-5.8 (-28.0, 16.5)	0.604
			B	D	14	14	24.8 (9.21)	25.0 (9.26)	-0.2 (-22.8, 22.4)	0.988
		45 mins	A	C	15	15	19.3 (9.09)	39.6 (9.12)	-20.3 (-41.9, 1.4)	0.066
			B	C	14	15	26.1 (9.38)	39.6 (9.12)	-13.5 (-35.7, 8.7)	0.226
			A	D	15	14	19.3 (9.09)	32.4 (9.44)	-13.1 (-35.3, 9.2)	0.241
			B	D	14	14	26.1 (9.38)	32.4 (9.44)	-6.3 (-28.9, 16.2)	0.574
		60 mins	A	C	15	15	20.6 (9.18)	45.5 (9.22)	-24.9 (-46.4, -3.4)	0.025
			B	C	14	15	29.3 (9.47)	45.5 (9.22)	-16.3 (-38.3, 5.8)	0.144
			A	D	15	14	20.6 (9.18)	35.5 (9.53)	-14.8 (-37.0, 7.3)	0.183
			B	D	14	14	29.3 (9.47)	35.5 (9.53)	-6.2 (-28.6, 16.2)	0.579
		75 mins	A	C	15	15	21.7 (9.27)	50.3 (9.31)	-28.6 (-50.5, -6.8)	0.012
			B	C	14	15	33.5 (9.57)	50.3 (9.31)	-16.8 (-39.2, 5.7)	0.139
			A	D	15	14	21.7 (9.27)	39.7 (9.63)	-18.0 (-40.5, 4.5)	0.113
			B	D	14	14	33.5 (9.57)	39.7 (9.63)	-6.1 (-28.9, 16.6)	0.588
		90 mins	A	C	15	15	23.3 (9.26)	52.5 (9.30)	-29.2 (-51.2, -7.1)	0.011
			B	C	14	15	37.5 (9.56)	52.5 (9.30)	-14.9 (-37.6, 7.7)	0.189
			A	D	15	14	23.3 (9.26)	42.3 (9.62)	-19.1 (-41.7, 3.6)	0.097
			B	D	14	14	37.5 (9.56)	42.3 (9.62)	-4.8 (-27.8, 18.1)	0.673

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
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D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

HobsonR: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_02_06.sas 11NOV2013 10:04

Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
ITT	9	15 mins	A	C	15	15	16.3 (9.02)	19.8 (9.06)	-3.5 (-24.9, 17.9)	0.742
			B	C	14	15	27.7 (9.31)	19.8 (9.06)	7.9 (-14.0, 29.9)	0.468
			A	D	15	14	16.3 (9.02)	28.5 (9.32)	-12.2 (-34.1, 9.6)	0.265
			B	D	14	14	27.7 (9.31)	28.5 (9.32)	-0.8 (-22.9, 21.4)	0.946
		30 mins	A	C	15	15	15.2 (9.10)	25.3 (9.14)	-10.1 (-30.9, 10.6)	0.329
			B	C	14	15	30.2 (9.38)	25.3 (9.14)	4.9 (-16.4, 26.1)	0.646
			A	D	15	14	15.2 (9.10)	36.5 (9.39)	-21.3 (-42.5, -0.1)	0.049
			B	D	14	14	30.2 (9.38)	36.5 (9.39)	-6.3 (-27.8, 15.2)	0.554
		45 mins	A	C	15	15	15.7 (9.01)	33.2 (9.04)	-17.6 (-36.7, 1.6)	0.071
			B	C	14	15	32.0 (9.25)	33.2 (9.04)	-1.2 (-20.9, 18.4)	0.899
			A	D	15	14	15.7 (9.01)	42.3 (9.26)	-26.6 (-46.2, -7.1)	0.009
			B	D	14	14	32.0 (9.25)	42.3 (9.26)	-10.3 (-30.1, 9.5)	0.299
		60 mins	A	C	15	15	16.3 (8.86)	40.0 (8.89)	-23.7 (-41.7, -5.6)	0.012
			B	C	14	15	34.6 (9.09)	40.0 (8.89)	-5.4 (-23.9, 13.2)	0.562
			A	D	15	14	16.3 (8.86)	44.3 (9.10)	-28.0 (-46.5, -9.5)	0.004
			B	D	14	14	34.6 (9.09)	44.3 (9.10)	-9.7 (-28.5, 9.0)	0.299
		75 mins	A	C	15	15	17.5 (8.74)	43.7 (8.77)	-26.2 (-43.9, -8.5)	0.005
			B	C	14	15	38.2 (8.96)	43.7 (8.77)	-5.4 (-23.6, 12.7)	0.547
			A	D	15	14	17.5 (8.74)	47.2 (8.97)	-29.8 (-47.8, -11.7)	0.002
			B	D	14	14	38.2 (8.96)	47.2 (8.97)	-9.0 (-27.3, 9.3)	0.325

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
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Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
ITT	9 (ctd.)	90 mins	A	C	15	15	19.2 (8.37)	46.1 (8.39)	-26.9 (-44.3, -9.5)	0.003
			B	C	14	15	41.3 (8.59)	46.1 (8.39)	-4.8 (-22.7, 13.1)	0.589
			A	D	15	14	19.2 (8.37)	50.7 (8.59)	-31.4 (-49.2, -13.6)	<0.001
			B	D	14	14	41.3 (8.59)	50.7 (8.59)	-9.3 (-27.4, 8.7)	0.301
	10	15 mins	A	C	15	15	16.1 (9.67)	36.2 (9.65)	-20.0 (-46.2, 6.1)	0.130
			B	C	14	15	30.1 (10.04)	36.2 (9.65)	-6.0 (-32.7, 20.6)	0.649
			A	D	15	14	16.1 (9.67)	44.8 (10.01)	-28.7 (-55.4, -2.0)	0.036
			B	D	14	14	30.1 (10.04)	44.8 (10.01)	-14.7 (-41.9, 12.4)	0.279
		30 mins	A	C	15	15	17.2 (9.09)	44.3 (9.07)	-27.0 (-50.8, -3.2)	0.027
			B	C	14	15	34.2 (9.42)	44.3 (9.07)	-10.0 (-34.3, 14.2)	0.408
			A	D	15	14	17.2 (9.09)	50.8 (9.40)	-33.5 (-57.9, -9.2)	0.008
			B	D	14	14	34.2 (9.42)	50.8 (9.40)	-16.5 (-41.2, 8.1)	0.183
		45 mins	A	C	15	15	23.3 (8.83)	50.6 (8.81)	-27.2 (-49.1, -5.4)	0.016
			B	C	14	15	39.0 (9.13)	50.6 (8.81)	-11.6 (-33.9, 10.7)	0.300
			A	D	15	14	23.3 (8.83)	57.1 (9.11)	-33.8 (-56.1, -11.4)	0.004
			B	D	14	14	39.0 (9.13)	57.1 (9.11)	-18.1 (-40.7, 4.6)	0.114
		60 mins	A	C	15	15	30.3 (8.48)	55.5 (8.47)	-25.2 (-44.9, -5.5)	0.013
			B	C	14	15	44.1 (8.75)	55.5 (8.47)	-11.4 (-31.5, 8.7)	0.258
			A	D	15	14	30.3 (8.48)	59.3 (8.73)	-29.0 (-49.1, -8.8)	0.006
			B	D	14	14	44.1 (8.75)	59.3 (8.73)	-15.2 (-35.6, 5.2)	0.140

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
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D: Untreated
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HobsonR: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_02_06.sas 11NOV2013 10:04

Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
ITT	10 (ctd.)	75 mins	A	C	15	15	35.8 (8.30)	58.3 (8.29)	-22.4 (-41.2, -3.7)	0.020
			B	C	14	15	48.5 (8.56)	58.3 (8.29)	-9.7 (-28.9, 9.5)	0.311
			A	D	15	14	35.8 (8.30)	62.8 (8.54)	-27.0 (-46.2, -7.8)	0.007
			B	D	14	14	48.5 (8.56)	62.8 (8.54)	-14.3 (-33.8, 5.2)	0.145
		90 mins	A	C	15	15	39.2 (8.19)	60.5 (8.18)	-21.3 (-40.1, -2.5)	0.027
			B	C	14	15	51.0 (8.45)	60.5 (8.18)	-9.5 (-28.7, 9.7)	0.322
			A	D	15	14	39.2 (8.19)	67.0 (8.43)	-27.8 (-47.0, -8.6)	0.006
			B	D	14	14	51.0 (8.45)	67.0 (8.43)	-16.0 (-35.5, 3.5)	0.104
	11	15 mins	A	C	15	15	34.6 (9.16)	74.5 (9.09)	-39.9 (-65.1, -14.7)	0.003
			B	C	14	15	52.8 (9.42)	74.5 (9.09)	-21.6 (-47.0, 3.7)	0.092
			A	D	15	14	34.6 (9.16)	65.8 (9.40)	-31.3 (-56.8, -5.7)	0.018
			B	D	14	14	52.8 (9.42)	65.8 (9.40)	-13.0 (-38.8, 12.9)	0.316
		30 mins	A	C	15	15	44.5 (9.00)	76.2 (8.93)	-31.6 (-56.5, -6.8)	0.014
			B	C	14	15	52.5 (9.26)	76.2 (8.93)	-23.6 (-48.7, 1.4)	0.063
			A	D	15	14	44.5 (9.00)	68.6 (9.24)	-24.1 (-49.3, 1.1)	0.060
			B	D	14	14	52.5 (9.26)	68.6 (9.24)	-16.1 (-41.6, 9.3)	0.207
		45 mins	A	C	15	15	50.9 (8.73)	75.9 (8.66)	-25.0 (-49.4, -0.6)	0.045
			B	C	14	15	55.9 (8.98)	75.9 (8.66)	-20.0 (-44.6, 4.5)	0.106
			A	D	15	14	50.9 (8.73)	71.5 (8.96)	-20.6 (-45.4, 4.1)	0.099
			B	D	14	14	55.9 (8.98)	71.5 (8.96)	-15.7 (-40.7, 9.3)	0.211

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
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HobsonR: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_02_06.sas 11NOV2013 10:04

Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
ITT	11 (ctd.)	60 mins	A	C	15	15	54.5 (8.13)	77.0 (8.07)	-22.5 (-44.9, 0.0)	0.050
			B	C	14	15	59.9 (8.37)	77.0 (8.07)	-17.1 (-39.6, 5.5)	0.134
			A	D	15	14	54.5 (8.13)	75.2 (8.35)	-20.7 (-43.5, 2.1)	0.073
			B	D	14	14	59.9 (8.37)	75.2 (8.35)	-15.3 (-38.3, 7.7)	0.186
		75 mins	A	C	15	15	58.4 (7.70)	77.7 (7.64)	-19.4 (-40.2, 1.5)	0.068
			B	C	14	15	61.9 (7.92)	77.7 (7.64)	-15.8 (-36.8, 5.2)	0.135
			A	D	15	14	58.4 (7.70)	78.3 (7.90)	-20.0 (-41.2, 1.2)	0.064
			B	D	14	14	61.9 (7.92)	78.3 (7.90)	-16.4 (-37.8, 4.9)	0.128
		90 mins	A	C	15	15	61.8 (7.22)	78.3 (7.16)	-16.5 (-35.9, 2.9)	0.094
			B	C	14	15	64.0 (7.42)	78.3 (7.16)	-14.3 (-33.8, 5.2)	0.146
			A	D	15	14	61.8 (7.22)	80.4 (7.41)	-18.5 (-38.2, 1.2)	0.064
			B	D	14	14	64.0 (7.42)	80.4 (7.41)	-16.4 (-36.3, 3.5)	0.103
Per Protocol 4		15 mins	A	C	14	14	12.9 (8.50)	13.3 (8.63)	-0.3 (-20.6, 19.9)	0.973
			B	C	14	14	14.8 (8.53)	13.3 (8.63)	1.5 (-19.4, 22.4)	0.886
			A	D	14	14	12.9 (8.50)	19.5 (8.58)	-6.5 (-27.2, 14.1)	0.526
			B	D	14	14	14.8 (8.53)	19.5 (8.58)	-4.7 (-24.9, 15.5)	0.641
		30 mins	A	C	14	14	17.7 (8.96)	19.4 (9.09)	-1.7 (-23.3, 19.9)	0.876
			B	C	14	14	16.3 (8.98)	19.4 (9.09)	-3.1 (-25.3, 19.1)	0.781
			A	D	14	14	17.7 (8.96)	26.7 (9.05)	-9.0 (-30.9, 13.0)	0.413
			B	D	14	14	16.3 (8.98)	26.7 (9.05)	-10.4 (-31.9, 11.2)	0.335

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

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Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
Per Protocol	4 (ctd.)	45 mins	A	C	14	14	19.1 (9.28)	22.3 (9.42)	-3.2 (-25.5, 19.1)	0.774
			B	C	14	14	19.6 (9.31)	22.3 (9.42)	-2.7 (-25.6, 20.3)	0.815
			A	D	14	14	19.1 (9.28)	32.0 (9.37)	-12.9 (-35.6, 9.8)	0.258
			B	D	14	14	19.6 (9.31)	32.0 (9.37)	-12.4 (-34.6, 9.9)	0.267
		60 mins	A	C	14	14	19.7 (9.40)	25.2 (9.55)	-5.5 (-28.5, 17.5)	0.631
			B	C	14	14	22.6 (9.43)	25.2 (9.55)	-2.6 (-26.2, 21.0)	0.825
			A	D	14	14	19.7 (9.40)	33.9 (9.50)	-14.2 (-37.6, 9.2)	0.227
			B	D	14	14	22.6 (9.43)	33.9 (9.50)	-11.3 (-34.2, 11.6)	0.324
		75 mins	A	C	14	14	20.8 (9.37)	28.4 (9.51)	-7.6 (-31.5, 16.3)	0.523
			B	C	14	14	25.2 (9.39)	28.4 (9.51)	-3.2 (-27.7, 21.2)	0.791
			A	D	14	14	20.8 (9.37)	35.7 (9.46)	-14.9 (-39.1, 9.4)	0.222
			B	D	14	14	25.2 (9.39)	35.7 (9.46)	-10.5 (-34.3, 13.3)	0.377
		90 mins	A	C	14	14	23.5 (9.27)	29.7 (9.42)	-6.2 (-30.1, 17.6)	0.600
			B	C	14	14	27.7 (9.30)	29.7 (9.42)	-2.0 (-26.5, 22.4)	0.867
			A	D	14	14	23.5 (9.27)	36.4 (9.37)	-12.9 (-37.1, 11.3)	0.287
			B	D	14	14	27.7 (9.30)	36.4 (9.37)	-8.7 (-32.5, 15.1)	0.462
	5	15 mins	A	C	14	14	11.8 (8.91)	34.9 (8.98)	-23.1 (-46.5, 0.4)	0.054
			B	C	14	14	8.9 (8.93)	34.9 (8.98)	-26.0 (-49.6, -2.4)	0.032
			A	D	14	14	11.8 (8.91)	22.6 (8.92)	-10.8 (-34.2, 12.6)	0.355
			B	D	14	14	8.9 (8.93)	22.6 (8.92)	-13.7 (-37.1, 9.6)	0.242

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
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D: Untreated
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HobsonR: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_02_06.sas 11NOV2013 10:04

Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
Per Protocol 5 (ctd.)		30 mins	A	C	14	14	16.7 (9.28)	38.8 (9.36)	-22.1 (-45.1, 0.9)	0.059
			B	C	14	14	12.9 (9.30)	38.8 (9.36)	-25.9 (-49.0, -2.8)	0.029
			A	D	14	14	16.7 (9.28)	24.4 (9.29)	-7.7 (-30.5, 15.2)	0.499
			B	D	14	14	12.9 (9.30)	24.4 (9.29)	-11.5 (-34.3, 11.3)	0.314
		45 mins	A	C	14	14	21.3 (9.47)	38.9 (9.54)	-17.6 (-39.8, 4.6)	0.117
			B	C	14	14	17.0 (9.49)	38.9 (9.54)	-21.9 (-44.4, 0.5)	0.055
			A	D	14	14	21.3 (9.47)	28.9 (9.48)	-7.6 (-29.7, 14.5)	0.491
			B	D	14	14	17.0 (9.49)	28.9 (9.48)	-11.9 (-34.1, 10.2)	0.281
		60 mins	A	C	14	14	25.5 (9.72)	40.9 (9.80)	-15.4 (-38.1, 7.3)	0.178
			B	C	14	14	19.9 (9.75)	40.9 (9.80)	-21.0 (-43.9, 1.9)	0.071
			A	D	14	14	25.5 (9.72)	32.9 (9.73)	-7.3 (-29.9, 15.2)	0.514
			B	D	14	14	19.9 (9.75)	32.9 (9.73)	-12.9 (-35.5, 9.7)	0.253
		75 mins	A	C	14	14	27.8 (9.91)	41.0 (9.99)	-13.2 (-35.9, 9.6)	0.249
			B	C	14	14	23.5 (9.94)	41.0 (9.99)	-17.4 (-40.4, 5.5)	0.133
			A	D	14	14	27.8 (9.91)	35.4 (9.93)	-7.6 (-30.2, 15.1)	0.503
			B	D	14	14	23.5 (9.94)	35.4 (9.93)	-11.8 (-34.4, 10.8)	0.297
		90 mins	A	C	14	14	29.9 (9.88)	40.3 (9.96)	-10.4 (-32.9, 12.1)	0.354
			B	C	14	14	26.1 (9.91)	40.3 (9.96)	-14.2 (-36.8, 8.5)	0.212
			A	D	14	14	29.9 (9.88)	36.9 (9.89)	-7.0 (-29.3, 15.3)	0.529
			B	D	14	14	26.1 (9.91)	36.9 (9.89)	-10.8 (-33.1, 11.5)	0.333

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

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Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
Per Protocol 6		15 mins	A	C	14	14	11.5 (8.61)	25.0 (8.67)	-13.5 (-37.4, 10.3)	0.258
			B	C	14	14	9.8 (8.60)	25.0 (8.67)	-15.2 (-39.0, 8.6)	0.203
			A	D	14	14	11.5 (8.61)	15.9 (8.61)	-4.5 (-28.1, 19.2)	0.704
			B	D	14	14	9.8 (8.60)	15.9 (8.61)	-6.2 (-29.8, 17.5)	0.600
		30 mins	A	C	14	14	14.6 (9.21)	34.1 (9.28)	-19.5 (-43.9, 4.8)	0.113
			B	C	14	14	12.6 (9.20)	34.1 (9.28)	-21.5 (-45.8, 2.7)	0.080
			A	D	14	14	14.6 (9.21)	20.9 (9.22)	-6.3 (-30.4, 17.8)	0.601
			B	D	14	14	12.6 (9.20)	20.9 (9.22)	-8.3 (-32.4, 15.9)	0.491
		45 mins	A	C	14	14	18.6 (9.46)	36.0 (9.53)	-17.4 (-41.4, 6.7)	0.152
			B	C	14	14	14.5 (9.44)	36.0 (9.53)	-21.5 (-45.5, 2.5)	0.077
			A	D	14	14	18.6 (9.46)	25.4 (9.46)	-6.8 (-30.6, 17.0)	0.568
			B	D	14	14	14.5 (9.44)	25.4 (9.46)	-10.9 (-34.7, 12.9)	0.360
		60 mins	A	C	14	14	21.4 (9.56)	39.7 (9.63)	-18.2 (-41.9, 5.5)	0.128
			B	C	14	14	17.8 (9.55)	39.7 (9.63)	-21.9 (-45.5, 1.7)	0.068
			A	D	14	14	21.4 (9.56)	28.5 (9.57)	-7.1 (-30.5, 16.4)	0.544
			B	D	14	14	17.8 (9.55)	28.5 (9.57)	-10.7 (-34.2, 12.7)	0.360
		75 mins	A	C	14	14	22.5 (9.63)	41.4 (9.70)	-18.9 (-42.3, 4.6)	0.111
			B	C	14	14	22.4 (9.62)	41.4 (9.70)	-19.0 (-42.3, 4.4)	0.109
			A	D	14	14	22.5 (9.63)	31.0 (9.64)	-8.5 (-31.7, 14.7)	0.462
			B	D	14	14	22.4 (9.62)	31.0 (9.64)	-8.6 (-31.8, 14.6)	0.458

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
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D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

HobsonR: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_02_06.sas 11NOV2013 10:04

Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
Per Protocol	6 (ctd.)	90 mins	A	C	14	14	23.9 (9.69)	43.9 (9.76)	-20.0 (-42.9, 2.9)	0.085
			B	C	14	14	25.6 (9.68)	43.9 (9.76)	-18.3 (-41.1, 4.4)	0.111
			A	D	14	14	23.9 (9.69)	32.5 (9.70)	-8.6 (-31.2, 14.0)	0.445
			B	D	14	14	25.6 (9.68)	32.5 (9.70)	-6.9 (-29.6, 15.7)	0.538
	7	15 mins	A	C	14	14	9.5 (7.85)	18.2 (7.91)	-8.7 (-28.4, 11.1)	0.379
			B	C	14	14	18.6 (7.85)	18.2 (7.91)	0.4 (-19.2, 20.1)	0.966
			A	D	14	14	9.5 (7.85)	18.5 (7.90)	-8.9 (-28.6, 10.7)	0.362
			B	D	14	14	18.6 (7.85)	18.5 (7.90)	0.1 (-19.6, 19.8)	0.990
		30 mins	A	C	14	14	11.3 (8.43)	27.0 (8.49)	-15.8 (-38.4, 6.9)	0.166
			B	C	14	14	18.4 (8.43)	27.0 (8.49)	-8.6 (-31.2, 13.9)	0.443
			A	D	14	14	11.3 (8.43)	23.8 (8.48)	-12.5 (-35.1, 10.0)	0.266
			B	D	14	14	18.4 (8.43)	23.8 (8.48)	-5.4 (-28.0, 17.2)	0.631
		45 mins	A	C	14	14	13.9 (8.77)	37.2 (8.83)	-23.3 (-46.1, -0.5)	0.045
			B	C	14	14	20.1 (8.77)	37.2 (8.83)	-17.1 (-39.8, 5.6)	0.135
			A	D	14	14	13.9 (8.77)	30.9 (8.83)	-17.1 (-39.8, 5.6)	0.135
			B	D	14	14	20.1 (8.77)	30.9 (8.83)	-10.9 (-33.6, 11.9)	0.338
		60 mins	A	C	14	14	15.7 (8.92)	43.9 (8.98)	-28.1 (-51.1, -5.2)	0.018
			B	C	14	14	24.0 (8.92)	43.9 (8.98)	-19.8 (-42.7, 3.0)	0.087
			A	D	14	14	15.7 (8.92)	33.3 (8.98)	-17.5 (-40.3, 5.3)	0.129
			B	D	14	14	24.0 (8.92)	33.3 (8.98)	-9.2 (-32.1, 13.7)	0.420

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
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Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
Per Protocol	7 (ctd.)	75 mins	A	C	14	14	16.4 (8.94)	48.4 (9.00)	-31.9 (-54.7, -9.2)	0.007
			B	C	14	14	27.2 (8.94)	48.4 (9.00)	-21.1 (-43.8, 1.6)	0.067
			A	D	14	14	16.4 (8.94)	33.7 (9.00)	-17.3 (-40.0, 5.4)	0.131
			B	D	14	14	27.2 (8.94)	33.7 (9.00)	-6.4 (-29.2, 16.3)	0.570
		90 mins	A	C	14	14	17.3 (8.85)	51.6 (8.91)	-34.3 (-56.6, -12.0)	0.004
			B	C	14	14	30.4 (8.85)	51.6 (8.91)	-21.2 (-43.4, 1.1)	0.061
			A	D	14	14	17.3 (8.85)	34.1 (8.91)	-16.8 (-39.0, 5.4)	0.134
			B	D	14	14	30.4 (8.85)	34.1 (8.91)	-3.7 (-26.0, 18.6)	0.740
	8	15 mins	A	C	14	14	10.5 (8.67)	20.6 (8.71)	-10.1 (-31.5, 11.3)	0.346
			B	C	14	14	21.9 (8.67)	20.6 (8.71)	1.3 (-20.1, 22.8)	0.902
			A	D	14	14	10.5 (8.67)	22.2 (8.72)	-11.8 (-33.2, 9.7)	0.274
			B	D	14	14	21.9 (8.67)	22.2 (8.72)	-0.4 (-21.8, 21.1)	0.974
		30 mins	A	C	14	14	13.8 (8.96)	29.3 (9.01)	-15.5 (-37.4, 6.5)	0.162
			B	C	14	14	23.2 (8.96)	29.3 (9.01)	-6.1 (-28.1, 15.9)	0.580
			A	D	14	14	13.8 (8.96)	23.9 (9.02)	-10.0 (-32.1, 12.0)	0.362
			B	D	14	14	23.2 (8.96)	23.9 (9.02)	-0.6 (-22.6, 21.4)	0.953
		45 mins	A	C	14	14	14.1 (9.14)	38.2 (9.19)	-24.2 (-46.4, -1.9)	0.034
			B	C	14	14	24.3 (9.14)	38.2 (9.19)	-13.9 (-36.2, 8.3)	0.212
			A	D	14	14	14.1 (9.14)	31.0 (9.20)	-17.0 (-39.2, 5.3)	0.131
			B	D	14	14	24.3 (9.14)	31.0 (9.20)	-6.7 (-29.0, 15.5)	0.542

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
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D: Untreated
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Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
Per Protocol	8 (ctd.)	60 mins	A	C	14	14	15.6 (9.27)	43.8 (9.32)	-28.3 (-50.5, -6.0)	0.014
			B	C	14	14	27.3 (9.27)	43.8 (9.32)	-16.5 (-38.8, 5.8)	0.142
			A	D	14	14	15.6 (9.27)	33.9 (9.33)	-18.4 (-40.7, 3.9)	0.103
			B	D	14	14	27.3 (9.27)	33.9 (9.33)	-6.6 (-28.9, 15.7)	0.551
		75 mins	A	C	14	14	16.7 (9.40)	48.6 (9.45)	-31.9 (-54.6, -9.2)	0.007
			B	C	14	14	31.6 (9.40)	48.6 (9.45)	-16.9 (-39.6, 5.8)	0.139
			A	D	14	14	16.7 (9.40)	38.2 (9.45)	-21.5 (-44.2, 1.2)	0.063
			B	D	14	14	31.6 (9.40)	38.2 (9.45)	-6.6 (-29.3, 16.1)	0.562
		90 mins	A	C	14	14	18.5 (9.44)	51.1 (9.50)	-32.6 (-55.5, -9.8)	0.006
			B	C	14	14	35.7 (9.44)	51.1 (9.50)	-15.4 (-38.2, 7.5)	0.181
			A	D	14	14	18.5 (9.44)	41.0 (9.50)	-22.5 (-45.4, 0.4)	0.054
			B	D	14	14	35.7 (9.44)	41.0 (9.50)	-5.2 (-28.1, 17.6)	0.646
	9	15 mins	A	C	14	14	10.7 (9.06)	20.6 (9.10)	-9.9 (-31.0, 11.2)	0.347
			B	C	14	14	26.2 (9.06)	20.6 (9.10)	5.6 (-15.5, 26.7)	0.594
			A	D	14	14	10.7 (9.06)	27.5 (9.07)	-16.8 (-37.8, 4.3)	0.115
			B	D	14	14	26.2 (9.06)	27.5 (9.07)	-1.2 (-22.3, 19.8)	0.906
		30 mins	A	C	14	14	9.4 (9.10)	25.2 (9.14)	-15.8 (-36.5, 4.8)	0.129
			B	C	14	14	28.3 (9.11)	25.2 (9.14)	3.0 (-17.6, 23.7)	0.767
			A	D	14	14	9.4 (9.10)	35.0 (9.12)	-25.6 (-46.2, -5.1)	0.016
			B	D	14	14	28.3 (9.11)	35.0 (9.12)	-6.8 (-27.3, 13.8)	0.509

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
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Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
Per Protocol 9 (ctd.)		45 mins	A	C	14	14	9.7 (8.90)	31.9 (8.93)	-22.2 (-41.5, -2.9)	0.025
			B	C	14	14	29.5 (8.90)	31.9 (8.93)	-2.5 (-21.7, 16.8)	0.796
			A	D	14	14	9.7 (8.90)	40.1 (8.91)	-30.4 (-49.6, -11.2)	0.003
			B	D	14	14	29.5 (8.90)	40.1 (8.91)	-10.7 (-29.8, 8.5)	0.267
		60 mins	A	C	14	14	10.3 (8.69)	38.3 (8.72)	-28.0 (-46.2, -9.8)	0.004
			B	C	14	14	31.8 (8.69)	38.3 (8.72)	-6.5 (-24.7, 11.7)	0.472
			A	D	14	14	10.3 (8.69)	41.9 (8.70)	-31.6 (-49.7, -13.4)	0.001
			B	D	14	14	31.8 (8.69)	41.9 (8.70)	-10.1 (-28.2, 8.0)	0.267
		75 mins	A	C	14	14	11.5 (8.53)	41.8 (8.56)	-30.3 (-48.1, -12.5)	0.001
			B	C	14	14	35.3 (8.53)	41.8 (8.56)	-6.5 (-24.3, 11.3)	0.464
			A	D	14	14	11.5 (8.53)	44.6 (8.54)	-33.2 (-50.9, -15.4)	<0.001
			B	D	14	14	35.3 (8.53)	44.6 (8.54)	-9.3 (-27.0, 8.4)	0.293
		90 mins	A	C	14	14	13.4 (8.22)	44.9 (8.25)	-31.5 (-48.9, -14.1)	<0.001
			B	C	14	14	38.7 (8.22)	44.9 (8.25)	-6.2 (-23.5, 11.2)	0.478
			A	D	14	14	13.4 (8.22)	48.4 (8.23)	-35.0 (-52.3, -17.7)	<0.001
			B	D	14	14	38.7 (8.22)	48.4 (8.23)	-9.7 (-27.0, 7.6)	0.264
	10	15 mins	A	C	14	14	10.5 (9.75)	38.4 (9.72)	-27.8 (-53.8, -1.8)	0.037
			B	C	14	14	29.3 (9.73)	38.4 (9.72)	-9.0 (-35.0, 16.9)	0.485
			A	D	14	14	10.5 (9.75)	44.6 (9.71)	-34.1 (-60.0, -8.1)	0.012
			B	D	14	14	29.3 (9.73)	44.6 (9.71)	-15.3 (-41.2, 10.6)	0.239

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
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Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
Per Protocol 10 (ctd.)		30 mins	A	C	14	14	11.5 (9.04)	46.7 (9.01)	-35.2 (-58.2, -12.2)	0.004
			B	C	14	14	33.3 (9.03)	46.7 (9.01)	-13.4 (-36.4, 9.5)	0.243
			A	D	14	14	11.5 (9.04)	50.4 (9.01)	-39.0 (-62.0, -16.0)	0.001
			B	D	14	14	33.3 (9.03)	50.4 (9.01)	-17.2 (-40.1, 5.8)	0.137
		45 mins	A	C	14	14	18.0 (8.84)	53.0 (8.81)	-35.0 (-55.9, -14.0)	0.002
			B	C	14	14	37.9 (8.82)	53.0 (8.81)	-15.0 (-36.0, 5.9)	0.154
			A	D	14	14	18.0 (8.84)	56.7 (8.81)	-38.6 (-59.6, -17.7)	<0.001
			B	D	14	14	37.9 (8.82)	56.7 (8.81)	-18.7 (-39.7, 2.2)	0.078
		60 mins	A	C	14	14	25.4 (8.56)	57.3 (8.54)	-31.8 (-50.9, -12.8)	0.002
			B	C	14	14	42.9 (8.55)	57.3 (8.54)	-14.3 (-33.4, 4.7)	0.134
			A	D	14	14	25.4 (8.56)	58.6 (8.54)	-33.2 (-52.2, -14.2)	0.001
			B	D	14	14	42.9 (8.55)	58.6 (8.54)	-15.7 (-34.7, 3.3)	0.103
		75 mins	A	C	14	14	31.3 (8.41)	60.5 (8.39)	-29.1 (-47.1, -11.2)	0.002
			B	C	14	14	47.5 (8.40)	60.5 (8.39)	-13.0 (-30.9, 5.0)	0.151
			A	D	14	14	31.3 (8.41)	62.4 (8.39)	-31.0 (-49.0, -13.1)	0.001
			B	D	14	14	47.5 (8.40)	62.4 (8.39)	-14.8 (-32.8, 3.1)	0.102
		90 mins	A	C	14	14	35.0 (8.28)	63.3 (8.26)	-28.3 (-46.1, -10.4)	0.003
			B	C	14	14	50.2 (8.27)	63.3 (8.26)	-13.1 (-30.8, 4.7)	0.145
			A	D	14	14	35.0 (8.28)	66.8 (8.26)	-31.8 (-49.6, -14.0)	<0.001
			B	D	14	14	50.2 (8.27)	66.8 (8.26)	-16.6 (-34.4, 1.2)	0.067

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

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Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
Per Protocol 11		15 mins	A	C	14	14	34.5 (9.72)	74.7 (9.61)	-40.2 (-67.1, -13.4)	0.004
			B	C	14	14	52.6 (9.59)	74.7 (9.61)	-22.1 (-48.5, 4.3)	0.098
			A	D	14	14	34.5 (9.72)	65.6 (9.58)	-31.1 (-57.8, -4.5)	0.023
			B	D	14	14	52.6 (9.59)	65.6 (9.58)	-13.0 (-39.4, 13.4)	0.324
		30 mins	A	C	14	14	42.7 (9.52)	75.8 (9.41)	-33.1 (-59.5, -6.7)	0.015
			B	C	14	14	52.1 (9.39)	75.8 (9.41)	-23.7 (-49.6, 2.2)	0.072
			A	D	14	14	42.7 (9.52)	68.3 (9.38)	-25.6 (-51.8, 0.6)	0.055
			B	D	14	14	52.1 (9.39)	68.3 (9.38)	-16.2 (-42.1, 9.7)	0.213
		45 mins	A	C	14	14	48.8 (9.21)	76.0 (9.11)	-27.2 (-53.0, -1.4)	0.040
			B	C	14	14	55.5 (9.09)	76.0 (9.11)	-20.5 (-45.9, 4.9)	0.110
			A	D	14	14	48.8 (9.21)	71.3 (9.08)	-22.5 (-48.1, 3.1)	0.083
			B	D	14	14	55.5 (9.09)	71.3 (9.08)	-15.8 (-41.2, 9.6)	0.214
		60 mins	A	C	14	14	52.3 (8.58)	76.8 (8.48)	-24.5 (-48.2, -0.8)	0.043
			B	C	14	14	59.5 (8.46)	76.8 (8.48)	-17.4 (-40.7, 5.9)	0.139
			A	D	14	14	52.3 (8.58)	74.9 (8.45)	-22.5 (-46.1, 1.0)	0.060
			B	D	14	14	59.5 (8.46)	74.9 (8.45)	-15.4 (-38.7, 7.9)	0.188
		75 mins	A	C	14	14	56.4 (8.13)	77.4 (8.03)	-21.0 (-43.1, 1.1)	0.062
			B	C	14	14	61.4 (8.02)	77.4 (8.03)	-16.0 (-37.7, 5.7)	0.144
			A	D	14	14	56.4 (8.13)	77.9 (8.00)	-21.6 (-43.5, 0.4)	0.054
			B	D	14	14	61.4 (8.02)	77.9 (8.00)	-16.5 (-38.3, 5.2)	0.131

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

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Table 14.2.2.6 Statistical Analysis of % of Time that Each Electrode is pH < 4 Over Various Time

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
Per Protocol	11 (ctd.)	90 mins	A	C	14	14	60.0 (7.62)	78.1 (7.53)	-18.2 (-38.7, 2.4)	0.081
			B	C	14	14	63.5 (7.52)	78.1 (7.53)	-14.7 (-34.8, 5.5)	0.149
			A	D	14	14	60.0 (7.62)	80.0 (7.50)	-20.0 (-40.4, 0.4)	0.054
			B	D	14	14	63.5 (7.52)	80.0 (7.50)	-16.5 (-36.7, 3.7)	0.106

Data Source: Appendix 16.1.9.5
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

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14.2.2.7 Statistical Analysis of Mean Percentage of Time with pH <4 at Electrodes 1, 2, and 3 during Four 1-hour Periods

Table 14.2.2.7 Statistical Analysis of Mean % of Time with pH < 4 at Electrodes 1, 2 and 3 During 4 x One Hour Periods

Population	Electrode	Timepoint (post treatment)	Comparison		Number of Subjects		LS Mean (Standard Error)		Test-Reference		
			Test	Ref.	Test	Ref.	Test	Reference	LS Mean Difference 95% Confidence Interval		p-value
ITT	Mean of 1 - 3	0 - 1 hour	A	C	15	15	14.0 (5.13)	16.3 (5.14)	-2.2 (-16.1, 11.6)		0.745
			B	C	14	15	15.6 (5.37)	16.3 (5.14)	-0.7 (-15.0, 13.7)		0.926
			A	D	15	14	14.0 (5.13)	24.5 (5.32)	-10.5 (-24.7, 3.7)		0.143
			B	D	14	14	15.6 (5.37)	24.5 (5.32)	-8.9 (-23.3, 5.5)		0.217
		1 - 2 hours	A	C	15	15	21.5 (5.47)	18.7 (5.48)	2.9 (-12.0, 17.7)		0.694
			B	C	14	15	23.3 (5.72)	18.7 (5.48)	4.6 (-10.8, 20.0)		0.544
			A	D	15	14	21.5 (5.47)	24.4 (5.68)	-2.9 (-18.1, 12.4)		0.703
			B	D	14	14	23.3 (5.72)	24.4 (5.68)	-1.1 (-16.6, 14.3)		0.881
		2 - 3 hours	A	C	15	15	22.8 (5.47)	12.5 (5.47)	10.3 (-5.3, 25.9)		0.188
			B	C	14	15	23.6 (5.71)	12.5 (5.47)	11.2 (-4.9, 27.3)		0.168
			A	D	15	14	22.8 (5.47)	22.5 (5.67)	0.3 (-15.7, 16.2)		0.973
			B	D	14	14	23.6 (5.71)	22.5 (5.67)	1.1 (-15.2, 17.4)		0.891
		3 - 4 hours	A	C	15	15	17.9 (4.94)	8.8 (4.95)	9.1 (-4.8, 23.0)		0.192
			B	C	14	15	16.4 (5.16)	8.8 (4.95)	7.6 (-6.7, 21.9)		0.289
			A	D	15	14	17.9 (4.94)	21.0 (5.12)	-3.1 (-17.3, 11.1)		0.658
			B	D	14	14	16.4 (5.16)	21.0 (5.12)	-4.6 (-19.1, 9.8)		0.519

Data Source: Appendix 16.1.9.6
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

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Table 14.2.2.7 Statistical Analysis of Mean % of Time with pH < 4 at Electrodes 1, 2 and 3 During 4 x One Hour Periods

Population	Electrode	Timepoint (post treatment)	Comparison		Number of Subjects		LS Mean (Standard Error)		Test-Reference	
			Test	Ref.	Test	Ref.	Test	Reference	LS Mean Difference 95% Confidence Interval	p-value
Per Protocol	Mean of 1 - 3	0 - 1 hour	A	C	14	14	9.1 (4.76)	15.3 (4.79)	-6.1 (-19.3, 7.1)	0.353
			B	C	14	14	14.7 (4.80)	15.3 (4.79)	-0.6 (-14.0, 12.8)	0.928
			A	D	14	14	9.1 (4.76)	23.9 (4.76)	-14.7 (-27.9, -1.5)	0.030
			B	D	14	14	14.7 (4.80)	23.9 (4.76)	-9.2 (-22.4, 4.0)	0.166
		1 - 2 hours	A	C	14	14	16.7 (5.14)	17.1 (5.18)	-0.4 (-14.8, 14.1)	0.959
			B	C	14	14	22.2 (5.18)	17.1 (5.18)	5.1 (-9.6, 19.8)	0.484
			A	D	14	14	16.7 (5.14)	23.6 (5.14)	-6.9 (-21.4, 7.6)	0.339
			B	D	14	14	22.2 (5.18)	23.6 (5.14)	-1.4 (-15.9, 13.1)	0.844
		2 - 3 hours	A	C	14	14	17.7 (5.16)	13.0 (5.19)	4.8 (-9.8, 19.4)	0.512
			B	C	14	14	23.1 (5.20)	13.0 (5.19)	10.1 (-4.7, 25.0)	0.176
			A	D	14	14	17.7 (5.16)	22.4 (5.16)	-4.7 (-19.3, 10.0)	0.521
			B	D	14	14	23.1 (5.20)	22.4 (5.16)	0.7 (-14.0, 15.3)	0.927
		3 - 4 hours	A	C	14	14	13.9 (4.71)	10.4 (4.75)	3.5 (-9.5, 16.4)	0.592
			B	C	14	14	15.7 (4.75)	10.4 (4.75)	5.3 (-7.8, 18.5)	0.418
			A	D	14	14	13.9 (4.71)	20.9 (4.71)	-7.0 (-20.0, 5.9)	0.280
			B	D	14	14	15.7 (4.75)	20.9 (4.71)	-5.1 (-18.1, 7.8)	0.426

Data Source: Appendix 16.1.9.6
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

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14.2.2.8 Statistical Analysis of Mean Percentage of Time with pH <4 at Electrodes 1, 2, and 3 over 4 Hours

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Table 14.2.2.8 Statistical Analysis of Mean % of Time with pH < 4 at Electrodes 1 - 3 Over 4 Hours

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
ITT	Mean of 1 - 3	0 - 4 hours	A	C	15	15	19.1 (4.95)	14.1 (4.96)	5.0 (-8.9, 18.9)	0.469
			B	C	14	15	19.6 (5.18)	14.1 (4.96)	5.5 (-8.8, 19.8)	0.440
			A	D	15	14	19.1 (4.95)	23.0 (5.14)	-3.9 (-18.1, 10.3)	0.577
			B	D	14	14	19.6 (5.18)	23.0 (5.14)	-3.4 (-17.8, 11.0)	0.633
Per Protocol	Mean of 1 - 3	0 - 4 hours	A	C	14	14	14.4 (4.64)	13.9 (4.68)	0.4 (-12.6, 13.5)	0.947
			B	C	14	14	18.9 (4.68)	13.9 (4.68)	5.0 (-8.3, 18.2)	0.450
			A	D	14	14	14.4 (4.64)	22.7 (4.64)	-8.3 (-21.4, 4.7)	0.203
			B	D	14	14	18.9 (4.68)	22.7 (4.64)	-3.8 (-16.8, 9.3)	0.560

Data Source: Appendix 16.1.9.7
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

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14.2.2.9 Statistical Analysis of Mean Percentage of Time with pH <4 at Electrodes 4 to 7 during Four 1-hour Periods

Table 14.2.2.9 Statistical Analysis of Mean % of Time with pH < 4 at Electrodes 4 - 7 During 4 x One Hour Periods

Population	Electrode	Timepoint (post treatment)	Comparison		Number of Subjects		LS Mean (Standard Error)		Test-Reference	
									LS Mean Difference	
			Test	Ref.	Test	Ref.	Test	Reference	95% Confidence Interval	p-value
ITT	Mean of 4 - 7	0 - 1 hour	A	C	15	15	25.9 (8.46)	39.4 (8.49)	-13.5 (-32.6, 5.6)	0.161
			B	C	14	15	23.2 (8.72)	39.4 (8.49)	-16.2 (-35.9, 3.5)	0.104
			A	D	15	14	25.9 (8.46)	33.5 (8.76)	-7.6 (-27.4, 12.1)	0.438
			B	D	14	14	23.2 (8.72)	33.5 (8.76)	-10.3 (-30.2, 9.5)	0.299
		1 - 2 hours	A	C	15	15	41.2 (8.81)	54.7 (8.84)	-13.5 (-34.2, 7.2)	0.196
			B	C	14	15	45.5 (9.09)	54.7 (8.84)	-9.2 (-30.5, 12.2)	0.391
			A	D	15	14	41.2 (8.81)	43.2 (9.14)	-2.1 (-23.5, 19.3)	0.845
			B	D	14	14	45.5 (9.09)	43.2 (9.14)	2.2 (-19.3, 23.8)	0.834
		2 - 3 hours	A	C	15	15	49.3 (7.52)	52.6 (7.55)	-3.3 (-24.2, 17.6)	0.750
			B	C	14	15	51.4 (7.81)	52.6 (7.55)	-1.3 (-22.6, 20.1)	0.906
			A	D	15	14	49.3 (7.52)	45.4 (7.84)	4.0 (-17.4, 25.4)	0.710
			B	D	14	14	51.4 (7.81)	45.4 (7.84)	6.0 (-15.7, 27.7)	0.578
		3 - 4 hours	A	C	15	15	52.3 (7.20)	45.0 (7.22)	7.3 (-13.2, 27.7)	0.480
			B	C	14	15	50.7 (7.46)	45.0 (7.22)	5.6 (-15.3, 26.5)	0.591
			A	D	15	14	52.3 (7.20)	49.9 (7.49)	2.4 (-18.5, 23.3)	0.819
			B	D	14	14	50.7 (7.46)	49.9 (7.49)	0.8 (-20.5, 22.0)	0.942

Data Source: Appendix 16.1.9.8
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

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Table 14.2.2.9 Statistical Analysis of Mean % of Time with pH < 4 at Electrodes 4 - 7 During 4 x One Hour Periods

Population	Electrode	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	p-value
Per Protocol	Mean of 4 - 7	0 - 1 hour	A	C	14	14	20.3 (8.41)	38.7 (8.51)	-18.3 (-37.6, 0.9)	0.061
			B	C	14	14	20.9 (8.42)	38.7 (8.51)	-17.7 (-37.1, 1.6)	0.072
			A	D	14	14	20.3 (8.41)	31.4 (8.46)	-11.1 (-30.2, 8.1)	0.249
			B	D	14	14	20.9 (8.42)	31.4 (8.46)	-10.5 (-29.6, 8.6)	0.274
		1 - 2 hours	A	C	14	14	35.8 (8.83)	53.7 (8.94)	-17.9 (-39.1, 3.3)	0.096
			B	C	14	14	43.4 (8.84)	53.7 (8.94)	-10.3 (-31.6, 11.1)	0.336
			A	D	14	14	35.8 (8.83)	41.3 (8.88)	-5.5 (-26.6, 15.6)	0.598
			B	D	14	14	43.4 (8.84)	41.3 (8.88)	2.1 (-18.9, 23.1)	0.841
		2 - 3 hours	A	C	14	14	44.2 (7.42)	55.0 (7.51)	-10.8 (-31.2, 9.6)	0.290
			B	C	14	14	50.5 (7.43)	55.0 (7.51)	-4.5 (-25.0, 15.9)	0.658
			A	D	14	14	44.2 (7.42)	44.7 (7.46)	-0.6 (-20.9, 19.7)	0.955
			B	D	14	14	50.5 (7.43)	44.7 (7.46)	5.7 (-14.5, 26.0)	0.571
		3 - 4 hours	A	C	14	14	47.8 (6.78)	50.3 (6.86)	-2.5 (-21.7, 16.6)	0.790
			B	C	14	14	49.7 (6.79)	50.3 (6.86)	-0.6 (-19.9, 18.6)	0.948
			A	D	14	14	47.8 (6.78)	49.3 (6.82)	-1.5 (-20.6, 17.6)	0.871
			B	D	14	14	49.7 (6.79)	49.3 (6.82)	0.4 (-18.7, 19.5)	0.968

Data Source: Appendix 16.1.9.8
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with treatment, baseline, treatment period and treatment day as fixed effects and a random effect for subject.

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14.2.2.10 Statistical Analysis of Number of Liquid, Gas and Mixed Reflux Episodes Occurring in the 2- and 4-hour Periods

Table 14.2.2.10 Statistical Analysis of Number of Liquid, Gas and Mixed Reflux Episodes Occurring in the 2- and 4-Hour Periods

			Comparison		Number of Subjects		LS Mean (Standard Error)		Test-Reference	
Number of	Population	Timepoint (post treatment)	Test	Ref.	Test	Ref.	Test	Reference	LS Mean Difference 95% Confidence Interval	p-value
Liquid Episodes	ITT	2 hours	A	C	14	14	2.5 (0.90)	3.5 (0.93)	-1.0 (-3.1, 1.2)	0.378
			B	C	13	14	2.9 (0.93)	3.5 (0.93)	-0.5 (-2.8, 1.7)	0.620
			A	D	14	13	2.5 (0.90)	2.8 (0.92)	-0.3 (-2.4, 1.9)	0.810
			B	D	13	13	2.9 (0.93)	2.8 (0.92)	0.1 (-2.0, 2.3)	0.893
		4 hours	A	C	14	14	3.4 (1.25)	5.0 (1.28)	-1.5 (-4.2, 1.2)	0.259
			B	C	13	14	4.5 (1.29)	5.0 (1.28)	-0.5 (-3.3, 2.3)	0.708
			A	D	14	13	3.4 (1.25)	4.1 (1.28)	-0.6 (-3.3, 2.1)	0.643
			B	D	13	13	4.5 (1.29)	4.1 (1.28)	0.4 (-2.3, 3.1)	0.775
	Per Protocol	2 hours	A	C	13	13	2.4 (0.93)	3.0 (0.95)	-0.6 (-2.9, 1.6)	0.578
			B	C	13	13	2.8 (0.92)	3.0 (0.95)	-0.2 (-2.4, 2.1)	0.862
			A	D	13	13	2.4 (0.93)	2.6 (0.91)	-0.3 (-2.5, 1.9)	0.808
			B	D	13	13	2.8 (0.92)	2.6 (0.91)	0.2 (-2.0, 2.3)	0.877
		4 hours	A	C	13	13	3.3 (1.30)	4.5 (1.33)	-1.1 (-4.0, 1.7)	0.423
			B	C	13	13	4.3 (1.30)	4.5 (1.33)	-0.2 (-3.0, 2.7)	0.911
			A	D	13	13	3.3 (1.30)	3.9 (1.29)	-0.6 (-3.3, 2.2)	0.677
			B	D	13	13	4.3 (1.30)	3.9 (1.29)	0.4 (-2.3, 3.1)	0.763

Data Source: Appendix 16.1.9.9
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with baseline, treatment, treatment period and treatment day as fixed effects and a random effect for subject.

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Table 14.2.2.10 Statistical Analysis of Number of Liquid, Gas and Mixed Reflux Episodes Occurring in the 2- and 4-Hour Periods

Number of	Population	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	Test-Reference p-value
Gas Episodes	ITT	2 hours	A	C	14	14	0.6 (0.20)	0.6 (0.21)	-0.1 (-0.6, 0.4)	0.728
			B	C	13	14	0.4 (0.21)	0.6 (0.21)	-0.2 (-0.8, 0.3)	0.366
			A	D	14	13	0.6 (0.20)	0.3 (0.21)	0.2 (-0.3, 0.8)	0.344
			B	D	13	13	0.4 (0.21)	0.3 (0.21)	0.1 (-0.4, 0.6)	0.721
		4 hours	A	C	14	14	1.5 (0.38)	1.2 (0.39)	0.3 (-0.7, 1.2)	0.563
			B	C	13	14	1.2 (0.39)	1.2 (0.39)	0.1 (-0.9, 1.0)	0.900
			A	D	14	13	1.5 (0.38)	0.6 (0.39)	0.8 (-0.1, 1.8)	0.094
			B	D	13	13	1.2 (0.39)	0.6 (0.39)	0.6 (-0.4, 1.6)	0.221
	Per Protocol	2 hours	A	C	13	13	0.6 (0.22)	0.6 (0.22)	0.0 (-0.6, 0.5)	0.888
			B	C	13	13	0.4 (0.22)	0.6 (0.22)	-0.2 (-0.8, 0.3)	0.417
			A	D	13	13	0.6 (0.22)	0.3 (0.22)	0.3 (-0.3, 0.8)	0.293
			B	D	13	13	0.4 (0.22)	0.3 (0.22)	0.1 (-0.4, 0.6)	0.714
		4 hours	A	C	13	13	1.6 (0.40)	1.2 (0.41)	0.3 (-0.7, 1.3)	0.499
			B	C	13	13	1.3 (0.40)	1.2 (0.41)	0.1 (-1.0, 1.1)	0.912
			A	D	13	13	1.6 (0.40)	0.7 (0.40)	0.9 (-0.1, 1.9)	0.075
			B	D	13	13	1.3 (0.40)	0.7 (0.40)	0.6 (-0.4, 1.6)	0.220

Data Source: Appendix 16.1.9.9
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with baseline, treatment, treatment period and treatment day as fixed effects and a random effect for subject.

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Table 14.2.2.10 Statistical Analysis of Number of Liquid, Gas and Mixed Reflux Episodes Occurring in the 2- and 4-Hour Periods

Number of	Population	Timepoint (post treatment)	Comparison		Number of Subjects		LS Mean (Standard Error)		Test-Reference	
			Test	Ref.	Test	Ref.	Test	Reference	LS Mean Difference 95% Confidence Interval	p-value
Mixed Episodes	ITT	2 hours	A	C	14	14	1.5 (0.62)	2.0 (0.65)	-0.5 (-2.1, 1.1)	0.513
			B	C	13	14	2.4 (0.65)	2.0 (0.65)	0.4 (-1.3, 2.0)	0.647
			A	D	14	13	1.5 (0.62)	1.7 (0.69)	-0.2 (-1.9, 1.5)	0.815
			B	D	13	13	2.4 (0.65)	1.7 (0.69)	0.7 (-1.1, 2.5)	0.424
		4 hours	A	C	14	14	2.5 (0.92)	2.4 (0.96)	0.1 (-2.2, 2.4)	0.949
			B	C	13	14	3.6 (0.97)	2.4 (0.96)	1.1 (-1.3, 3.5)	0.341
			A	D	14	13	2.5 (0.92)	3.0 (1.03)	-0.5 (-3.0, 2.0)	0.692
			B	D	13	13	3.6 (0.97)	3.0 (1.03)	0.6 (-2.0, 3.1)	0.647
	Per Protocol	2 hours	A	C	13	13	1.7 (0.66)	2.0 (0.68)	-0.3 (-2.0, 1.4)	0.745
			B	C	13	13	2.4 (0.66)	2.0 (0.68)	0.5 (-1.2, 2.2)	0.580
			A	D	13	13	1.7 (0.66)	1.6 (0.72)	0.1 (-1.7, 2.0)	0.886
			B	D	13	13	2.4 (0.66)	1.6 (0.72)	0.9 (-1.0, 2.7)	0.341
		4 hours	A	C	13	13	2.7 (0.98)	2.3 (1.02)	0.4 (-2.1, 2.9)	0.744
			B	C	13	13	3.6 (0.98)	2.3 (1.02)	1.3 (-1.2, 3.8)	0.301
			A	D	13	13	2.7 (0.98)	2.8 (1.07)	-0.1 (-2.8, 2.6)	0.926
			B	D	13	13	3.6 (0.98)	2.8 (1.07)	0.8 (-1.9, 3.4)	0.569

Data Source: Appendix 16.1.9.9
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with baseline, treatment, treatment period and treatment day as fixed effects and a random effect for subject.

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14.2.2.11 Statistical Analysis of Number of Acid and Weakly Acidic Reflux Episodes Occurring in the 2- and 4-hour Periods

Table 14.2.2.11 Statistical Analysis of Number of Acid and Weakly Acidic Reflux Episodes Occurring in the 2- and 4-Hour Periods

			Comparison		Number of Subjects		LS Mean (Standard Error)		Test-Reference	
Number of	Population	Timepoint (post treatment)	Test	Ref.	Test	Ref.	Test	Reference	LS Mean Difference 95% Confidence Interval	p-value
Weakly Acidic	ITT	2 hours	A	C	14	14	2.2 (0.73)	2.7 (0.75)	-0.5 (-2.2, 1.2)	0.541
			B	C	13	14	3.3 (0.76)	2.7 (0.75)	0.6 (-1.2, 2.3)	0.505
			A	D	14	13	2.2 (0.73)	1.3 (0.76)	0.9 (-0.8, 2.6)	0.278
			B	D	13	13	3.3 (0.76)	1.3 (0.76)	2.0 (0.3, 3.8)	0.025
		4 hours	A	C	14	14	3.1 (1.08)	3.7 (1.11)	-0.6 (-2.9, 1.7)	0.616
			B	C	13	14	4.5 (1.12)	3.7 (1.11)	0.8 (-1.5, 3.2)	0.483
			A	D	14	13	3.1 (1.08)	2.2 (1.12)	0.9 (-1.4, 3.2)	0.441
			B	D	13	13	4.5 (1.12)	2.2 (1.12)	2.3 (-0.1, 4.7)	0.059
	Per Protocol	2 hours	A	C	13	13	2.4 (0.77)	2.5 (0.79)	-0.1 (-1.9, 1.6)	0.884
			B	C	13	13	3.3 (0.77)	2.5 (0.79)	0.8 (-1.0, 2.5)	0.375
			A	D	13	13	2.4 (0.77)	1.3 (0.77)	1.1 (-0.6, 2.8)	0.187
			B	D	13	13	3.3 (0.77)	1.3 (0.77)	2.0 (0.3, 3.7)	0.023
		4 hours	A	C	13	13	3.4 (1.14)	3.5 (1.17)	-0.1 (-2.5, 2.3)	0.934
			B	C	13	13	4.6 (1.14)	3.5 (1.17)	1.1 (-1.3, 3.5)	0.379
			A	D	13	13	3.4 (1.14)	2.3 (1.14)	1.2 (-1.2, 3.5)	0.321
			B	D	13	13	4.6 (1.14)	2.3 (1.14)	2.3 (-0.1, 4.7)	0.055

Data Source: Appendix 16.1.9.10
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with baseline, treatment, treatment period and treatment day as fixed effects and a random effect for subject.

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Table 14.2.2.11 Statistical Analysis of Number of Acid and Weakly Acidic Reflux Episodes Occurring in the 2- and 4-Hour Periods

Number of	Population	Timepoint (post treatment)	Comparison		Number of Subjects		LS Mean (Standard Error)		Test-Reference	
			Test	Ref.	Test	Ref.	Test	Reference	LS Mean Difference 95% Confidence Interval	p-value
Acid	ITT	2 hours	A	C	14	14	1.9 (0.62)	2.5 (0.65)	-0.6 (-2.4, 1.1)	0.478
			B	C	13	14	2.4 (0.65)	2.5 (0.65)	-0.1 (-1.9, 1.7)	0.917
			A	D	14	13	1.9 (0.62)	2.6 (0.65)	-0.8 (-2.5, 1.0)	0.386
			B	D	13	13	2.4 (0.65)	2.6 (0.65)	-0.2 (-2.0, 1.6)	0.794
		4 hours	A	C	14	14	3.0 (1.02)	3.4 (1.06)	-0.4 (-3.2, 2.4)	0.796
			B	C	13	14	4.0 (1.07)	3.4 (1.06)	0.6 (-2.3, 3.5)	0.676
			A	D	14	13	3.0 (1.02)	4.1 (1.06)	-1.1 (-3.9, 1.7)	0.440
			B	D	13	13	4.0 (1.07)	4.1 (1.06)	-0.1 (-3.0, 2.8)	0.935
	Per Protocol	2 hours	A	C	13	13	1.9 (0.65)	2.3 (0.68)	-0.4 (-2.2, 1.5)	0.676
			B	C	13	13	2.3 (0.65)	2.3 (0.68)	0.0 (-1.9, 1.8)	0.986
			A	D	13	13	1.9 (0.65)	2.4 (0.65)	-0.5 (-2.3, 1.3)	0.606
			B	D	13	13	2.3 (0.65)	2.4 (0.65)	-0.1 (-1.9, 1.7)	0.915
		4 hours	A	C	13	13	3.1 (1.06)	3.1 (1.11)	0.0 (-3.1, 3.0)	0.974
			B	C	13	13	3.8 (1.06)	3.1 (1.11)	0.7 (-2.3, 3.7)	0.641
			A	D	13	13	3.1 (1.06)	3.7 (1.06)	-0.6 (-3.6, 2.3)	0.675
			B	D	13	13	3.8 (1.06)	3.7 (1.06)	0.1 (-2.8, 3.1)	0.926

Data Source: Appendix 16.1.9.10
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with baseline, treatment, treatment period and treatment day as fixed effects and a random effect for subject.

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14.2.2.12 Statistical Analysis of Number of Reflux Episodes Reaching 15 cm Above the Lower Oesophageal Sphincter During the 2- and 4-Hour Periods

Table 14.2.2.12 Statistical Analysis of Number of Reflux Episodes Reaching 15 cm Above the LOS During the 2- and 4-Hour Periods

Population	Timepoint (post treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	Test-Reference p-value
ITT	2 hours	A	C	14	14	0.9 (0.56)	1.2 (0.57)	-0.2 (-1.2, 0.8)	0.634
		B	C	13	14	1.2 (0.57)	1.2 (0.57)	0.1 (-1.0, 1.1)	0.902
		A	D	14	13	0.9 (0.56)	0.8 (0.57)	0.1 (-0.9, 1.1)	0.835
		B	D	13	13	1.2 (0.57)	0.8 (0.57)	0.4 (-0.6, 1.4)	0.420
	4 hours	A	C	14	14	1.0 (0.62)	1.2 (0.64)	-0.2 (-1.3, 0.9)	0.724
		B	C	13	14	1.6 (0.64)	1.2 (0.64)	0.4 (-0.7, 1.6)	0.445
		A	D	14	13	1.0 (0.62)	1.1 (0.64)	-0.2 (-1.3, 1.0)	0.777
		B	D	13	13	1.6 (0.64)	1.1 (0.64)	0.5 (-0.6, 1.6)	0.395
Per Protocol	2 hours	A	C	13	13	0.9 (0.40)	0.4 (0.41)	0.5 (-0.2, 1.1)	0.160
		B	C	13	13	0.9 (0.40)	0.4 (0.41)	0.6 (-0.1, 1.2)	0.095
		A	D	13	13	0.9 (0.40)	0.5 (0.40)	0.3 (-0.3, 1.0)	0.305
		B	D	13	13	0.9 (0.40)	0.5 (0.40)	0.4 (-0.2, 1.1)	0.187
	4 hours	A	C	13	13	0.9 (0.51)	0.4 (0.52)	0.5 (-0.3, 1.3)	0.230
		B	C	13	13	1.3 (0.51)	0.4 (0.52)	0.9 (0.1, 1.8)	0.033
		A	D	13	13	0.9 (0.51)	0.8 (0.51)	0.1 (-0.7, 0.9)	0.856
		B	D	13	13	1.3 (0.51)	0.8 (0.51)	0.5 (-0.3, 1.3)	0.227

Data Source: Appendix 16.1.9.11
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with baseline, treatment, treatment period and treatment day as fixed effects and a random effect for subject.

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14.2.2.13 Statistical Analysis of Oesophageal Bolus Exposure to Reflux During the 2- and 4-Hour Periods

Table 14.2.2.13 Statistical Analysis of Oesophageal Bolus Exposure to Reflux During the 2- and 4-Hour Periods

Population	Timepoint (post-treatment)	Comparison Test	Comparison Ref.	Number of Subjects Test	Number of Subjects Ref.	LS Mean (Standard Error) Test	LS Mean (Standard Error) Reference	Test-Reference LS Mean Difference 95% Confidence Interval	Test-Reference p-value
ITT	2 hours	A	C	14	14	0.6 (0.19)	1.1 (0.20)	-0.4 (-0.9, 0.0)	0.055
		B	C	13	14	1.2 (0.20)	1.1 (0.20)	0.1 (-0.4, 0.6)	0.711
		A	D	14	13	0.6 (0.19)	0.8 (0.20)	-0.2 (-0.7, 0.2)	0.332
		B	D	13	13	1.2 (0.20)	0.8 (0.20)	0.3 (-0.2, 0.8)	0.193
	4 hours	A	C	14	14	0.4 (0.14)	0.7 (0.15)	-0.2 (-0.5, 0.1)	0.143
		B	C	13	14	0.8 (0.15)	0.7 (0.15)	0.2 (-0.2, 0.5)	0.329
		A	D	14	13	0.4 (0.14)	0.6 (0.15)	-0.2 (-0.5, 0.1)	0.186
		B	D	13	13	0.8 (0.15)	0.6 (0.15)	0.2 (-0.2, 0.5)	0.276
Per Protocol	2 hours	A	C	13	13	0.6 (0.20)	1.0 (0.21)	-0.4 (-0.8, 0.1)	0.134
		B	C	13	13	1.1 (0.20)	1.0 (0.21)	0.1 (-0.3, 0.6)	0.542
		A	D	13	13	0.6 (0.20)	0.8 (0.20)	-0.2 (-0.7, 0.3)	0.405
		B	D	13	13	1.1 (0.20)	0.8 (0.20)	0.3 (-0.2, 0.8)	0.193
	4 hours	A	C	13	13	0.4 (0.15)	0.6 (0.16)	-0.2 (-0.5, 0.1)	0.265
		B	C	13	13	0.8 (0.15)	0.6 (0.16)	0.2 (-0.1, 0.5)	0.261
		A	D	13	13	0.4 (0.15)	0.6 (0.15)	-0.2 (-0.5, 0.1)	0.242
		B	D	13	13	0.8 (0.15)	0.6 (0.15)	0.2 (-0.2, 0.5)	0.274

Data Source: Appendix 16.1.9.12
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Least Squares Means are obtained from a mixed effects model with baseline, treatment, treatment period and treatment day as fixed effects and a random effect for subject.

HobsonR: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_02_02_13.sas 11NOV2013 10:08

14.3 Safety Data Summaries

14.3.1 Displays of Adverse Events

14.3.1.1 Overall Summary of Treatment-emergent Adverse Events (Safety Population)

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Table 14.3.1.1 Overall Summary of Treatment-Emergent Adverse Events
Safety Population (N=16)

	Number (%) of Subjects(1) and [Number of Events]			
	Treatment			
AE Category	A (N=15)	B (N=14)	C (N=15)	Overall (N=15)
Any TEAE	5 (33.3%) [6]	2 (14.3%) [2]	5 (33.3%) [5]	7 (46.7%) [13]
Any mild TEAE	4 (26.7%) [4]	2 (14.3%) [2]	4 (26.7%) [4]	7 (46.7%) [10]
Any moderate TEAE	2 (13.3%) [2]	0	1 (6.7%) [1]	2 (13.3%) [3]
Any severe TEAE	0	0	0	0
Any TEAE related to study medication	1 (6.7%) [2]	1 (7.1%) [1]	1 (6.7%) [1]	3 (20.0%) [4]
Any TEAE leading to discontinuation of treatment	0	0	0	0
Any SAE	0	0	0	0
Any SAE related to study medication	0	0	0	0
Any life-threatening SAE	0	0	0	0
Any SAE leading to death	0	0	0	0

Data Source: Listing 16.2.7.1
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
(1) Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
All adverse events starting or worsening after commencement of treatment with investigational product.
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_01_01.sas 15OCT2013 12:02

14.3.1.2 Summary of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Treatment (Safety Population)

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Table 14.3.1.2 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Treatment
Safety Population (N=16)

System Organ Class (SOC) MedDRA Preferred Term (PT)	Number (%) of Subjects(1) and [Number of Events] Treatment A (N=15)	B (N=14)	C (N=15)	Overall (N=15)
Subjects with any TEAE	5 (33.3%) [6]	2 (14.3%) [2]	5 (33.3%) [5]	7 (46.7%) [13]
General disorders and administration site conditions	1 (6.7%) [1]	2 (14.3%) [2]	0	2 (13.3%) [3]
Fatigue	1 (6.7%) [1]	1 (7.1%) [1]	0	1 (6.7%) [2]
Medical device discomfort	0	1 (7.1%) [1]	0	1 (6.7%) [1]
Musculoskeletal and connective tissue disorders	1 (6.7%) [1]	0	0	1 (6.7%) [1]
Back pain	1 (6.7%) [1]	0	0	1 (6.7%) [1]
Nervous system disorders	2 (13.3%) [2]	0	4 (26.7%) [4]	4 (26.7%) [6]
Headache	2 (13.3%) [2]	0	4 (26.7%) [4]	4 (26.7%) [6]
Respiratory, thoracic and mediastinal disorders	1 (6.7%) [2]	0	1 (6.7%) [1]	2 (13.3%) [3]
Nasal discomfort	1 (6.7%) [1]	0	0	1 (6.7%) [1]
Oropharyngeal pain	0	0	1 (6.7%) [1]	1 (6.7%) [1]
Rhinorrhoea	1 (6.7%) [1]	0	0	1 (6.7%) [1]

Data Source: Listing 16.2.7.1
MedDRA Version 15.0 used
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
(1) Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
All adverse events starting or worsening after commencement of treatment with investigational product.
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_01_02.sas 15OCT2013 12:02

14.3.1.3 Summary of Treatment-emergent Adverse Events by System Organ Class, Preferred Term, Intensity Grade and Treatment (Safety Population)

Table 14.3.1.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, Severity Grade and Treatment
Safety Population (N=16)

System Organ Class (SOC) MedDRA Preferred Term (PT)	Severity Grade	Number (%) of Subjects(1) and [Number of Events] Treatment A (N=15)	B (N=14)	C (N=15)	Overall (N=15)
Subjects with any TEAE	Mild	3 (20.0%) [4]	2 (14.3%) [2]	4 (26.7%) [4]	5 (33.3%) [10]
	Moderate	2 (13.3%) [2]	0	1 (6.7%) [1]	2 (13.3%) [3]
General disorders and administration site conditions	Mild	1 (6.7%) [1]	2 (14.3%) [2]	0	2 (13.3%) [3]
Fatigue	Mild	1 (6.7%) [1]	1 (7.1%) [1]	0	1 (6.7%) [2]
Medical device discomfort	Mild	0	1 (7.1%) [1]	0	1 (6.7%) [1]
Musculoskeletal and connective tissue disorders	Mild	1 (6.7%) [1]	0	0	1 (6.7%) [1]
Back pain	Mild	1 (6.7%) [1]	0	0	1 (6.7%) [1]
Nervous system disorders	Mild	1 (6.7%) [1]	0	3 (20.0%) [3]	2 (13.3%) [4]
	Moderate	1 (6.7%) [1]	0	1 (6.7%) [1]	2 (13.3%) [2]
Headache	Mild	1 (6.7%) [1]	0	3 (20.0%) [3]	2 (13.3%) [4]

Data Source: Listing 16.2.7.1
MedDRA Version 15.0 used
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
(1) Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
Note: All adverse events starting or worsening after commencement of treatment with investigational product.
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_01_03.sas 15OCT2013 12:03

Table 14.3.1.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, Severity Grade and Treatment
Safety Population (N=16)

System Organ Class (SOC) MedDRA Preferred Term (PT)	Severity Grade	Number (%) of Subjects(1) and [Number of Events] Treatment A (N=15)	B (N=14)	C (N=15)	Overall (N=15)
Headache	Moderate	1 (6.7%) [1]	0	1 (6.7%) [1]	2 (13.3%) [2]

Data Source: Listing 16.2.7.1
MedDRA Version 15.0 used
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
(1) Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
Note: All adverse events starting or worsening after commencement of treatment with investigational product.
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_01_03.sas 15OCT2013 12:03

Table 14.3.1.3 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, Severity Grade and Treatment
Safety Population (N=16)

System Organ Class (SOC) MedDRA Preferred Term (PT)	Severity Grade	Number (%) of Subjects(1) and [Number of Events] Treatment A (N=15)	B (N=14)	C (N=15)	Overall (N=15)
Respiratory, thoracic and mediastinal disorders	Mild	0 [1]	0	1 (6.7%) [1]	1 (6.7%) [2]
	Moderate	1 (6.7%) [1]	0	0	1 (6.7%) [1]
Nasal discomfort	Moderate	1 (6.7%) [1]	0	0	1 (6.7%) [1]
Oropharyngeal pain	Mild	0	0	1 (6.7%) [1]	1 (6.7%) [1]
Rhinorrhoea	Mild	1 (6.7%) [1]	0	0	1 (6.7%) [1]

Data Source: Listing 16.2.7.1
MedDRA Version 15.0 used
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
(1) Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
Note: All adverse events starting or worsening after commencement of treatment with investigational product.
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_01_03.sas 15OCT2013 12:03

14.3.1.4 Summary of Treatment-emergent Adverse Events by System Organ Class, Preferred Term, Relationship to Study Drug and Treatment (Safety Population)

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Table 14.3.1.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, Relationship to Study Drug and Treatment
Safety Population (N=16)

System Organ Class (SOC) / MedDRA Preferred Term (PT)	Relationship to Test Article	Number (%) of Subjects(1) and [Number of Events]			
		Treatment			
		A (N=15)	B (N=14)	C (N=15)	Overall (N=15)
Subjects with any TEAE	Definite	1 (6.7%) [2]	1 (7.1%) [1]	0	2 (13.3%) [3]
	Probable	0	0	1 (6.7%) [1]	1 (6.7%) [1]
	Unlikely	3 (20.0%) [3]	1 (7.1%) [1]	4 (26.7%) [4]	4 (26.7%) [8]
	None	1 (6.7%) [1]	0	0	0 [1]
General disorders and administration site conditions	Definite	0	1 (7.1%) [1]	0	1 (6.7%) [1]
	Unlikely	1 (6.7%) [1]	1 (7.1%) [1]	0	1 (6.7%) [2]
Fatigue	Unlikely	1 (6.7%) [1]	1 (7.1%) [1]	0	1 (6.7%) [2]
Medical device discomfort	Definite	0	1 (7.1%) [1]	0	1 (6.7%) [1]
Musculoskeletal and connective tissue disorders	None	1 (6.7%) [1]	0	0	1 (6.7%) [1]
Back pain	None	1 (6.7%) [1]	0	0	1 (6.7%) [1]

Data Source: Listing 16.2.7.1
MedDRA Version 15.0 used
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
(1) Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
All adverse events starting or worsening after commencement of treatment with investigational product
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_01_04.sas 15OCT2013 12:03

Table 14.3.1.4 Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, Relationship to Study Drug and Treatment
Safety Population (N=16)

System Organ Class (SOC) MedDRA Preferred Term (PT)	Relationship to Test Article	Number (%) of Subjects(1) and [Number of Events] Treatment A (N=15)	B (N=14)	C (N=15)	Overall (N=15)
Nervous system disorders	Unlikely	2 (13.3%) [2]	0	4 (26.7%) [4]	4 (26.7%) [6]
Headache	Unlikely	2 (13.3%) [2]	0	4 (26.7%) [4]	4 (26.7%) [6]
Respiratory, thoracic and mediastinal disorders	Definite	1 (6.7%) [2]	0	0	1 (6.7%) [2]
	Probable	0	0	1 (6.7%) [1]	1 (6.7%) [1]
Nasal discomfort	Definite	1 (6.7%) [1]	0	0	1 (6.7%) [1]
Oropharyngeal pain	Probable	0	0	1 (6.7%) [1]	1 (6.7%) [1]
Rhinorrhoea	Definite	1 (6.7%) [1]	0	0	1 (6.7%) [1]

Data Source: Listing 16.2.7.1
MedDRA Version 15.0 used
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
(1) Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
All adverse events starting or worsening after commencement of treatment with investigational product
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_01_04.sas 15OCT2013 12:03

14.3.2 Listings of Deaths, Other Serious and Certain Significant Adverse Events

14.3.2.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events (Safety Population)

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Table 14.3.2.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events
Safety Population (N=16)

Enrolment Number	Subject Number	TEAE	Treatment	MedDRA Preferred Term (MP) MedDRA Body System (MS) CRF Description (C)	Start Date/Time (ON) Stop Date/Time (DR) Duration of event (D) Onset Relative to Last Dose (OR)	Serious (SER) Serious Criteria (SC) Relationship to Study Medication (R) Maximum Severity (MS) Action Taken with Study Drug (A) Outcome (OUT)
No Data Reported						

Data Source: Listing 16.2.7.1
MedDRA Version 15.0 used
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_02_01.sas 15OCT2013 12:03

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Not applicable.

14.3.4 Abnormal Laboratory Value Listing

Not applicable.

14.3.5 Additional Safety Data Summaries

14.3.5.1 Vital Signs (Safety Population)

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Table 14.3.5.1 Vital Signs
Safety Population (N=26)

Vital Sign	Time Point	Summary Statistic	Treatment A Absolute Change	Treatment B Absolute Change	Treatment C Absolute Change	Treatment D Absolute Change	Overall Absolute Change
SBP (mmHg)	Screening	n					26
		Mean					118.3
		SD					13.02
		CV(%)					11.00
		Minimum					98
		Median					119.0
		Maximum					141
	VP Treatment Period 1 Day 1	n					10 10
		Mean					120.9 6.6
		SD					10.71 7.99
		CV(%)					8.86
		Minimum					101 -4
		Median					123.5 9.0
		Maximum					134 16
	VP Treatment Period 1 Day 3	n					8 8
		Mean					118.9 6.6
		SD					10.75 12.26
		CV(%)					9.04
		Minimum					106 -12
		Median					116.5 5.5
		Maximum					138 25

Data Source: Listing 16.2.9.1
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_05_01.sas 15OCT2013 12:03

Reckitt Benckiser Healthcare (UK) Ltd Study GA1116 (0543/031)

Table 14.3.5.1 Vital Signs
Safety Population (N=26)

Vital Sign	Time Point	Summary Statistic	Treatment A		Treatment B		Treatment C		Treatment D		Overall	
			Absolute	Change	Absolute	Change	Absolute	Change	Absolute	Change	Absolute	Change
SBP (mmHg)	VP Follow-up	n									10	10
		Mean									117.4	3.1
		SD									12.94	13.02
		CV(%)									11.02	
		Minimum									97	-18
		Median									118.5	-0.5
		Maximum									143	30
	CP Treatment Period 1 Day 1	n									16	16
		Mean									125.3	4.4
		SD									16.35	14.54
		CV(%)									13.05	
		Minimum									97	-19
		Median									119.5	3.0
		Maximum									155	33
	CP Treatment Period 1 Day 3	n	4	4	4	4	4	4	3	3	15	15
		Mean	113.8	-6.8	119.8	5.5	124.5	3.0	112.0	-10.3	117.9	-1.6
		SD	2.87	15.04	23.04	13.92	13.10	9.09	9.17	8.39	13.79	12.73
		CV(%)	2.53		19.24		10.52		8.18		11.70	
		Minimum	110	-22	98	-12	109	-9	104	-20	98	-22
		Median	114.5	-9.5	117.5	6.0	124.0	4.0	110.0	-6.0	116.0	-5.0
		Maximum	116	14	146	22	141	13	122	-5	146	22

Data Source: Listing 16.2.9.1
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_05_01.sas 15OCT2013 12:03

Reckitt Benckiser Healthcare (UK) Ltd Study GA1116 (0543/031)

Table 14.3.5.1 Vital Signs
Safety Population (N=26)

Vital Sign	Time Point	Summary Statistic	Treatment A		Treatment B		Treatment C		Treatment D		Overall	
			Absolute	Change	Absolute	Change	Absolute	Change	Absolute	Change	Absolute	Change
SBP (mmHg)	CP Treatment Period 2 Day 1	n									15	15
		Mean									121.9	2.4
		SD									17.76	17.44
		CV(%)									14.57	
		Minimum									95	-30
		Median									117.0	-1.0
		Maximum									169	45
	CP Treatment Period 2 Day 3	n	4	4	4	4	3	3	3	3	14	14
		Mean	111.3	-6.8	112.5	-7.8	114.0	-3.3	130.0	10.3	116.2	-2.6
		SD	13.65	10.05	12.26	10.21	10.44	7.51	9.17	11.59	12.81	11.35
		CV(%)	12.27		10.90		9.16		7.05		11.03	
		Minimum	92	-18	100	-16	102	-11	120	-2	92	-18
		Median	114.5	-6.5	113.0	-10.5	119.0	-3.0	132.0	12.0	119.5	-2.5
		Maximum	124	4	124	6	121	4	138	21	138	21
	CP Follow-up	n									15	15
		Mean									118.9	-0.6
		SD									15.99	13.76
		CV(%)									13.45	
		Minimum									89	-22
		Median									117.0	1.0
		Maximum									151	23

Data Source: Listing 16.2.9.1
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_05_01.sas 15OCT2013 12:03

Reckitt Benckiser Healthcare (UK) Ltd Study GA1116 (0543/031)

Table 14.3.5.1 Vital Signs
Safety Population (N=26)

Vital Sign	Time Point	Summary Statistic	Treatment A Absolute Change	Treatment B Absolute Change	Treatment C Absolute Change	Treatment D Absolute Change	Overall Absolute Change
DBP (mmHg)	Screening	n					26
		Mean					71.7
		SD					8.48
		CV(%)					11.83
		Minimum					55
		Median					72.0
		Maximum					89
	VP Treatment Period 1 Day 1	n					10 10
		Mean					70.2 5.3
		SD					7.47 7.09
		CV(%)					10.63
		Minimum					57 -6
		Median					72.5 4.5
		Maximum					77 15
	VP Treatment Period 1 Day 3	n					8 8
		Mean					72.0 8.0
		SD					8.05 8.60
		CV(%)					11.19
		Minimum					61 -9
		Median					76.0 9.0
		Maximum					82 17

Data Source: Listing 16.2.9.1
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_05_01.sas 15OCT2013 12:03

Reckitt Benckiser Healthcare (UK) Ltd Study GA1116 (0543/031)

Table 14.3.5.1 Vital Signs
Safety Population (N=26)

Vital Sign	Time Point	Summary Statistic	Treatment A		Treatment B		Treatment C		Treatment D		Overall	
			Absolute	Change	Absolute	Change	Absolute	Change	Absolute	Change	Absolute	Change
DBP (mmHg)	VP Follow-up	n									10	10
		Mean									66.7	1.8
		SD									6.78	9.50
		CV(%)									10.17	
		Minimum									55	-12
		Median									68.0	2.0
		Maximum									78	19
	CP Treatment Period 1 Day 1	n									16	16
		Mean									75.3	-0.7
		SD									9.82	10.34
		CV(%)									13.03	
		Minimum									61	-15
		Median									74.0	-0.5
		Maximum									101	14
	CP Treatment Period 1 Day 3	n	4	4	4	4	4	4	3	3	15	15
		Mean	73.5	-1.3	68.0	-3.8	75.3	-4.5	65.0	-12.7	70.8	-5.1
		SD	4.93	5.50	12.57	7.37	6.18	9.95	14.00	20.55	9.62	10.81
		CV(%)	6.71		18.49		8.22		21.54		13.58	
		Minimum	68	-6	55	-13	68	-13	51	-34	51	-34
		Median	73.0	-2.5	66.0	-3.5	75.0	-5.5	65.0	-11.0	73.0	-4.0
		Maximum	80	6	85	5	83	6	79	7	85	7

Data Source: Listing 16.2.9.1
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_05_01.sas 15OCT2013 12:03

Reckitt Benckiser Healthcare (UK) Ltd Study GA1116 (0543/031)

Table 14.3.5.1 Vital Signs
Safety Population (N=26)

Vital Sign	Time Point	Summary Statistic	Treatment A		Treatment B		Treatment C		Treatment D		Overall	
			Absolute	Change	Absolute	Change	Absolute	Change	Absolute	Change	Absolute	Change
DBP (mmHg)	CP Treatment Period 2 Day 1	n									15	15
		Mean									70.7	-5.2
		SD									8.67	10.48
		CV(%)									12.27	
		Minimum									48	-24
		Median									71.0	-2.0
		Maximum									82	9
	CP Treatment Period 2 Day 3	n	4	4	4	4	3	3	3	3	14	14
		Mean	63.3	-10.8	69.8	-8.0	64.3	-10.3	79.3	2.7	68.8	-7.0
		SD	11.35	8.77	10.21	8.37	4.62	13.80	6.66	9.87	10.19	10.34
		CV(%)	17.95		14.64		7.18		8.39		14.82	
		Minimum	54	-22	60	-15	59	-26	72	-4	54	-26
		Median	60.0	-10.0	67.5	-10.5	67.0	-5.0	81.0	-2.0	67.0	-6.5
		Maximum	79	-1	84	4	67	0	85	14	85	14
	CP Follow-up	n									15	15
		Mean									69.3	-6.6
		SD									9.00	8.64
		CV(%)									12.99	
		Minimum									57	-24
		Median									71.0	-5.0
		Maximum									84	7

Data Source: Listing 16.2.9.1
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_05_01.sas 15OCT2013 12:03

Reckitt Benckiser Healthcare (UK) Ltd Study GA1116 (0543/031)

Table 14.3.5.1 Vital Signs
Safety Population (N=26)

Vital Sign	Time Point	Summary Statistic	Treatment A Absolute Change	Treatment B Absolute Change	Treatment C Absolute Change	Treatment D Absolute Change	Overall Absolute Change
Heart Rate (bpm)	Screening	n					26
		Mean					68.2
		SD					8.28
		CV(%)					12.14
		Minimum					57
		Median					66.0
		Maximum					91
	VP Treatment Period 1 Day 1	n					10 10
		Mean					75.3 7.4
		SD					9.96 4.25
		CV(%)					13.22
		Minimum					69 1
		Median					71.5 8.5
		Maximum					102 12
	VP Treatment Period 1 Day 3	n					8 8
		Mean					75.4 7.4
		SD					9.23 11.73
		CV(%)					12.24
		Minimum					57 -10
		Median					77.5 13.0
		Maximum					86 20

Data Source: Listing 16.2.9.1
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_05_01.sas 15OCT2013 12:03

Reckitt Benckiser Healthcare (UK) Ltd Study GA1116 (0543/031)

Table 14.3.5.1 Vital Signs
Safety Population (N=26)

Vital Sign	Time Point	Summary Statistic	Treatment A		Treatment B		Treatment C		Treatment D		Overall	
			Absolute	Change	Absolute	Change	Absolute	Change	Absolute	Change	Absolute	Change
Heart Rate (bpm)	VP Follow-up	n									10	10
		Mean									74.7	6.8
		SD									9.35	11.69
		CV(%)									12.51	
		Minimum									63	-16
		Median									73.5	7.5
		Maximum									91	25
	CP Treatment Period 1 Day 1	n									16	16
		Mean									73.7	5.3
		SD									6.34	8.23
		CV(%)									8.61	
		Minimum									63	-12
		Median									71.0	6.0
		Maximum									88	23
	CP Treatment Period 1 Day 3	n	4	4	4	4	4	4	3	3	15	15
		Mean	78.8	7.3	71.0	4.8	76.8	10.3	69.3	-2.0	74.3	5.5
		SD	13.00	7.93	2.16	6.50	11.47	8.77	1.15	7.94	9.02	8.22
		CV(%)	16.50		3.04		14.95		1.67		12.14	
		Minimum	70	-1	69	-4	60	-1	68	-11	60	-11
		Median	73.5	6.0	70.5	6.0	80.5	11.5	70.0	1.0	71.0	5.0
		Maximum	98	18	74	11	86	19	70	4	98	19

Data Source: Listing 16.2.9.1
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_05_01.sas 15OCT2013 12:03

Table 14.3.5.1 Vital Signs
Safety Population (N=26)

Vital Sign	Time Point	Summary Statistic	Treatment A		Treatment B		Treatment C		Treatment D		Overall	
			Absolute	Change	Absolute	Change	Absolute	Change	Absolute	Change	Absolute	Change
Heart Rate (bpm)	CP Treatment Period 2 Day 1	n									15	15
		Mean									80.6	11.9
		SD									12.84	12.71
		CV(%)									15.94	
		Minimum									63	-7
		Median									75.0	10.0
		Maximum									101	42
	CP Treatment Period 2 Day 3	n	4	4	4	4	3	3	3	3	14	14
		Mean	68.8	-0.5	70.5	0.0	74.7	7.3	81.0	13.3	73.1	4.3
		SD	6.40	12.45	13.43	4.08	8.08	12.42	5.29	12.06	9.40	10.93
		CV(%)	9.30		19.05		10.83		6.53		12.85	
		Minimum	62	-16	58	-3	66	-7	75	2	58	-16
		Median	68.5	0.5	67.5	-1.5	76.0	14.0	83.0	12.0	73.5	3.5
		Maximum	76	13	89	6	82	15	85	26	89	26
	CP Follow-up	n									15	15
		Mean									68.7	-0.1
		SD									7.72	10.77
		CV(%)									11.24	
		Minimum									55	-17
		Median									67.0	-1.0
		Maximum									85	28

Data Source: Listing 16.2.9.1
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_05_01.sas 15OCT2013 12:03

Table 14.3.5.1 Vital Signs
Safety Population (N=26)

Vital Sign	Time Point	Summary Statistic	Treatment A Absolute Change	Treatment B Absolute Change	Treatment C Absolute Change	Treatment D Absolute Change	Overall Absolute Change
Oral Temperature (deg. C)	Screening	n					26
		Mean					36.53
		SD					0.445
		CV(%)					1.22
		Minimum					36.0
		Median					36.55
		Maximum					37.4
	VP Treatment Period 1 Day 1	n					10 10
		Mean					36.40 -0.15
		SD					0.620 0.715
		CV(%)					1.70
		Minimum					35.0 -1.6
		Median					36.60 -0.25
		Maximum					37.0 0.8
	VP Treatment Period 1 Day 3	n					8 8
		Mean					36.80 0.21
		SD					0.385 0.647
		CV(%)					1.05
		Minimum					36.1 -0.6
		Median					36.85 0.35
		Maximum					37.3 1.1

Data Source: Listing 16.2.9.1
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_05_01.sas 15OCT2013 12:03

Table 14.3.5.1 Vital Signs
Safety Population (N=26)

Vital Sign	Time Point	Summary Statistic	Treatment A		Treatment B		Treatment C		Treatment D		Overall	
			Absolute	Change	Absolute	Change	Absolute	Change	Absolute	Change	Absolute	Change
Oral Temperature (deg. C)	VP Follow-up	n									10	10
		Mean									36.35	-0.20
		SD									0.255	0.638
		CV(%)									0.70	
		Minimum									36.1	-1.2
		Median									36.25	-0.15
		Maximum									36.8	0.4
	CP Treatment Period 1 Day 1	n									16	16
		Mean									36.48	-0.05
		SD									0.229	0.412
		CV(%)									0.63	
		Minimum									36.1	-0.7
		Median									36.45	0.05
		Maximum									36.8	0.8
	CP Treatment Period 1 Day 3	n	4	4	4	4	4	4	3	3	15	15
		Mean	36.65	0.20	36.68	0.10	36.28	-0.08	36.60	-0.13	36.55	0.03
		SD	0.238	0.294	0.450	0.392	0.206	0.465	0.100	0.643	0.309	0.419
		CV(%)	0.65		1.23		0.57		0.27		0.85	
		Minimum	36.4	-0.2	36.3	-0.4	36.1	-0.5	36.5	-0.6	36.1	-0.6
		Median	36.65	0.25	36.60	0.15	36.25	-0.15	36.60	-0.40	36.50	0.10
		Maximum	36.9	0.5	37.2	0.5	36.5	0.5	36.7	0.6	37.2	0.6

Data Source: Listing 16.2.9.1
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_05_01.sas 15OCT2013 12:03

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Table 14.3.5.1 Vital Signs
Safety Population (N=26)

Vital Sign	Time Point	Summary Statistic	Treatment A		Treatment B		Treatment C		Treatment D		Overall	
			Absolute	Change	Absolute	Change	Absolute	Change	Absolute	Change	Absolute	Change
Oral Temperature (deg. C)	CP Treatment Period 2 Day 1	n									15	15
		Mean									36.36	-0.15
		SD									0.408	0.542
		CV(%)									1.12	
		Minimum									35.4	-1.7
		Median									36.30	-0.10
		Maximum									37.0	0.6
	CP Treatment Period 2 Day 3	n	4	4	4	4	3	3	3	3	14	14
		Mean	36.55	-0.23	36.53	0.20	36.50	0.03	36.50	0.07	36.52	0.01
		SD	0.480	0.640	0.222	0.566	0.173	0.231	0.100	0.681	0.267	0.526
		CV(%)	1.31		0.61		0.47		0.27		0.73	
		Minimum	36.1	-1.0	36.2	-0.6	36.3	-0.1	36.4	-0.7	36.1	-1.0
		Median	36.45	-0.10	36.60	0.40	36.60	-0.10	36.50	0.30	36.60	0.25
		Maximum	37.2	0.3	36.7	0.6	36.6	0.3	36.6	0.6	37.2	0.6
	CP Follow-up	n									15	15
		Mean									36.44	-0.07
		SD									0.320	0.459
		CV(%)									0.88	
		Minimum									36.0	-1.1
		Median									36.50	-0.10
		Maximum									37.2	0.7

Data Source: Listing 16.2.9.1
Treatment Codes - A: Gaviscon Double Action Liquid (20 mL)
B: Gaviscon Advance Liquid (10 mL)
C: Placebo Liquid (20 mL)
D: Untreated
Kachirayila: dub-filer-01/ids$/stats/0543/031/Final/Original/Reporting/Programs/TFL/T14_03_05_01.sas 15OCT2013 12:03

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16 APPENDICES

16.1 Study Information

This appendix contains the following sections:

16.1.1 Protocol and Protocol Amendments (350 pages)

16.1.2 Sample Case Report Form (Unique Pages Only) (145 pages)

16.1.3 List of IECs (133 pages)

16.1.4 List and Description of Investigators and Other Important Participants in the Study (13 pages)

16.1.5 Signature of Principal/Chief/Coordinating Investigator(s) (2 pages)

16.1.6 Listing of Subjects Receiving Study Drug(s)/Investigational Product from Specific Batches, where more than One Batch was Used (1 page)

16.1.7 Randomisation Scheme and Codes (Subject Identification and Treatment Assigned) (2 pages)

16.1.8 Audit Certificates (2 pages)

16.1.9 Documentation of Statistical Methods (819 pages)

16.1.10 Documentation of Inter-Laboratory Standardisation Methods and QA Procedures if Used (1 page)

16.1.11 Publications Based on the Study (1 page)

16.1.12 Important Publications Referenced in the Report (1 page)

16.1.1 Protocol and Protocol Amendments

This appendix contains (350 pages):

- Final Protocol Version 1, dated 24 May 2012 (60 pages).
- Final Protocol Version 2, dated 01 Jun 2012 (58 pages).
- Non-substantial Amendment No. 1, dated 03 Aug 2012 (2 pages).
- Non-substantial Amendment No. 2, dated 25 Sep 2012 (4 pages).
- Substantial Amendment No. 1, dated 19 Oct 2012 (8 pages).
- Non-substantial Amendment No. 3, dated 14 Dec 2012 (3 pages).
- Non-substantial Amendment No. 4, dated 10 Jan 2013 (3 pages).
- Substantial Amendment No. 2, dated 01 Feb 2013 (7 pages).
- Final Protocol Version 3, dated 01 Feb 2013 (60 pages).
- Non-substantial Amendment No. 5, dated 27 Mar 2013 (6 pages).
- Final Protocol Version 4, dated 27 Mar 2013 (60 pages).
- Substantial Amendment No. 3, dated 17 Apr 2013 (3 pages).
- Final Protocol Version 5, dated 17 Apr 2013 (59 pages).
- Note to File: pH Data File Repairs by Sandhill, dated 09 Sep 2013 (8 pages).
- Note to File: Weak Acid Episodes post pH File Repair, dated 09 Sep 2013 (5 pages).
- Note to File: Timings, dated 12 Sep 2013 (3 pages).

16.1.2 Sample Case Report Form (Unique Pages Only)

This appendix contains (145 pages):

- Screening.
- Validation Phase Treatment Period 1 Day 1.
- Validation Phase Treatment Period 1 Day 2.
- Validation Phase Treatment Period 1 Day 3.
- Validation Phase Follow-up.
- Clinical Phase Treatment Period 1 Day 1.
- Clinical Phase Treatment Period 1 Day 2.
- Clinical Phase Treatment Period 1 Day 3.
- Clinical Phase Treatment Period 2 Day 1.
- Clinical Phase Treatment Period 2 Day 2.
- Clinical Phase Treatment Period 2 Day 3.
- Clinical Phase Follow-up.
- Prior/Concomitant Medication.
- Adverse Events/Adverse Device Effect.
- Repeat Measurements.
- Unscheduled Assessments.
- Comments.
- Study Completion/Early Termination.
- Impedance Data Worksheet.

16.1.3 List of IECs

This appendix contains (133 pages):

- Name and address of ethics committee used in the study.
- Sample consent form Final Version 1.0, 08 Jun 2012 (2 pages).
- Written information Validation Phase Final Version 1.0, 08 Jun 2012 (14 pages).
- Written information Clinical Phase Final Version 1.0, 08 Jun 2012 (14 pages).
- Sample consent form Validation Phase Final Version 2.0, 09 Aug 2012 (2 pages).
- Sample consent form Clinical Phase Final Version 2.0, 09 Aug 2012 (2 pages).
- Written information Validation Phase Final Version 2.0, 09 Aug 2012 (14 pages).
- Written information Clinical Phase Final Version 2.0, 09 Aug 2012 (14 pages).
- Written information Validation Phase Final Version 3.0, 23 Oct 2012 (14 pages).
- Written information Clinical Phase Final Version 3.0, 23 Oct 2012 (14 pages).
- Written information Clinical Phase Final Version 4.0, 29 Nov 2012 (14 pages).
- Written information Clinical Phase Final Version 5.0, 07 Feb 2013 (14 pages).
- Written information Clinical Phase Final Version 6.0, 17 Apr 2013 (14 pages).

National Research Ethics Service Committee East Midlands - Northampton:

The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

16.1.4 List and Description of Investigators and Other Important Participants in the Study

This appendix contains (13 pages):

- Table listing the names and affiliations of the individuals whose participation materially affected the conduct of the study, together with their role (1 page).
- Curricula Vitae of:

Principal Investigators (7 pages)

Statistician (1 page)

Report author (3 pages)

Names and Affiliations of Important Participants in the Study

Title and Name	Qualifications	Job Title	Work Address	Study Role
Dr Simon Singer	BSc MB, ChB MRCS	Senior Clinical Research Physician	ICON Development Solutions, Skelton House, Lloyd Street North, Manchester, M15 6SH, United Kingdom	Principal Investigator (01 Mar 2012 until 13 Mar 2013)
Dr Peter Dewland	BSc MA, MBBS, FFPM, DCPSA	Medical Director		Principal Investigator (13 Mar 2013 until 17 Apr 2013)
Dr Pui Man Leung	MBChB, MRCP, MFPM	Senior Director/ Chief Principal Investigator		Principal Investigator (17 Apr 2013 until 21 May 2013)
Ms Sally Anderton	MSc	Manager, Biostatistics		Statistician
Mr Leon Conradie	BA Hons	Senior Medical Writer	ICON Clinical Research, Decentralised, Eastleigh	Report Author

16.1.5 Signature of Principal Investigator

Reckitt Benckiser

PRINCIPAL INVESTIGATOR'S SIGNATURE

Study Number:	GA1116
Study Title:	A single-centre, randomised, four-way crossover study to investigate the measurement of the acid pocket and subsequent gastro-oesophageal reflux episodes using a novel pH/impedance catheter in subjects receiving Gaviscon® Double Action, Gaviscon® Advance and Placebo Liquid versus no treatment
Phase of Development:	II

Principal Investigator:

By my signature below, I hereby state that I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study. I agree its conclusions and do not wish to make an additional statement regarding the safety of the product under test.

Dr P Dewland, BSc MA, MBBS, FFPM, DCPSA
ICON Development Solutions
Skelton House
Lloyd Street North
Manchester
M15 6SH
United Kingdom

Tel: 0161 232 2711

Date

16.1.6 Listing of Subjects Receiving Study Drug(s)/Investigational Product from Specific Batches, Where More Than One Batch was Used

All subjects in this study received Gaviscon® Double Action Aniseed Liquid, Gaviscon® Advance Aniseed Liquid and Placebo Aniseed Liquid, each from one batch, so this appendix is not applicable.

16.1.7 Randomisation Scheme and Codes (Subject Identification and Treatment Assigned)

This appendix contains:

- Description of the randomisation method.

Randomisation was conducted using SAS 9.2 according to the following process:

1) Create a list of numbers at least as large as the number of subjects.

2) Create a blocking variable that indicates subjects in the same block with block size of 8.

3) Create a treatment sequence variable such that there is 1 of each treatment sequence in each block of 8.

4) Create a random number variable using a study unique random seed number.

5) Sort subjects within each block by the random variable.

6) Create a subject number variable in ascending order of the sorted data.

- Table of randomisation codes.

Subjects were randomised to one of the following 8 sequences:

Treatment Sequence	**Treatment**			
	Period 1		**Period 2**	
	Day 2	**Day 3**	**Day 2**	**Day 3**
ACBD	A	C	B	D
ACDB	A	C	D	B
CABD	C	A	B	D
CADB	C	A	D	B
BDAC	B	D	A	C
BDCA	B	D	C	A
DBAC	D	B	A	C
DBCA	D	B	C	A

Treatment A: Gaviscon® Double Action Aniseed Liquid (20 ml)
Treatment B: Gaviscon® Advance Aniseed Liquid (10 ml)
Treatment C: Placebo Aniseed Liquid (20 ml)
Treatment D: Untreated state

16.1.8 Audit Certificates

This appendix contains the following audit certificates (2 pages):

- Reckitt Benckiser GCP audit certificate (1 page).
- Clinical study report (1 page).

16.1.9 Documentation of Statistical Methods

This appendix contains (819 pages):

- Final Version 1.3 SAP, dated 23 Aug 2013 (36 pages).
- Final Version 1.2 Table Shells, dated 25 Apr 2013 (23 pages).
- Final Version 1.2 Listing Shells, dated 25 Apr 2013 (36 pages).
- Appendix 16.1.9.1, SAS Output for the Statistical Analysis of the Time that Electrode is pH < 4 over 2 Hours (14 pages).
- Appendix 16.1.9.2, SAS Output for the Exploratory Analysis 1 of the Primary Endpoint, by Population (14 pages).
- Appendix 16.1.9.3, SAS Output for the Exploratory Analysis 2 of the Primary Endpoint, by Population (16 pages).
- Appendix 16.1.9.4, SAS Output for the Statistical Analysis of the Time that Electrode is pH < 4 Over 4 hours, by Population (16 pages).
- Appendix 16.1.9.5, SAS Output for the Statistical Analysis of the Time that Each Electrode is pH < 4 Over Various Times, by Population (384 pages).
- Appendix 16.1.9.6, SAS Output for the Statistical Analysis of the Mean Percentage of Time with pH < 4 at Electrodes 1, 2 and 3 during 4 x 1-hour Periods (49 pages).
- Appendix 16.1.9.7, SAS Output for the Statistical Analysis of the Mean Percentage of Time pH < 4 at Electrodes 1, 2 and 3 Over 4 Hours (14 pages).
- Appendix 16.1.9.8, SAS Output for the Statistical Analysis of the Mean Percentage of Time with pH < 4 at Electrodes 4 to 7 Over 4 x 1-hour Periods, by Population (48 pages).
- Appendix 16.1.9.9, SAS Output for the Statistical Analysis of Number of Liquid, Gas and Mixed Reflux Episodes Occurring in the 2- and 4-hour Periods (72 pages).
- Appendix 16.1.9.10, SAS Output for the Statistical Analysis of Number of Acid and Weakly Acidic Reflux Episodes Occurring in the 2- and 4-hour Periods, by Analysis of Variance (49 pages).

- Appendix 16.1.9.11, SAS Output for the Statistical Analysis of Number of Reflux Episodes Occurring Reaching 15 cm Above the LOS during the 2- and 4-hour Periods (24 pages).
- Appendix 16.1.9.12, SAS Output for the Statistical Analysis of Oesophageal Bolus Exposure to Reflux during the 2- and 4-hour Periods (24 pages).

16.1.10 Documentation of Inter-laboratory Standardisation Methods and Quality Assurance Procedures if Used

This appendix is not relevant for this study as each parameter was analysed at a single laboratory.

16.1.11 Publications Based on the Study

There are no publications based on this study, so this appendix is not applicable.

16.1.12 Important Publications Referenced in the Report

No publications referred to in the report are appended. All references are available on request.

16.2 Subject Data Listings

This appendix contains the following sections:

16.2.1 Discontinued Subjects (7 pages)

16.2.2 Protocol Deviations (2 pages)

16.2.3 Subjects Excluded from Analysis (2 pages)

16.2.4 Demographic Data (36 pages)

16.2.5 Compliance Data (36 pages)

16.2.6 Individual pH and Reflux Response Data (267 pages)

16.2.7 Adverse Event Listings (11 pages)

16.2.8 Individual Laboratory Measurements by Subject (99 pages)

16.2.9 Additional Safety Measurements by Subject (15 pages)

16.2.10 General Comments (50 pages)

16.2.1 Discontinued Subjects

16.2.2 Protocol Deviations

16.2.3 Subjects Excluded from Analysis

16.2.4 Demographic Data

16.2.5 Compliance Data

16.2.6 Individual pH and Reflux Response Data

16.2.7 Adverse Event Listings

16.2.8 Individual Laboratory Measurements by Subject

16.2.9 Additional Safety Measurements by Subject

16.2.10 General Comments

16.3 Case Report Forms

This appendix is not relevant because no subjects died, experienced SAEs, or withdrew due to AEs in this study.