Reckitt Benckiser

1 ABBREVIATED STUDY REPORT TITLE PAGE

EudraCT/IND Number:	2010-021630-63
ISRCTN number	ISRCTN52169198
Study Number:	GA1001
Protocol Title:	A randomised, double blind Placebo controlled study in patients with reflux symptoms to assess suppression of gastro-oesophageal reflux by 'Gaviscon Double Action Peppermint liquid' using the BRAVO system
Study Phase:	IV
Date First Subject Enrolled:	22nd June 2011
Date Last Subject Completed:	30th October 2011
Report Date:	19-Nov-2012
Principal Investigator:	Terry Wong MD, MA, MRCP, Oesophageal Laboratory, Department of Gastroenterology, St. Thomas' Hospital, Lambeth Palace Road, London, SE1 7EH, UK
Study Conduct Statement:	This study was conducted in accordance with ICH Good Clinical Practice and the ethical principles contained within the Declaration of Helsinki (South Africa, 1996), as referenced in EU Directive 2001/20/EC. Documents defined by ICH GCP as "essential documents" will be archived in the RB company archive in Hull, HU8 7DS, UK

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2 SYNOPSIS

Title of Trial: A randomised, double blind Placebo controlled study in patients with reflux symptoms to assess suppression of gastro-oesophageal reflux by 'Gaviscon Double Action Peppermint liquid' using the BRAVO system	
Investigator(s): Terry Wong MD, MA, MRCP	
Trial Site(s): Oesophageal Laboratory, Dept of Gastroenterology, St. Thomas' Hospital, London, UK	
Publication (reference): None	
Studied Period: 143 days **Date first subject enrolled:** 22nd June 2011 **Date last subject completed:** 30th October 2011	**Phase of Development:** IV

Objectives:

The primary objective of this study was to compare the effectiveness of Gaviscon Double Action or a closely matched placebo on suppression of acid reflux events in patients with typical reflux symptoms. The primary endpoint was the number of acid reflux events during 48hr Gaviscon Double Action or matched placebo study period compared to the 48hr "no treatment" study period.

Secondary objectives including comparing the effectiveness of Gaviscon Double Action or a Placebo on suppression of oesophageal acid exposure, pepsin in expectorated saliva and clinical benefit in terms of subject reports of reflux symptoms.

These data were required to confirm the mechanism of action of Gaviscon Double Action Peppermint liquid and provide power calculations ahead of large scale, community based, clinical trials in subjects with reflux symptoms.

Methodology:

Subjects were recruited from those referred to St. Thomas Hospital Oesophageal Laboratory for investigation of predominant, typical reflux symptoms (heartburn, acid regurgitation) who agreed to withhold medications that affect gastric acid secretion and motility prior to and during monitoring. Subjects were recruited following their initial investigation by high resolution manometry, performed to exclude primary oesophageal dysmotility. Questionnaires were completed detailing symptoms, psychological state and perceived quality of life. Subjects commenced the treatment peroiods within one month of confirmation of study eligibility.

Subjects were randomised to receive either Gaviscon Double Action Peppermint liquid or a Placebo for two days during a four day assessment period. Gaviscon Double Action Peppermint liquid or a Placebo was self-administered four times a day after meals and before bed for two days and no treatment was administered on the other two days. For all subjects, acid reflux events and symptoms were recorded over all four days. No rescue medication was provided.

Placement of Bravo capsules was performed during endoscopy under sedation. During the study, reflux events, reflux symptoms and activities of daily living (i.e. meal times, bedtimes)

were logged on the wireless data receiver (subjects could also record symptoms on a paper diary). Subjects also completed the symptom relief questionnaire each day. After the first 48hr period, the patient returned to the hospital to download pH and symptom data from the receiver. If normal function was confirmed then the second 48hr period was completed before data was downloaded and the receiver returned.

Number of Subjects: **Planned:** 40

Entered into ITT analysis: 22

Diagnosis and Main Criteria for Inclusion:

Age: ≥ 18 years ≤ 70 years.

Those with self-rated at least moderate heartburn or acid regurgitation within 60 minutes following ingestion of a refluxogenic meal on at least 3 occasions a week at the screening visit.

Agreement to withhold from Proton Pump Inhibitors (PPIs), H2 receptor blocking medications and other medications that affect gastro-intestinal function for 6 days and 3 days respectively prior to the test and during the 4 days of monitoring.

Agreement to withhold antacids or alginate preparations, except those administered as part of study procedures for 1 day prior to the test and during 4 days of monitoring

Exclusion Criteria:

Those with prominent gastrointestinal symptoms or disease other than reflux (including atypical symptoms e.g. cough, sore throat, belching, nausea)

Those with difficulty swallowing (dysphagia), gastrointestinal bleeding, weight loss (>5% body weight) or other alarm symptoms suggestive of neoplastic or severe inflammatory disease within the last 12 months

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

Those with a history of upper GI surgery or endoscopic interventions such as oesophageal dilatations or mucosal resection.

Test Product: Gaviscon Double Action Peppermint liquid, Batch number 932984

PL00063/0156, 20 ml taken orally 4 times per day, after each main meal (breakfast, lunch, dinner) and before bed

Duration of Treatment: Each patient had 4 days of investigation (2 days of treatment and 2 days of no treatment). The duration of each patient's active participation in the study was approximately five days, including screening and follow-up assessments.

Reference Therapy: Placebo syrup (prune flavoured), Item code 0244943

Batch number 44001/179, 20 ml taken orally 4 times per day, after each main meal (breakfast, lunch, dinner) and before bed

Criteria for Evaluation:

Efficacy: The primary endpoint was the number of acid reflux events during 48hr Gaviscon Double Action or Placebo study period compared to the 48hr "no treatment" study period.

An acid reflux event was defined as a fall in pH to less than pH4 with duration of at least 12 seconds. (i.e. two consecutive measurements since Bravo logged pH data every 6 seconds and signal detection recognition required two consecutive pH measurements at pH<4 to register an acid reflux event).

Secondary endpoints:

The combined number of acid reflux events *and* weakly acid reflux events during the Gaviscon Double Action or matched placebo study period compared to the 48hr "no treatment" study period. A weakly acid reflux event is defined as any fall in pH of more than 2 pH units in an interval of less than 1 minute which is maintained for a duration of at least 12 seconds.

Oesophageal acid exposure (percentage of time with pH less than pH 4) during the Gaviscon Double Action or Placebo study period compared to the 48hr "no treatment" study period.

Categorical presence / absence and concentration of pepsin in expectorated saliva acquired 2hr after the main evening meal on each test day at detection threshold 16ng/ml of 'pepsin lateral flow test' (Technostics, Hull, UK (PeptestTM))

Severity and Duration of symptoms / Time until symptomatic relief, documented by study patients in the patient diary

The number of typical reflux symptoms (heartburn, acid regurgitation) documented by study participants on data logger / receiver and diary card during the Gaviscon Double Action or Placebo study period compared to the 48hr "no treatment" study period.

The number of typical reflux symptoms (heartburn, acid regurgitation) in the postprandial and night-time periods in the 2hr period after self-administration of the test product during the Gaviscon Double Action or Placebo study period compared to the 48hr "no treatment" study period.

Sub-analyses:

The number of acid reflux events *in the upright position and in the supine position* during 48hr Gaviscon Double Action or Placebo study period compared to the 48hr "no treatment" study period were analyzed.

Statistical Methods:

For each of the endpoints the difference between the value during the 48-hour treatment period (Gaviscon Double Action or Placebo) and the value during the no treatment period was calculated (corrected where necessary for continuous (24 hours per day) monitoring).

For each of the endpoints the comparison between the treatment groups was performed using linear regression analysis with change in value for the endpoint (from treatment period to no treatment period) as the dependent variable and gender, treatment order and randomisation group as independent variables. Where treatment order and/or gender had no significant relationship (p>0.1) the analysis was repeated with these variables omitted.

Where non-parametric analysis was deemed appropriate the Mann-Whitney Test was used to

compare the 2 treatment groups.

Binary logistic regression was performed for analysis of secondary endpoint change in number of days pepsin was present in expectorated saliva acquired 2 hours after the main evening meal on each test day.

SUMMARY

1) Primary endpoint: Number of Reflux Events

The mean number of reflux events was lower during Gaviscon Double Action treatment compared to "no treatment"; however no reduction is seen with Placebo. This was evident in the raw data (table 1, figure 2) and the linear regression analysis (table 2) that demonstrates a numeric trend to acid reflux suppression by the test medication compared to placebo (p=0.137).

2) Secondary endpoints

a) Combined number of acid reflux events *and* weakly acid reflux events during the Gaviscon Double Action or matched placebo study period compared to the 48hr "no treatment" study period

This secondary endpoint was not pursued due to it not being possible to separate acidic from weakly acidic events using the available Bravo capsule analysis software.

b) Oesophageal acid exposure (percentage of time with pH less than 4)

The mean oesophageal acid exposure was lower during Gaviscon Double Action treatment compared to "no treatment" whereas only a small reduction is seen with Placebo. This is evident in the raw data (table 3, figure 3) and the linear regression analysis (table 4), although this is not statistically significant (p=0.549).

c) The number of episodes of heartburn as recorded on the data logger and d) The number of episodes of regurgitation as recorded on the data logger

The number of heartburn (tables 5, 6) or regurgitation (tables 7, 8) symptoms reported during the study was not significantly different between Gaviscon Double Action and Placebo treatment (p=0.556 and p=0.301, respectively).

e) The Eraflux score

Gaviscon Double Action reduced the severity of symptoms compared to "off most effective treatment" but less effective than "on most effective treatment" (table 9); however the effects between treatments were not significant (p=0.321). The average effect of Gaviscon Double Action on reflux symptoms as assessed by Eraflux score was also numerically greater than that on Placebo treatment (table 10) by -3.5 points, where a reduction in 2 points is clinically relevant.

f) Mean pepsin concentration 2 hours after the main evening meal and g) The number of days pepsin is present in expectorated saliva acquired 2 hour after the main evening meal on each test day

Measurements of pepsin concentration were highly variable and no significant effects or trend to effects were obtained when comparing Gaviscon Double Action and Placebo (table 12). Applying a categorical cut-off to define the presence / absence of pepsin in the expectorated

saliva (25ng/ml), showed no statistical difference when comparing Gaviscon Double Action and Placebo (figure 4, table 13).

SUB-ANALYSES;

Number of acid reflux events (upright position) and number of acid reflux events (supine position)

The mean number of reflux events was highly variable but lower during Gaviscon Double Action treatment compared to no treatment in the upright and supine positions, whereas, no reduction was seen with Placebo (table 18 and 20, respectively). The comparison between Gaviscon Double Action and placebo approached statistical significance in the upright position (p=0.088); however this was not the case in the supine position (table 21, p=0.375).

Oesophageal acid exposure (percentage time pH less than 4) [upright position] and oesophageal acid exposure (percentage time pH less than 4) [supine position]

The mean oesophageal acid exposure was lower during both the Gaviscon Double Action and placebo treatment periods compared to the no treatment periods in the upright and supine positions (tables 22 and 24, respectively). This effect approached statistical significance in favour of Gaviscon Double Action compared to placebo in the supine position (table 25, p=0.099); however this was not the case in the upright position (table 24, p=0.831).

SAFETY RESULTS:

29 Adverse Events were recorded during this study. These are discussed in Section 8 and 10.

CONCLUSION:

Interpretation of the results should be made cautiously because of the small sample size. It was intended to recruit 40 subjects into the study (approximately 20 subjects in each treatment group); however only 22 (Gaviscon: 8, Placebo: 14) completed the study and entered the ITT population with adequate data in both for analysis. A full description of the study population can be seen in Section 6.1.

There was no significant difference in the number of typical reflux symptoms (heartburn, regurgitation) reported by patients between the two study groups (p=0.32). The effect on reflux symptoms as assessed by Eraflux score was greater for Gaviscon Double Action than Placebo treatment by an average -3.5 points (a reduction in 2 points is clinically relevant), although this did not reach statistical significance.

There was no difference in the mean pepsin concentration between the Gaviscon and Placebo group. Similarly there was no difference in the frequency of positive tests based on categorical cut-off test result of >25 ng/ml.

These results are consistent with Gaviscon Double Action providing effective reflux suppression. Although there was no improvement in the frequency of typical symptoms reported during the study or recall assessment of patient symptoms (Eraflux score) the numerical values favoured the alginate preparations in most cases.

The results provide methodological information regarding assessment of reflux suppression using the Bravo system and provide adequate data for power calculations required for future studies.

Date of the report: 19-Nov-2012

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11.3 INDIVIDUAL SUBJECT DATA LISTINGS FOR SAFETY DATA (US ARCHIVAL LISTINGS)

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	Abbreviation in Full
AE	Adverse event
CTA	Clinical Trial Application
CRF	Case Report Form
EU	European Union
GORD	Gastro-oesophageal reflux disease
ICH	International Conference on Harmonisation
ITT	Intent-to-treat
PPI	Proton Pump Inhibitor
RB	Reckitt Benckiser
R&D	Research and Development
SAE	Serious adverse event
UK	United Kingdom (of Great Britain and Northern Ireland)
US	United States (of America)

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan – Description

The study protocol and Amendments 1-5 are included as Appendix 11.1.1. Unique pages from the case report form (CRF) are included as Appendix 11.1.2.

A randomised controlled, double blind, parallel group study in which subjects recruited to the study were randomised to receive 20ml of either Gaviscon Double Action Peppermint liquid or a Placebo for two days during a four day assessment period. Gaviscon Double Action Peppermint liquid or a Placebo were self-administered four times a day after meals and before bed for two days and no treatment was administered on the other two days. The sequence of these periods, which followed consecutively, was determined by prior randomisation. It was intended that for all subjects, acid reflux events and symptoms were recorded over all four days. Drop-outs were replaced, with the intention that 40 subjects completed the 4 day pH monitoring and study procedures.

The study population consisted of subjects aged between 18 and 70 years, who had been referred to the Oesophageal Laboratory at the Department of Gastroenterology, St Thomas' Hospital, London for investigation of predominant typical reflux symptoms (heartburn, acid regurgitation). Consecutive subjects with self-rated at least moderate heartburn or acid regurgitation within 60 minutes following ingestion of a refluxogenic meal on at least 3 occasions a week at the screening visit were invited to participate. Subjects were entered into the study and randomised following their initial investigation by high resolution manometry, performed to exclude primary oesophageal dysmotility.

Prolonged wireless pH monitoring over the 96 hours was provided by the Bravo data logger to document the clinical effectiveness of the preparations on suppressing reflux events. The Bravo capsule was placed at endoscopy under light sedation on Day 1 and logged pH data every 6 seconds. The data logger was not expected to be recording for each full 24 hour period, therefore the time the logger was operational was recorded. Counts recorded by the data logger were standardised to 24 hours by dividing the count by the proportion of time the system was operational. Daily samples of expectorated saliva were taken to be tested for the presence and concentration of pepsin. Questionnaires were completed by the patients detailing their symptoms, psychological state and perceived quality of life. Eraflux questionnaires were used to compare Gaviscon and placebo to the most effective prior treatment used by the patient (referred to as ‘on most effective treatment’) i.e. to assess whether Gaviscon double action can provide comparable relief to those patients taking alternative acid-reducing medications.

Changes in the conduct of the study are described in Section 5.2

5.2 Changes in the Conduct of the Study or Planned Analyses

5.2.1 Changes in the Conduct of the Study

There were 6 protocol amendments issued during the course of the study, all of which are described below.

Amendment 1 – Substantial, dated 14-Jan-2011.
St Thomas Hospital changed the quality of life questionnaire (SF-36) to an easier and less bureaucratic EQ-5D questionnaire. **From:** Page 49 – Appendix 1 - The SF-36 Health Status Questionnaire (UK version). **To:** Page 49 – Appendix 1 - The EQ-5D Health questionnaire (UK version). Ethical approval for this amendment was achieved on 08-Feb-2011, prior to regulatory approval being obtained, hence this amendment formed part of the original Clinical Trials Authorisation (CTA) submission.

Amendment 2 - Non substantial, dated 02-Mar-2011
a) Appendix III of the protocol was replaced with the 'Pepsin Test procedure' – incorporating the 'Saliva Samples' document.
b) Page 11 and 34 Secondary Endpoints were changed as follows; **From:** Categorical presence/absence of pepsin in expectorated saliva acquired 2 hr after the main evening meal on each test day at detection threshold 16ng/ml of 'pepsin lateral flow test' (Technostics, Hull, UK). **To:** Categorical presence/absence **and concentration** of pepsin in expectorated saliva acquired 2 hr after the main evening meal on each test day at detection threshold 16ng/ml of 'pepsin lateral flow test' (Technostics, Hull, UK **(Peptest™)**)
c) Page 11 and 35 – The secondary endpoint 'Pepsin concentration in expectorated saliva acquired 2 hr after the main evening meal on each test day assess by ELISA (Technostics, Hull, UK)' was deleted.
d) Page 19 - Trial procedures was updated as follows; **From:** Patients will return the 2 labelled tubes containing saliva samples and they must be placed in a fridge. Saliva samples will be tested for the presence of pepsin using the Peptest diagnostic kit on the day received (SOP 2143 version 1, Appendix 111). This will be done at St Thomas' Hospital. After testing the remaining saliva sample should be stored promptly in the freezer. Saliva samples should be couriered overnight on ice packs to Technostics Ltd when 24 samples / 6 Patients have been accrued. These saliva samples will be tested for pepsin levels by ELISA (SOP 2042 version 4, Appendix 111). **To:** Patients will return the 2 labelled tubes containing saliva samples and they must be placed in a fridge. Saliva samples will be couriered to Technostics Ltd, Hull on a two weekly bases and tested for the presence of pepsin using the Peptest

diagnostic kit on the day received (SOP 2143 version 1, Appendix 111) at Technostics Ltd, Hull, UK. After testing the remaining saliva sample should be stored promptly in the freezer

e) Page 21 - Clinical Assessments at Day 3 and Day 5 was amended as follows; **From:** Testing of saliva samples for presence/absence of pepsin (Peptest). **To:** Testing of saliva samples for presence/absence **and concentration** of pepsin (Peptest)

Amendment 3 - Non-substantial, dated 12-May-2011–

Section 18.1 - CRF's, text was updated as follows; From: The Investigator and other staff who have been delegated responsibility for entering data into the CRF at each visit will be trained in the use of the paper CRFs / No carbon required (NCR) CRFs before the first patient at that site is enrolled. The paper CRF / NCR CRF system will keep an audit trail of all changes made after the CRF pages are initially completed and submitted. Following monitoring of each patient's paper CRF / NCR CRF, the investigator will electronically sign the e CRF. Re-signature by the Investigator may be required prior to database lock after resolution of interim data queries. The top copy will be submitted to RB for onward transmission to the organisation responsible for data management and a second copy will be retained by the Investigator in the Trial Site File. Following completion of the study, the investigator will no longer be able to access the paper CRFs / NCR CRFs. Therefore, they will be provided with a certified paper copy of each of the CRFs from their centre by the data management group. **To:** The Investigator and other staff who have been delegated responsibility for entering data into the CRF at each visit will be trained in the use of the paper CRFs before the first patient at that site is enrolled. The paper CRF system will keep an audit trail of all changes made after the CRF pages are initially completed and submitted. Following monitoring of each patient's paper CRF the investigator will sign the CRF. Re-signature by the Investigator may be required prior to database lock after resolution of interim data queries. Original case report forms will be forwarded to RB and scanned copies will be retained by the Investigator and stored alongside the Trial Site File.

Amendment 4 - Non-substantial, dated 09-Jun-2011

VAS scales were removed from the CRF.

Amendment 5 - Non-substantial, dated 07-Jul-2012

Removal of data capture points from the BRAVO information as it is derived from statistical analyses not direct from the downloaded/printed Bravo data used as source. EQ-5D questionnaire is for baseline only. Eraflux to be completed after each 48 hours, not after each 24 hours. The CRF was amended as follows:

From: BRAVO Data Capture Information - Acid + Weakly acid episodes, Postprandial typical symptoms and Nocturnal typical symptoms, Eraflux Day 1, Eraflux Questionnaire Day 2**,** Eraflux Questionnaire Day 4, Eraflux Day 3, EQ-5D Questionnaire (first 48 hours and second 48 hours). **To:** BRAVO Data Capture Information – remove the above from Bravo data capture information, Remove Eraflux Day 1, Eraflux Questionnaire First 48 hours, Eraflux Questionnaire Second 48 hours, Remove Eraflux Day 3, Remove EQ-5D Questionnaire (first 48 hours and second 48 hours).

Amendment 6 - Administrative, dated 03-Oct-2011
Addition of Co Investigator to study contact details

5.2.2 Changes to the Planned Analyses

No changes were made in the planned statistical analyses, however, because so few subjects complied with the Protocol, no statistical comparison was made between the treatment groups for the Per Protocol sample. Additional analysis was also carried out using relaxed ITT entry criteria (>24hrs data recorded) and the results of this can be seen in Appendix 11.3.

6 STUDY SUBJECTS

6.1 Disposition of Subjects

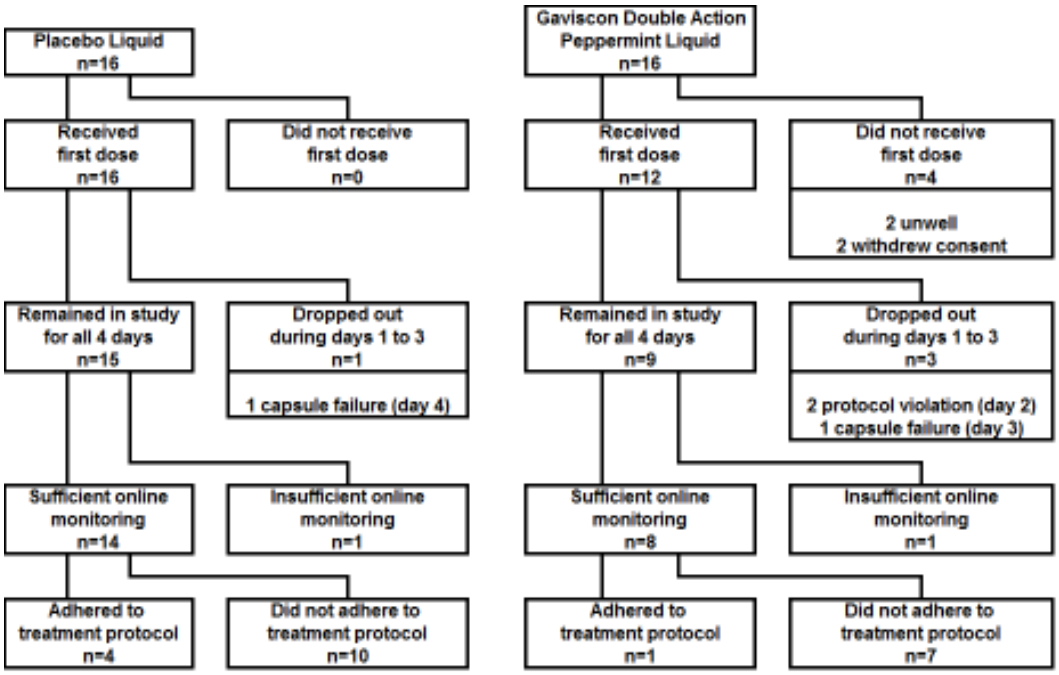
It was intended that 40 subjects with data for all 4 study days would be recruited. Subjects who failed to complete the trial would be replaced.

The study was closed after 32 subjects were randomised (Placebo:16, Gaviscon:16) because the Placebo preparation had reached its expiration date.

Study progress is detailed in figure 1. Four subjects failed to start the study; two were unwell and 2 withdrew when attending the clinic at the start of the study (all 4 in the Gaviscon randomisation group). Four subjects completed only 3 study days or less (Placebo: 1, Gaviscon: 3). Two subjects completed all 4 study days but the BRAVO data recorder was operative for less than 36 hours during the treatment period (Placebo:1, Gaviscon:1). Thus, 22 subjects completed all 4 study days with the BRAVO data recorder operating for at least 36 hours during the treatment period (Placebo:14, Gaviscon:8). Applying the revised entry criteria approved by the ethics committee, 24 subjects completed all 4 study days with the BRAVO data recorder operating for at least 24 hours during the treatment period (Placebo:15, Gaviscon:9). This data is presented in the statistical report (Appendix Section 11.3).

Only 5 subjects met the criteria for per protocol analysis (Placebo: 4, Gaviscon: 1). 17 subjects in the ITT sample failed to comply. The definition for lack of compliance in the study protocol was “failure to self-administer test products during the treatment arm in accordance with the protocol (less than three or more than five 20 ml doses on any test day) as assessed by weight of returned medication bottle.”

Figure 1: Flow of subjects through the study.



*Adherence to treatment protocol was determined by assessment of medication left in medicine bottle on return to the department.

7 EFFICACY EVALUATION

Analysis populations

All patients recruited to the study were included in the All Patients population for presentation of information on patient disposition, withdrawals and protocol deviations (n=32).

Safety Evaluation

All patients who were recruited to the study and received at least one dose of study medication (n=28). Summaries of demography and safety are provided for this population in Section 10.

Intention to treat (ITT) and Per Protocol (PP) population

All patients recruited to the study who completed and had efficacy data for both the treatment and no treatment study assessment periods were used for summaries of ITT efficacy data. All patients who completed the study with adequate treatment compliance and no major protocol deviations have been used for summaries of PP efficacy data.

The ITT population has 22 subjects (Placebo:14, Gaviscon:8) who completed the study and had efficacy data for both the treatment and no treatment study assessment periods based on at least 36 hours in each study condition.

The ITT population with revised entry criteria has 24 subjects (Placebo 15, Gaviscon 9) who completed the study and had efficacy data for both the treatment and no treatment study assessment periods based on at least 24hr Bravo pH monitoring (Note: all previous studies have reported 24hr or less pH data in each study arm). The results are very similar between the two ITT populations; however, due to the small numbers that completed, the addition of 2 patients using the revised entry criteria does add relevant information. This data is presented in Appendix 11.3.

1) Primary endpoint

Table 1: Number of acid reflux events in 48 hours by randomisation group and treatment / no treatment periods.

	N	Mean	Std. Deviation	Median	Minimum	Maximum
no tx (Placebo)	14	76.42	61.69	78.69	4.23	170.03
Placebo	14	80.75	71.26	67.76	.00	193.82
no tx (Gaviscon)	8	93.00	58.00	100.24	21.39	185.58
Gaviscon	8	77.06	64.90	56.35	6.91	175.76

Table 2: Linear regression analysis with change (from treatment period to no treatment period) in the number of reflux events as the dependent variable and randomisation group as independent variables

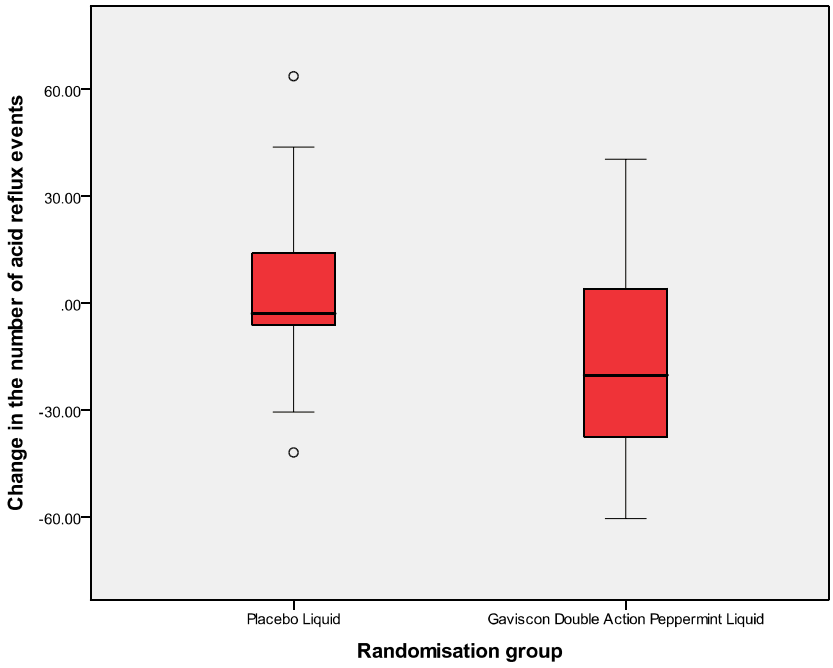
Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	4.328	7.892		.548	.589	-12.135	20.791
	Randomisation group	-20.260	13.088	-.327	-1.548	.137	-47.560	7.040

a. Dependent Variable: Change in the number of acid reflux events

These results were not statistically significant (p=0.137).

Figure 2: Change (from treatment period to no treatment period) in the number of reflux events by randomisation group



2) Secondary endpoints

a) Combined number of acid reflux events *and* weakly acid reflux events during the Gaviscon Double Action or matched placebo study period compared to the 48hr "no treatment" study period

This secondary endpoint was not pursued due to it not being possible to separate acidic from weakly acidic events using the available Bravo capsule analysis software.

b) Oesophageal acid exposure (percentage of time with pH less than 4)

Table 3: Oesophageal acid exposure (percentage of time with pH less than 4) by randomisation group and treatment / no treatment periods.

	N	Mean	Std. Deviation	Median	Minimum	Maximum
no tx (Placebo)	14	5.56	5.86	4.57	.00	18.84
Placebo	14	4.52	4.56	4.13	.00	13.85
no tx (Gaviscon)	8	6.37	5.14	6.05	.86	12.10
Gaviscon	8	4.05	3.66	2.99	.05	8.84

Table 4: Linear regression analysis with change (from treatment period to no treatment period) in the oesophageal acid exposure (%) as the dependent variable and gender and randomisation group as the independent variables.

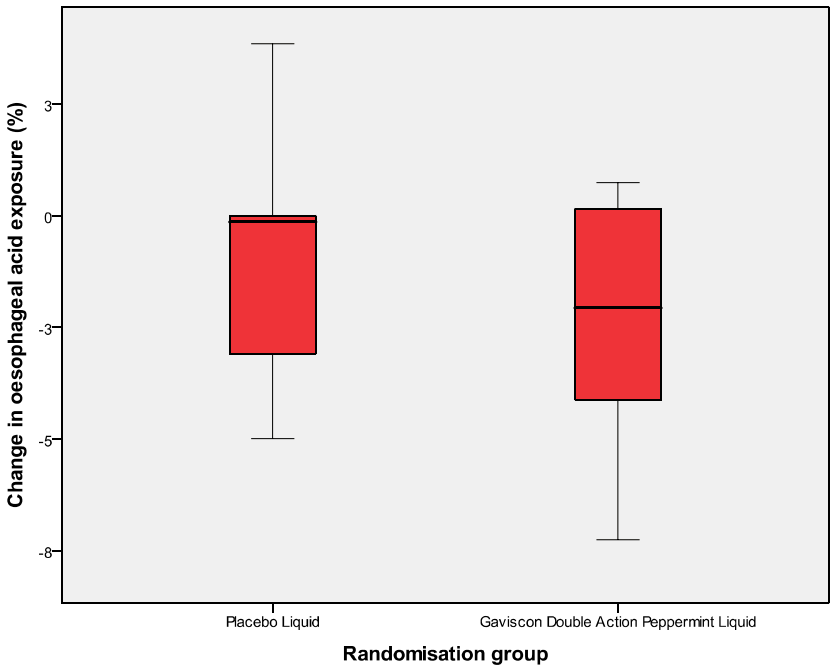
Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	-1.896	.800		-2.370	.029	-3.570	-.222
	Gender	1.982	1.141	.377	1.737	.099	-.407	4.371
	Randomisation group	-.674	1.105	-.132	-.610	.549	-2.987	1.639

a. Dependent Variable: Change in oesophageal acid exposure (%)

These results were not statistically significant (p=0.549).

Figure 3: Change (from treatment period to no treatment period) in the oesophageal acid exposure (%) by randomisation group



c) The number of episodes of heartburn as recorded on the data monitor

Table 5: Number of episodes of heartburn in 48 hours by randomisation group and treatment / no treatment periods

	N	Mean	Std. Deviation	Median	Minimum	Maximum
no tx (Placebo)	14	10.77	13.22	7.30	.00	50.00
Placebo	14	12.59	11.98	9.70	.00	36.34
no tx (Gaviscon)	8	19.77	12.34	18.04	.00	33.92
Gaviscon	8	18.77	12.72	17.43	4.38	41.11

Table 6: Linear regression analysis with change (from treatment period to no treatment period) in the number of episodes of heartburn as the dependent variable and randomisation group as the independent variable

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	1.821	2.843		.641	.529	-4.109	7.751
	Randomisation group	-2.820	4.714	-.133	-.598	.556	-12.653	7.014

a. Dependent Variable: Change in number of eisodes of heartburn

These results were not statistically significant (p=0.556).

d) The number of episodes of regurgitation as recorded on the data monitor

Table 7: Number of episodes of regurgitation in 48 hours by randomisation group and treatment / no treatment periods

	N	Mean	Std. Deviation	Median	Minimum	Maximum
no tx (Placebo)	14	7.92	14.87	1.01	.00	52.73
Placebo	14	5.26	7.50	.50	.00	22.06
no tx (Gaviscon)	8	5.66	10.19	2.00	.00	30.05
Gaviscon	8	7.64	20.75	.00	.00	58.98

Table 8: Linear regression analysis with change (from treatment period to no treatment period) in the number of episodes of regurgitation as the dependent variable and randomisation group as the independent variable

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	-2.659	2.634		-1.009	.325	-8.152	2.835
	Randomisation group	4.640	4.367	.231	1.062	.301	-4.470	13.750

a. Dependent Variable: Change in number of episodes of regurgitation

These results were not statistically significant (p=0.301).

e) The Eraflux score

Table 9: The Eraflux score for on best medication, off best medication for treatment period and no treatment period by randomisation group

	N	Mean	Std. Deviation	Median	Minimum	Maximum
on best medication (Placebo)	13	31.20	14.35	31.25	.00	50.00
off best medication (Placebo)	13	39.06	9.50	38.00	21.00	56.25
no tx (Placebo)	11	34.47	14.63	37.50	.00	56.25
Placebo	10	34.70	14.63	37.25	.00	56.25
on best medication (Gaviscon)	8	34.93	9.02	37.25	21.00	43.75
off best medication (Gaviscon)	8	41.53	7.14	41.00	32.00	56.25
no tx (Gaviscon)	6	36.08	8.98	35.75	23.00	50.00
Gaviscon	8	37.47	12.74	39.88	20.00	50.00

Table 10: Changes in Eraflux score by randomisation group

		N	Mean	Std. Deviation	Median	Minimum	Maximum	95% CI	
								Lower	Upper
Change: no tx versus on best medication	Placebo Liquid	10	5.91	14.28	6.60	-17.00	37.50	-4.31	16.13
	Gaviscon Double Action Peppermint Liquid	6	2.98	10.07	5.63	-14.50	12.60	-7.59	13.54
Change: no tx versus off best medication	Placebo Liquid	11	-3.16	8.00	0.00	-21.00	6.25	-8.54	2.21
	Gaviscon Double Action Peppermint Liquid	6	-2.92	9.45	-1.25	-20.75	6.25	-12.83	7
Change: tx versus on best medication	Placebo Liquid	9	4.16	17.90	5.75	-25.00	37.50	-9.6	17.91
	Gaviscon Double Action Peppermint Liquid	8	2.54	8.91	4.88	-17.50	13.00	-4.9	9.99
Change: tx versus off best medication	Placebo Liquid	8	-1.11	7.29	0.75	-18.75	6.25	-6.71	4.48
	Gaviscon Double Action Peppermint Liquid	8	-4.06	10.85	-3.00	-23.75	8.00	-13.14	5.01
Change: tx versus no tx	Placebo Liquid	9	0.42	6.03	0.00	-12.50	10.50	-4.21	5.06
	Gaviscon Double Action Peppermint Liquid	6	-2.79	5.71	-3.50	-11.00	6.25	-8.79	3.21

Table 11: Linear regression analysis with change (from treatment period to no treatment period) in Eraflux score as the dependent variable and randomisation group as the independent variable

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	.422	1.971		.214	.834	-3.836	4.681
	Randomisation group	-3.214	3.117	-.275	-1.031	.321	-9.947	3.520

a. Dependent Variable: Change in Eraflux score: tx versus no tx

These results were not statistically significant (p=0.321).

f) Mean pepsin concentration 2 hours after the main evening meal

Table 12: Mann-Whitney U Test comparing the change (between 2 days treatment and 2 days no treatment) in the mean pepsin concentration of saliva obtained 2 hours after the main evening meal.

Ranks

	Randomisation group	N	Mean Rank	Sum of Ranks
Difference in mean pepsin concentrations	Placebo Liquid	13	9.69	126.00
	Gaviscon Double Action Peppermint Liquid	6	10.67	64.00
	Total	19		

	Difference in mean pepsin concentrations
Mann-Whitney U	35.00
Exact Sig.	0.77

g) The number of days pepsin is present in expectorated saliva acquired 2 hours after the main evening meal on each test day

Table 13: The number of days pepsin is present in expectorated saliva acquired 2 hours after the main evening meal on each test day by treatment regime.

		Placebo		Gaviscon	
Days		no treatment	treatment	no treatment	treatment
0	N	7	6	2	2
	%	53.8%	46.2%	33.3%	33.3%
1	N	4	6	2	4
	%	30.8%	46.2%	33.3%	66.7%
2	N	2	1	2	0
	%	15.4%	7.7%	33.3%	0.0%
	mean (sd)	0.62 (0.77)	0.62 (0.65)	1.00 (0.89)	0.67 (0.52)

Table 14: Mann-Whitney U Test comparing the change (from the treatment period to the no treatment period) in the number of days pepsin is present in expectorated saliva acquired 2 hours after the main evening meal on each test day

Ranks

	Randomisation group	N	Mean Rank	Sum of Ranks
Change in number of days pepsin present	Placebo Liquid	13	10.69	139.00
	Gaviscon Double Action Peppermint Liquid	6	8.50	51.00
	Total	19		

Mann-Whitney U	30.00
Exact Sig	0.47

These results were not statistically significant (p=0.47).

Figure 4: The number of days pepsin (> 25 ng/ml) is present in expectorated saliva acquired 2 hours after the main evening meal on each test day by treatment regime

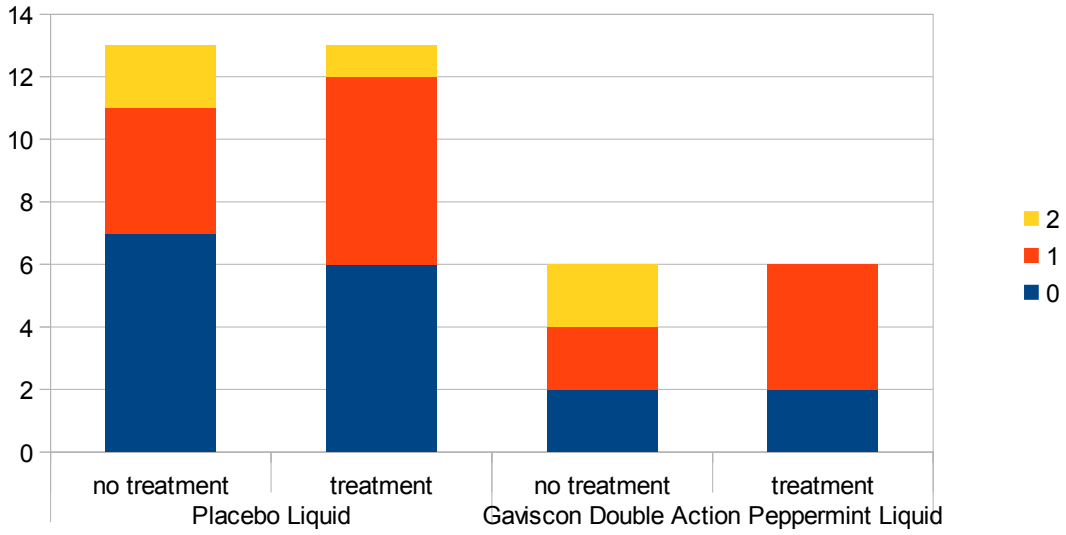


Table 15: The change (from the treatment period to the no treatment period) in the number of days pepsin is present in expectorated saliva acquired 2 hours after the main evening meal on each test day by treatment ['-1' days means that pepsin was present 1 less day under treatment than under no treatment]

		Randomisation group	
Days		Placebo	Gaviscon
-1	N	4	4
	%	30.8%	66.7%
0	N	5	0
	%	38.5%	0.0%
1	N	4	2
	%	30.8%	33.3%

Sub-analysis

1) Number of acid reflux events [upright position]

Table 16: Upper panel: Number of reflux events in the upright position in 48 hours by randomisation group and treatment/no treatment periods

Lower panel: Change (from treatment period to no treatment period) in the number of reflux events in the upright position by randomisation group

	N	Mean	Std. Deviation	Median	Minimum	Maximum
no tx (Placebo)	14	111.87	90.94	109.98	7.07	248.79
Placebo	8	127.36	77.71	131.94	30.41	264.44
no tx (Gaviscon)	14	117.02	102.13	96.62	.00	265.12
Gaviscon	8	101.61	83.07	77.45	8.84	229.51

							95% CI	
	N	Mean	Std. Deviation	Median	Minimum	Maximum	Lower	Upper
Placebo change	14	5.16	35.31	3.23	-63.11	87.04	-15.23	25.55
Gaviscon change	8	-25.74	44.87	-29.98	-105.74	45.08	-63.25	11.77

Table 17: Linear regression analysis with change (from treatment period to no treatment period) in the number of reflux events in the upright position as the dependent variable and randomisation group as the independent variable

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	5.156	10.403		.496	.626	-16.545	26.857
	Randomisation group	-30.899	17.252	-.372	-1.791	.088	-66.887	5.088

a. Dependent Variable: Change in the number of acid reflux events

These results approached statistical significance (p=0.088).

2) Number of acid reflux events [Supine position]

Table 18 Upper panel: Number of reflux events in the supine position in 48 hours by randomisation group and treatment/no treatment periods

Lower panel: Change (from treatment period to no treatment period) in the number of reflux events in the supine position by randomisation group

	N	Mean	Std. Deviation	Median	Minimum	Maximum
no tx (Placebo)	14	14.62	18.24	10.87	0.00	54.29
Placebo	14	21.09	35.20	9.03	0.00	122.26
no tx Gaviscon)	8	38.08	45.63	19.71	0.00	117.99
Gaviscon	8	30.89	47.43	9.64	0.00	130.43

							95% CI	
	N	Mean	Std. Deviation	Median	Minimum	Maximum	Lower	Upper
Placebo change	14	6.47	22.13	2.11	-25.81	67.98	-6.31	19.24
Gaviscon change	8	-7.18	48.76	0.00	-95.92	60.69	-47.94	33.58

Table 19: Linear regression analysis with change (from treatment period to no treatment period) in the number of reflux events in the supine position as the dependent variable and randomisation group as the independent variable

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	6.467	9.064		.713	.484	-12.441	25.375
	Randomisation group	-13.649	15.032	-.199	-.908	.375	-45.004	17.707

a. Dependent Variable: Change in the number of acid reflux events

These results were not statistically significant (p=0.375).

3) Oesophageal acid exposure (percentage time pH less than 4) [upright position]

Table 20: Upper panel: Oesophageal acid exposure (%) in the upright position treatment period by randomisation group and treatment/no treatment periods

Lower panel: Change (from treatment period to no treatment period) in Oesophageal acid exposure (%) in the upright position by randomisation group

	N	Mean	Std. Deviation	Median	Minimum	Maximum
no tx (Placebo)	14	7.18	7.29	5.98	0.00	24.55
Placebo	14	6.33	6.17	5.60	0.00	18.65
no tx (Gaviscon)	8	6.47	4.72	6.32	1.00	12.98
Gaviscon	8	5.37	4.69	4.39	0.10	11.56

						95% CI	
	N	Mean	Std. Deviation	Median	Minimum	Maximum	Lower	Upper
Placebo change	14	-0.85	2.90	-0.33	-5.90	5.27	-2.53	0.83
Gaviscon change	8	-1.09	1.77	-1.06	-4.80	1.01	-2.57	0.38

Table 21: Linear regression analysis with change (from treatment period to no treatment period) in oesophageal acid exposure in the upright position as the dependent variable and randomisation group as the independent variable

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	-.850	.685		-1.240	.229	-2.279	.580
	Randomisation group	-.245	1.137	-.048	-.216	.831	-2.616	2.126

a. Dependent Variable: Change in oesophageal acid exposure (%)

These results were not statistically significant (p=0.831).

4) Oesophageal acid exposure (percentage time pH less than 4) [supine position]

Table 22: Upper panel: Oesophageal acid exposure (%) in the supine position treatment period by randomisation group and treatment/no treatment periods

Lower panel: Change (from treatment period to no treatment period) in Oesophageal acid exposure (%) in the supine position by randomisation group

	N	Mean	Std. Deviation	Median	Minimum	Maximum
no tx (Placebo)	14	2.18	4.23	.38	.00	13.01
Placebo	14	1.51	2.71	.30	.00	7.98
no tx (Gaviscon)	8	5.79	7.88	.47	.00	17.27
Gaviscon	8	1.66	2.75	.34	.00	6.97

							95% CI	
	N	Mean	Std. Deviation	Median	Minimum	Maximum	Lower	Upper
Placebo change	14	-0.67	1.59	-0.05	-5.03	1.07	-1.59	0.25
Gaviscon change	8	-4.12	7.29	-0.37	-15.71	4.91	-10.22	1.97

Table 23: Linear regression analysis with change (from no treatment period to treatment period) in oesophageal acid exposure in the supine position as the dependent variable and randomisation group as the independent variable

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	-.672	1.203		-.559	.582	-3.180	1.836
	Randomisation group	-3.453	1.994	-.361	-1.732	.099	-7.613	.707

a. Dependent Variable: Change in oesophageal acid exposure (%)

These results approached statistical significance (p=0.099).

8 SAFETY EVALUATION

All subjects who received at least one dose of study medication are included in the safety analysis. Adverse events were monitored throughout the study for all subjects.

8.1 Extent of Exposure

Maximum dose – 20 ml x 4 per 24 hours (after breakfast/lunch/dinner/before bed) of Gaviscon or Placebo during the 48 hour treatment arm

Table 8.1.1 Demographics by treatment randomisation group

	Randomisation group	N	Mean	Std. Deviation	Median	Minimum	Maximum
Age	Placebo Liquid	16	42.31	11.01	42.00	28.00	63.00
	Gaviscon Double Action Peppermint Liquid	12	53.50	12.62	54.50	30.00	69.00
Height	Placebo Liquid	16	1.70	.11	1.67	1.55	1.96
	Gaviscon Double Action Peppermint Liquid	11	1.62	.07	1.62	1.50	1.74
Weight	Placebo Liquid	16	74.80	21.06	69.95	51.00	129.00
	Gaviscon Double Action Peppermint Liquid	11	74.70	19.55	73.00	51.00	120.70
BMI	Placebo Liquid	16	25.11	5.54	25.82	18.00	39.80
	Gaviscon Double Action Peppermint Liquid	11	28.10	8.37	24.80	19.00	45.00

8.2 Adverse Events (AEs)

The tables that follow describe adverse events occurring after the initiation of treatment with study medication. Where appropriate, abbreviated tables are included here, with full tables included in Section 10.4.

8.2.1 Brief Summary of Events

There were 29 adverse events experienced in 12 subjects during the course of the study. The most prevalent adverse events were chest pain and throat pain, with 5 and 4 events recorded, respectively.

8.2.1 Display of Adverse Events

Table 8.2.1 - All adverse events that occurred during the study, as captured in the subject diary.

Subject Number	Description of Event
003	Pain on swallowing
004	Some reflux
006	Cough and loss of voice
008	Vomiting and hiccups
013	Chest tender upon swallowing
015	Discomfort
019	Very sore oesophagus when swallowing
023	Foul taste in mouth, pain in chest and throat, vomiting and cystitis
028	Tight, tugging feeling
029	A lot of chest pain and belching, chest pain on swallowing and feeling sick
030	Constant chest pain and heartburn, feeling sick, waking up due to pain, belching and wind
031	Dizziness, painful/burning throat and chest pains, pain on movement, pain in right tonsil

Twelve subjects experienced adverse events. Of these 12, 6 subjects experienced more than one adverse event whilst taking study medication. The remaining 6 subjects all experienced one adverse event each.

Upon Investigator review, the tight, tugging feeling experienced by subject 028 and the pain on swallowing experienced by subjects 003, 013, 019 and 029 could be related to the presence of the Bravo capsule. None of the adverse events were deemed to be related to study medication.

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

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

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

8.3.1.1 Deaths

There were no deaths in this study.

8.3.1.2 Other Serious Adverse Events

There were no other serious adverse events in this study

8.3.1.3 Other Significant Adverse Events

No other significant adverse events occurred in this study

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

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

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

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

8.4 Clinical Laboratory Evaluation

Full results for the pepsin analysis can be seen in Appendix 11.3.

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

No other safety evaluations were performed in this study

8.6 Safety Conclusions

Not applicable.

DISCUSSION AND OVERALL CONCLUSIONS

9.1 Discussion

The primary objective of this study was to compare the effectiveness of Gaviscon Double Action and a Placebo on suppression of acid reflux events in patients with typical reflux symptoms, specifically, the number of acid reflux events during 48hr Gaviscon Double Action or Placebo study period compared to the 48hr "no treatment" study period (primary endpoint). Secondary endpoints included oesophageal acid exposure (total/upright and supine), number of episodes of heartburn and regurgitation, Eraflux score and mean pepsin concentration 2 hours after the main evening meal. Planned sub-analyses included a separate assessment of the number of acid reflux events in the upright and supine position

Efficacy analysis was presented using the Intention to treat (ITT) population. (ITT was defined as all patients recruited to the study who completed and had efficacy data for both the treatment and no treatment study assessment periods. This population was used for summaries of efficacy data). Additional analysis was also carried out using relaxed ITT entry criteria (>24hrs data recorded) and the results of this can be seen in Appendix 11.3.

Primary end point

The mean number of reflux events was lower during Gaviscon Double Action treatment compared to "no treatment"; whereas no reduction is seen with Placebo. This was evident in the raw data (table 1) and the linear regression analysis (table 2). Although not statistically significant, there is a trend to acid reflux suppression by the test medication (p=0.137), with an average reduction of 20 events in the Gaviscon Double Action treatment group compared to the Placebo group. As described in section 5.2.2, additional statistical analysis was carried out using the relaxed ITT

entry criteria. This analysis shows a further trend towards significance (p=0.120) and can be seen in Appendix 11.3.

Secondary end points:

Oesophageal acid exposure (% of time with pH < 4)

The mean oesophageal acid exposure was lower during Gaviscon Double Action treatment compared to "no treatment" whereas only a smaller reduction was seen with Placebo. This is evident in the raw data (table 3). The linear regression analysis (table 4) does not demonstrate statistical significance between treatments (p=0.549).

The number of episodes of heartburn as recorded on the data monitor

The study was not designed or powered to demonstrate an effect on reflux symptoms. The number of heartburn symptoms (tables 5, 6) reported by patients during the study was not different between Gaviscon Double Action and Placebo treatment (p=0.556).

Note that in this parallel group study the number of episodes of heartburn was lower in the patients randomized to the Placebo arm compared to the Gaviscon arm both during "treatment" and "no treatment" phases. The number of symptom events was, essentially, unchanged by treatment in both study groups.

The number of episodes of regurgitation as recorded on the data monitor

The study was not designed or powered to demonstrate an effect on reflux symptoms. Similar to the number of heartburn, the number of regurgitation symptoms reported during the study was not different with Gaviscon Double Action or Placebo treatment (table 8, p=0.301).

Eraflux score

The severity of reflux symptoms at screening and during the study was assessed by entries in the patient diary and also by a validated questionnaire (Eraflux score). Symptom information obtained included:

- Patient estimate of symptoms while on the most effective medication [day 0 screen]
- Patient estimate of symptoms while off the most effective medication [day 0 screen]
- Patient assessment of symptoms during the 2 “no-treatment” days
- Patient assessment of symptoms during the 2 “treatment” days

Overall Gaviscon Double Action reduced the severity of symptoms compared to the patient estimate of symptom severity “off treatment” but was less effective than “on most effective treatment” (table 9). This is an expected finding and is consistent with the view that Gaviscon Double Action provides symptom relief in Gastro-Oesophageal Reflux Disease (GORD). The effect of Gaviscon Double Action on reflux symptoms as assessed by Eraflux score was also numerically greater than that on Placebo treatment (table 10) by median -3.5 points, where a reduction in 2 points is clinically relevant. The comparison between Gaviscon Double Action and placebo was not significant on linear regression (table 11, p=0.321).

Mean pepsin concentration 2 hours after the main evening meal

Pepsin concentrations 2 hours after the main evening meal were recorded for each of the 4 days for 19 out of 22 patients. The mean of the concentration during the 2 days without treatment was subtracted from the mean of the concentration during the 2 days with treatment to provide the endpoint. No imputations were made and therefore no mean was calculated where one value was missing. A non-parametric test (Mann-Whitney U Test) was used to compare the change in mean pepsin concentration. A greater mean rank indicates a greater ranked pepsin increase (or smaller decrease) from no Treatment. The results show that measurements of pepsin concentration were highly variable and the difference between Gaviscon Double Action and Placebo was not significant (table 12, p=0.77).

These results are not unexpected. The pepsin test provides a measurement of pepsin in the pharynx at a single point in time and a single reflux event after the meal may be sufficient to produce a positive test. Thus, this test may provide a sensitive screening test for GORD but not an accurate assessment of disease severity or reflux suppression by Gaviscon Double Action (as suppression incomplete).

The number of days pepsin is present in expectorated saliva acquired 2 hours after the main evening meal on each test day

A non-parametric test (Mann-Whitney U Test) was used to compare the number of days pepsin is present in expectorated saliva acquired 2 hours after the main

evening meal on each test day. The results show that there was no significant differences between Gaviscon Double Action and Placebo (table 14, Figure 4, p=0.47).

Sub-analysis

Number of acid reflux events [upright position]
Number of acid reflux events [Supine position]

The mean number of reflux events was highly variable but lower during Gaviscon Double Action treatment compared to "no treatment" in the upright and supine positions. Whereas no reduction was seen with Placebo (table 16 and 18 respectively), the effect was relatively large during Gaviscon Double Action treatment and when compared to placebo approached statistical significance (p=0.088) in the upright position (table 17). A larger average reduction in the supine position (table 19) was observed in Gaviscon Double Action compared to the placebo treatment group but this did not reach statistical significance (p=0.375). In the additional analysis described in section 5.2.2, the trend was towards statistical significance in the upright position (p=0.084) but not in the supine position (p=0.372) and these can be seen in the full statistical report (Appendix 11.3).

These results provide some additional evidence that Gaviscon Double Action does suppress reflux in the upright position when taken after meals. The non-significant results for reflux suppression in the supine position (i.e. at night) do not necessarily mean that Gaviscon Double Action does not suppress nocturnal reflux when taken before bed. Reflux events are less frequent at night and Gaviscon was taken only once (not three times as during the day). Thus, this result may be due to a lack of events and, therefore, a lack of statistical power to demonstrate this effect.

Oesophageal acid exposure (percentage time pH less than 4) [upright position]
Oesophageal acid exposure (percentage time pH less than 4) [supine position]

Oesophageal acid exposure was lower during both Gaviscon Double Action and placebo treatment periods compared to the corresponding "no treatment" period in the upright and supine positions (table 20 and 22 respectively); however the comparison between Gaviscon Double Action and placebo did not approach statistical significance in the upright position (table 21, p=0.831) and showed only a weak trend (p=0.099) in the supine position (table 23).

The apparent discrepancy between these results and those from the full monitoring period are likely due to lack of statistical power (i.e. approximately half the time was

spent in the upright and supine positions). However the “direction of effect” for the primary and secondary outcome measures consistently support the view that Gaviscon Double Action can suppress reflux and reduce oesophageal acid exposure.

9.2 Conclusion

Interpretation of the results should be made cautiously because of the small sample size. The intention was to recruit 40 subjects (approximately 20 subjects in each treatment group); however only 22 (Gaviscon: 8, Placebo: 14) completed the study and entered the ITT population with adequate data in both for analysis.

Gaviscon Double Action treatment reduced the total number of acid reflux events (especially in the upright position) by a reduction in percentage time of oesophageal acid exposure.

There was no significant difference in the number of typical reflux symptoms (heartburn, regurgitation) reported by patients between the two study groups. The effect on reflux symptoms as assessed by Eraflux score was greater for Gaviscon Double Action than Placebo treatment by an average -3.5 points (a reduction in 2 points is clinically relevant), although this did not reach statistical significance.

There was no difference in the mean pepsin concentration between the Gaviscon and Placebo group. Similarly there was no difference in the frequency of positive tests based on categorical cut-off test result of >25ng/ml.

These results are consistent with Gaviscon Double Action providing effective reflux suppression. Although there was no improvement in the frequency of typical symptoms reported during the study or recall assessment of patient symptoms (Eraflux score) the numerical values favoured the alginate preparations in most cases.

The results provide methodological information regarding assessment of reflux suppression using the Bravo system and provide adequate data for power calculations required for future studies.

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

All tables and figures referred to in the text are included above.

10.1 Demographic Data

Table 10.1.1: Demographics.

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Age	28	47.11	12.80	46.50	28.00	69.00
Height	27	1.67	0.10	1.65	1.50	1.96
Weight	27	74.76	20.07	70.00	51.00	129.00
BMI	27	26.33	6.85	25.00	18.00	45.00

Table 10.2.1: Demographics and baseline characteristics

		n	%
Age	<20	0	0.0
	20-29	3	10.7
	30-39	6	21.4
	40-49	7	25.0
	50-59	7	25.0
	60-69	5	17.9
	>=70	0	0.0
Gender	male	7	25.0
	female	21	75.0
Ethnicity	caucasian	23	82.1
	asian	1	3.6
	afro-caribbean	3	10.7
	other	1	3.6
Tobacco use		4	14.3
Alcohol use		6	21.4
Illicit drug use		0	0.0
Regular use of medication		24	85.7
Use of medication in last 7 days		13	46.4
Regular use of antacids		4	14.3
Use of antacids in last 7 days		12	42.9

Table 10.1.3: Demographics by treatment randomisation group

	Randomisation group	N	Mean	Std. Deviation	Median	Minimum	Maximum
Age	Placebo Liquid	16	42.31	11.01	42.00	28.00	63.00
	Gaviscon Double Action Peppermint Liquid	12	53.50	12.62	54.50	30.00	69.00
Height	Placebo Liquid	16	1.70	.11	1.67	1.55	1.96
	Gaviscon Double Action Peppermint Liquid	11	1.62	.07	1.62	1.50	1.74
Weight	Placebo Liquid	16	74.80	21.06	69.95	51.00	129.00
	Gaviscon Double Action Peppermint Liquid	11	74.70	19.55	73.00	51.00	120.70
BMI	Placebo Liquid	16	25.11	5.54	25.82	18.00	39.80
	Gaviscon Double Action Peppermint Liquid	11	28.10	8.37	24.80	19.00	45.00

Table 10.1.4: Demographics and baseline characteristics by treatment randomisation group:

		Placebo Liquid		Gaviscon Double Action Peppermint Liquid	
		n	%	n	%
Age	20-29	3	18.8%	0	0.0%
	30-39	4	25.0%	2	16.7%
	40-49	5	31.3%	2	16.7%
	50-59	3	18.8%	4	33.3%
	60-69	1	6.3%	4	33.3%
Gender	male	6	37.5%	1	8.3%
	female	10	62.5%	11	91.7%
Race	caucasian	12	75.0%	11	91.7%
	black	2	12.5%	1	8.3%
	asian	1	6.3%	0	0.0%
	other	1	6.3%	0	0.0%
Tobacco use		2	12.5%	2	16.7%
Alcohol use		3	18.8%	3	25.0%
Illicit drug use		0	0.0%	0	0.0%
Regular use of medication		13	81.3%	11	91.7%
Use of medication in last 7 days		4	25.0%	9	75.0%
Regular use of antacids		3	18.8%	1	8.3%
Use of antacids in last 7 days		6	37.5%	6	50.0%

10.2 Efficacy Data

Please see section 6.

10.3 Safety Data

Please see section 8 and section 10.4.

10.4 Displays of Adverse Events

The table below describes all adverse events that occurred during the study, as captured in the subject diary;

Subject Number	Description of Event
003	Pain on swallowing
004	Some reflux
006	Cough and loss of voice
008	Vomiting and hiccups
013	Chest tender upon swallowing
015	Discomfort
019	Very sore oesophagus when swallowing
023	Foul taste in mouth, pain in chest and throat, vomiting and cystitis
028	Tight, tugging feeling
029	A lot of chest pain and belching, chest pain on swallowing and feeling sick
030	Constant chest pain and heartburn, feeling sick, waking up due to pain, belching and wind
031	Dizziness, painful/burning throat and chest pains, pain on movement, pain in right tonsil

There were 29 adverse events experienced in 12 subjects during the course of the study.

Upon Investigator review, the tight, tugging feeling experienced by subject 028 and the pain on swallowing experienced by subjects 003, 013, 019 and 029 could be related to the presence of the Bravo capsule. None of the adverse events were deemed to be related to study medication.

10.4.1 Listings of Deaths, other Serious and Significant Adverse Events

No Serious Adverse Events or deaths occurred in this study.

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

No Serious Adverse Events or deaths occurred in this study.

10.4.3 Clinically Significant Abnormal Laboratory Value Listing (each subject)

No clinical laboratory evaluations were performed in this study

APPENDICES

APPENDIX 11.1 STUDY INFORMATION

This Appendix contains the following sections:

11.1.1 Protocol and protocol amendments

11.1.2 Sample case report form (unique pages only)

11.1.3 Signature of Principal Investigator

APPENDIX 11.1.1 PROTOCOL AND PROTOCOL AMENDMENTS


GA1001 - Final Protocol


GA1001 - Admin Amendment


GA1001 - Protocol Amendment 1


GA1001 - Protocol Amendment 2


GA1001 - Protocol Amendment 3


GA1001 - Protocol Amendment 4


GA1001 - Protocol Amendment 5

APPENDIX 11.1.2 SAMPLE CASE REPORT FORM (UNIQUE PAGES ONLY).

This appendix contains:

- CRF page 5 – Medical History and Concomitant Medications (1 page)
- CRF page 44 – Concomitant Medications (1 page)

Phase: **SCREENING**

RELEVANT MEDICAL HISTORY

SYSTEM	SPECIFY ABNORMALITY (or tick "NONE")	START DATE	STOP DATE
EYES, EARS, NOSE, & THROAT	NONE ☐		
RESPIRATORY	NONE ☐		
CARDIOVASCULAR	NONE ☐		
GASTRO-INTESTINAL	NONE ☐		
MUSCULOSKELETAL	NONE ☐		
NEUROLOGICAL	NONE ☐		
ENDOCRINE & METABOLIC	NONE ☐		
DERMATOLOGIC	NONE ☐		
GENITO-URINARY	NONE ☐		
PSYCHIATRIC	NONE ☐		
ALLERGIC REACTIONS	NONE ☐		
OTHER	NONE ☐		

Enter only Relevant Medical History on this page.

CONCOMITANT MEDICATION CHECK

Concomitant Medication Check performed?	Yes ☐	No ☐
If subject consumed any Concomitant Medication, please complete the Concomitant Medication Page		

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

CONCOMITANT MEDICATIONS

Record all medication taken by the volunteer from 7 days prior to Screening through to the end of the study.
If "NONE" tick box: ☐

MEDICATION **(Use Generic Name except for combination medications. For combination medications, use Brand Name.)**	**DATE STARTED (dd/mm/yyyy)**	**DATE STOPPED OR CONT. (dd/mm/yyyy)**	**DOSE AND UNITS**	**FREQUENCY**	**ROUTE** IV PR IM SL PO IH SC TOP Other, Specify	**REASON FOR USE**	**INITIALS**
1.		OR ☐ Continuing					
2.		OR ☐ Continuing					
3.		OR ☐ Continuing					
4.		OR ☐ Continuing					
5.		OR ☐ Continuing					
6.		OR ☐ Continuing					

APPENDIX 11.1.3 SIGNATURE OF PRINCIPAL INVESTIGATOR

Reckitt Benckiser

PRINCIPAL INVESTIGATOR'S SIGNATURE

.

Study Number: GA1001

Report Title: A randomised, double blind Placebo controlled study in patients with reflux symptoms to assess suppression of gastro-oesophageal reflux by 'Gaviscon Double Action Peppermint liquid' using the BRAVO system

Phase: IV

Principal Investigator:

By my signature below, I hereby state that I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study. I agree its conclusions and do not wish to make an additional statement regarding the safety of the product under test.

Terry Wong MD,	MA, MRCP	Principal Investigator	Oesophageal Laboratory, Department of Gastroenterology, St. Thomas' Hospital, Lambeth Palace Road, London, SE1 7EH, UK Tel 02071882491.

APPENDIX 11.1.3 SIGNATURE OF PRINCIPAL INVESTIGATOR

Reckitt Benckiser

PRINCIPAL INVESTIGATOR'S SIGNATURE

Study Number: GA1001

Report Title: A randomised, double blind Placebo controlled study in patients with reflux symptoms to assess suppression of gastro-oesophageal reflux by 'Gaviscon Double Action Peppermint liquid' using the BRAVO system

Phase: IV

Principal Investigator:

By my signature below, I hereby state that I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study. I agree its conclusions and do not wish to make an additional statement regarding the safety of the product under test.

Terry Wong MD, MA, MRCP Principal Investigator Oesophageal Laboratory, Department of Gastroenterology, St. Thomas' Hospital, Lambeth Palace Road, London, SE1 7EH, UK
Tel 02071882491.

APPENDIX 11.2 CASE REPORT FORMS

This appendix is not relevant because no subjects died, experienced serious adverse events or withdrew due to adverse events in this study.

APPENDIX 11.2.1: CRFs FOR DEATHS, OTHER SERIOUS ADVERSE EVENTS AND WITHDRAWALS FOR AE

This appendix is not relevant because no subjects died, experienced serious adverse events or withdrew due to adverse events in this study.

APPENDIX 11.3 INDIVIDUAL SUBJECT DATA LISTINGS (US ARCHIVAL LISTINGS)

This Appendix contains the following sections:

Statistical Analysis: final version 5. July 2012 – Full Statistical Report produced by Derek Cooper, Statistician.

Subject Visit Listings.

Pepsin Analysis Results

Statistical Analysis Tables of Relaxed Entry Criteria – Number of reflux events

Statistical Analysis: final version 5. July 2012 – Full Statistical Report produced by Derek Cooper, Statistician.


GA1001 - Statistical Analysis Report

Subject Visit Listings.


GA1001 - Subject Visit Listings

Pepsin Analysis Results


GA1001 - Pepsin Analysis Results

Statistical Analysis Tables of Relaxed Entry Criteria – Number of reflux events.

Number of reflux events.Change (from treatment period to no treatment period) in the number of reflux events by randomisation group

							95% CI	
	N	Mean	Std. Deviation	Median	Minimum	Maximum	Lower	Upper
Placebo change	15	4.11	26.67	-1.62	-41.92	63.69	-10.66	18.88
Gaviscon change	9	-15.14	30.70	-17.13	-60.46	40.43	-38.74	8.46

Linear regression analysis with change (from treatment period to no treatment period) in the number of reflux events as the dependent variable and randomisation group as the independent variable.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	4.108	7.281		.564	.578	-10.992	19.209
	Randomisation group	-19.250	11.890	-.326	-1.619	.120	-43.909	5.408

a. Dependent Variable: Change in the number of acid reflux events

Number of reflux events in the upright position

Change (from treatment period to no treatment period) in the number of reflux events in the upright position by randomisation group

							95% CI	
	N	Mean	Std. Deviation	Median	Minimum	Maximum	Lower	Upper
Placebo change	15	4.91	34.04	1.85	-63.11	87.04	-13.95	23.76
Gaviscon change	9	-23.59	42.47	-25.03	-105.74	45.08	-56.23	9.05

Linear regression analysis with change (from treatment period to no treatment period) in the number of reflux events in the upright position as the dependent variable and randomisation group as the independent variable

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	4.907	9.638		.509	.616	-15.080	24.895
	Randomisation group	-28.496	15.738	-.360	-1.811	.084	-61.135	4.143

a. Dependent Variable: Change in the number of acid reflux events

Number of reflux events in the supine position

Change (from treatment period to no treatment period) in the number of reflux events in the supine position by randomisation group

							95% CI	
	N	Mean	Std. Deviation	Median	Minimum	Maximum	Lower	Upper
Placebo change	15	6.04	21.39	1.59	-25.81	67.98	-5.81	17.88
Gaviscon change	8	-7.18	48.76	0.00	-95.92	60.69	-47.94	33.58

Linear regression analysis with change (from treatment period to no treatment period) in the number of reflux events in the supine position as the dependent variable and randomisation group as the independent variable

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	6.036	8.553		.706	.488	-11.751	23.823
	Randomisation group	-13.217	14.503	-.195	-.911	.372	-43.377	16.943

a. Dependent Variable: Change in the number of acid reflux events