Study Title: A Multi-centred, Randomised, Open Label, Placebo-controlled, Two-period Crossover Study to Evaluate 4-hour Esophageal pH Change in GERD Patients After Administration of Compound Sodium Alginate Double Action Tablets or Placebo Tablets

ClinicalTrials.gov ID: NCT01872897

Final Protocol, dated 01-Mar-2013

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Reckitt Benckiser

1 STUDY PROTOCOL TITLE PAGE

CTA (China) Number:	2010L02452		
Study Number:	GA1202	**Project Name:**	Shanghai
Study Phase:	III	**Study Country:**	China
Indication:	Gastro-esophageal reflux disease (GERD)		
Test Product(s):	Compound Sodium Alginate Double Action Chewable Tablet.		
Reference Product(s):	Placebo Matching Compound Sodium Alginate Double Action Chewable Tablet.		
Study Title:	A multi-centred, randomised, open label, placebo-controlled, two-period crossover study to evaluate 4-hour esophageal pH change in GERD patients after administration of Compound Sodium Alginate Double Action Chewable Tablets or matching placebo tablets		
Short Study Title:	Compound Sodium Alginate Double Action Chewable Tablets 4-hour esophageal pH study in GERD patients		
Protocol Date:	1 March 2013		
Protocol Version:	Final version 2		
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 PROTOCOL APPROVAL

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Senior Statistician
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3 PROTOCOL SYNOPSIS

3.1 Rationale

This study is being conducted to assess the effectiveness of the Compound Sodium Alginate Double Action Chewable Tablets compared to placebo on acidic reflux events into the esophagus in patients diagnosed with GERD.

3.2 Objective(s)

The primary objective of this study is to compare the time during the 4 hour post dosing period where the pH is below pH 4 for Compound Sodium Alginate Double Action Chewable Tablets versus matching placebo tablets.

The secondary objectives of this study are to determine and compare the number of occasions and percentage of time during the 1 and 4 hour post dosing period when pH falls below pH 4 and pH 5. Other secondary objectives include comparing the longest reflux time and DeMeester scores during the 4 hour period.

3.3 Primary Endpoint

The primary efficacy endpoint will be the percentage of time during the 4 hour post dosing period with pH below pH 4 for Compound Sodium Alginate Double Action Chewable Tablets versus matching placebo tablets.

3.4 Secondary Endpoints

The following secondary endpoints will also be evaluated:

- Percentage of time during the 4 hour post dosing period with pH below pH 5
- Number of occasions during the 4 hour post dosing period when pH falls below pH 4
- Number of occasions during the 4 hour post dosing period when pH falls below pH 5
- Number of reflux episodes during the 4 hour post dosing period with pH below pH 4 for at least 5 minutes
- Percentage of time during the first hour post dosing with pH below pH 4
- Percentage of time during the first hour post dosing with pH below pH 5

- Number of occasions during the first hour post dosing when pH falls below pH 4
- Number of occasions during the first hour post dosing when pH falls below pH 5
- The longest reflux time during the 4 hour post dosing period (i.e. the longest period with pH below pH 4)
- The DeMeester scores during the 4 hour post dosing period

3.5 Design Summary

This is a multi-centre, randomised, open-label, placebo-controlled, two-period crossover study. After signing a written informed consent, patients will undergo a screening period of up to 10 days. Patients who satisfy the study entry requirements within 10 days of consent, will be randomised to receive either four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets following placement of a pH electrode and a standardised refluxogenic meal.

Upon completion of the 4-hour post-dose pH monitoring period patients will be instructed to begin taking supplied Compound Sodium Alginate Double Action Chewable Tablets (two tablets four times daily) for 7 days. Patients will return after the 7 day period for repeat catheter insertion and pH monitoring, receiving the alternative randomised treatment.

3.6 Sample Size

The number of patients enrolled for this study has been derived from experience of previous pH monitoring studies conducted with other Gaviscon® formulations. It is anticipated that 36 evaluable patients will be required to complete the study. In order to achieve this, 44 patients will be enrolled in this study.

3.7 Anticipated Study Timings

It is estimated that the clinical phase of this study will commence in May 2013 and last a period of 6-9 months.

The duration of each patient's participation in the study will be a maximum of 19 days (from screening visit to end of treatment visit) and involve 3 visits.

3.8 Inclusion Criteria

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

1. Informed consent has been obtained.

2. Age: ≥ 18 years to ≤ 65 years.

3. Sex: male or female.

4. Primary diagnosis: meet the diagnostic criteria for GERD with a GERD history of frequent episodes of GERD-related symptoms during the last 2 months prior to study screening. The patient must also meet the following criteria:

    a. The only or main symptom is heartburn (burning feeling back of breast bone) and/or acid reflux. Symptoms persists or have occurred repeatedly for more than 2 months;

    b. As assessed by the Investigator at screening by questioning of the patient, the frequency of occurrence of heartburn is ≥ 3 days/week and the score of severity of heartburn in general is ≥ Level 2 within 3 weeks before screening.

    The severity of heartburn will be evaluated as follows:

Level 0	no heartburn
Level 1	heartburn is mild in severity and is not obvious
Level 2	heartburn is moderate, or it is obvious when it occurs, the patient experiences discomfort
Level 3	heartburn is severe and significant, seriously interferes with daily activities

    The frequency of heartburn will be evaluated as number of days /week that heartburn is suffered (0, 1, 2, 3, 4, 5, 6 or 7 days).

5. Status: Patients will be patients at the clinic or members of the public who respond to an advertisement or via their doctor.

6. Patients who have not taken any antacids within 24 hours before randomisation (Visit 2) and be instructed not to take antacids, other than the Compound Sodium Alginate Double Action Chewable Tablets provided, throughout the remainder of the study.

7. Patients taking mucous membrane protection drugs or prokinetics may enter the study provided that these are discontinued for at least 5 days before screening and throughout the remainder of the study.

8. Systemic glucocorticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs, except for low dose aspirin which can be given for cardioprotection) can only be taken for up to 3 consecutive days in the 28 days prior to screening.

9. Absence of relevant abnormalities in the physical examination, endoscopy, ECG and laboratory safety results.

10. Patients who are willing to consume the entire standard refluxogenic test meal. Patients cannot be vegetarian.

3.9 Exclusion Criteria

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

1. Patients who have a history of drug, solvent or alcohol abuse (weekly alcohol intake ≥ 140g).

2. Patients who have suffered cardiac chest pain within the last year.

3. Patients who have suffered a recent, significant unexplained weight loss of more than 6 Kg in the last 6 months.

4. Female patients of childbearing potential who, for the duration of the study, are either unwilling or unable to take adequate contraceptive precautions (as defined in Section 10.3) or are unwilling to be sexually abstinent (as defined in Section 10.3).

5. Pregnancy or lactating mother.

6. Patients with a history and/or symptom profile suggestive of the following: any other gastrointestinal (GI) disease, erosive GERD (Los Angeles [LA] classification grades C-D), Barrett's esophagus, acute peptic ulcer and/or ulcer complications, Zollinger-Ellison syndrome, gastric carcinoma, pyloric stenosis, oesophageal or gastric surgery, intestinal obstruction, current pernicious anaemia, indication for H-pylori eradication therapy, known gastro-intestinal bleeding (hematochezia or hematemesis) within the last 3 months, and severe diseases of other major body systems.

7. Patients who are observed at screening to have a hiatus hernia with a diameter which exceeds 3cm.

8. Patients who have taken anti-cholinesterase drugs, traditional Chinese medicines for treating gastrointestinal disease, ulcerlmin or misoprostol preparations within 7 days prior to screening or throughout the study.

9. Patients who have taken PPIs during the 10 days prior to screening, prokinetics or H2 antagonists during the 5 days prior to screening or systemic glucocorticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs, except for low dose aspirin which can be given for cardioprotection) on more than 3 consecutive days or PPI-based triple or quadruple therapy for eradication of H-pylori during the last 28 days.

10. Patients taking or requiring to take macrolide antibiotics, such as erythromycin, azithromycin, from the day before screening.

11. Patients with difficulty in swallowing.

12. Patients with known hypophosphataemia, phenylketonuria or hypercalcaemia.

13. Patients with severe constipation, or history of intestinal obstruction.

14. In the opinion of the Investigator, patients with damaged heart or kidney function and patients who require a low sodium diet.

15. Patients either with any co-existing condition which, in the opinion of the Investigator, would be likely to compromise patient safety or interfere with assessment of efficacy; or with any clinically significant abnormal laboratory values; or in the Investigator's view to unable to comply fully with the study requirements.

16. Any previous history of allergy or known intolerance to any of the IMP's or following formulation constituents: macrogol 20,000, mannitol (E421), copovidone, acesulfame K, aspartame (E951), mint flavour, carmoisine lake (E122), magnesium stearate, xylitol DC (contains carmellose sodium) or the following formulation constituents: sodium alginate, calcium carbonate, sodium bicarbonate.

17. Previously randomised into the study.

18. Employee at study site.

19. Partner or first-degree relative of the Investigator.

20. Patients who failed screening will not be allowed to re-enter the study.

21. Participation in a clinical study in the previous 6 months or participation in a previous Compound Sodium Alginate Double Action Chewable Tablet study.

22. Unable in the opinion of the Investigator to comply fully with the study requirements.

3.10 Methodology

Schedule of Assessments

Items	Visit 1 (Screening Visit)	Visit 2 0-10 days after Visit 1	Visit 3 7 ± 2 days after Visit 2	Early Termination (ET) Visit
Assess patient's suitability to enter study	X	X		
Issue patient information sheet and obtain informed consent	X			
Assess concomitant medications	X	X	X	X
Medical history	X	X		
Physical examination	X		X	X
Blood samples for haematology & clinical chemistry, urine pregnancy tests	X		X	X
Vital signs	X		X	X
12-lead ECG	X			
Endoscopy	X			
Assess Adverse Events		X	X	X
Administer refluxogenic test meal (after fast)		X	X	
Administer single randomised dose of four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets 30 min after completion of test meal		X	X	
4-hour pH monitoring (from 30 min prior to dosing to 4 hours post dosing)		X	X	
Collect and record time pH data obtained		X	X	
Dispense one week NIMP Compound Sodium Alginate Double Action Chewable Tablets (2 tablets 4 times daily)		X		
Make appointment for next visit	X	X		
Collect returned unused & used medication (IMP & NIMP)			X	X
End of study Assessments			X	X

pH Monitoring

Visit	Time	First Dosing Visit Procedures
2	• Ensure patient has not taken symptomatic treatment for GERD (antacids etc) in the 24 hours prior to pH monitoring • Ensure the patient has abstained from alcohol for 24 hours prior to the test meal. • Ensure the patient has fasted for a minimum of 4 hours prior to insertion of manometry probe. • Insert manometry probe to aid positioning of esophageal pH sensor (prior to consuming test meal). • Record pH from 30 minutes prior to dosing to 4 hours post dosing.	
2	-4 hours	Abstain from food.
	-60 min	Eat test meal.
	-30 min	End of test meal. Start recording pH measurement.
	0	Administer four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets (as randomised).
	4 hours	End of esophageal pH measurement.
	Prior to departure	Question for adverse events. Leave Unit.
Visit	**Time**	**Second Dosing Visit Procedures**
3	• Ensure patient has not taken symptomatic treatment for GERD (antacids etc), including Compound Sodium Alginate Double Action Chewable Tablets, in the 24 hours prior to pH monitoring • Ensure the patient has abstained from alcohol for 24 hours prior to the test meal. • Ensure the patient has fasted for a minimum of 4 hours prior to insertion of manometry probe. • Insert manometry probe to aid positioning of esophageal pH sensor (prior to consuming test meal). • Record pH from 30 minutes prior to dosing to 4 hours post dosing.	
3	-4 hours	Abstain from food.
	-60 min	Eat test meal.
	-30 min	End of test meal. Start recording pH measurement.
	0	Administer four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets (as randomised).
	4 hours	End of esophageal pH measurement.

	Prior to departure	Question for adverse events. Follow-up assessments. Leave Unit.

3.11 Statistics

All statistical tests will be conducted using two-tailed tests at the 5% significance level.

The null hypothesis at all times will be the equality of the fixed effect being compared from the model.

The primary endpoint will be analysed primarily using an ANOVA of variance model with treatment, dosing visit treatment sequence as fixed effects and patient nested within treatment sequence as a random effect. The difference between treatment least square means will be used to represent the treatment differences. The effects for dosing visit and treatment sequence will also be assessed. A residual analysis will be performed. If there is a major departure from the assumptions of normality, independence or heteroscedasticity of residuals, then further analysis using transformed data will be used to support the original model results. If such assumptions still do not hold following an appropriate transformation then Wilcoxon Rank-Sum test will be used to compare the dosing visit difference (dosing visit 1 – dosing visit 2) between treatment sequence groups to represent the treatment comparison.

All secondary endpoints will be analysed identically to the primary endpoint.

All secondary endpoints and sensitivity or alternate analyses for the primary endpoint will serve as supportive evidence for the primary analysis only and therefore no adjustment for multiple comparisons will be made.

If less than 2 hours post-dosing monitoring data is available, for whatever reason, (or less than 1 hour post-dosing data within the first hour for parameters based on the first hour post-dosing) the derived parameters will be considered missing. If 2 or more hours post-dosing monitoring data is available, the parameters will be derived using the data available, and will be adjusted, where necessary, by multiplying by the factor (4 hours / time with data available). Any data recorded more than 4 hours post-dosing will be ignored when deriving these parameters.

4 TABLE OF CONTENTS

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

4.2 List of Appendices

There are no appendices.

4.3 List of Abbreviations

Table 4-1 List of Abbreviations

Abbreviation	Abbreviation in Full
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AR	Adverse Reaction
CA	Competent Authority
CIOMS	Council for International Organizations of Medical Sciences
CPM	Clinical Project Manager
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Application
CV	Curriculum Vitae
DSO	RB Drug Safety Officer
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GCLP	Good Clinical Laboratory Practice
GERD	Gastro-esophageal reflux disease
GMP	Good Manufacturing Practice
GVG	Global Vigilance Group
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent-to-Treat

Abbreviation	Abbreviation in Full
NCR	No Carbon Required
NERD	Nonerosive Esophageal Reflux Disease
NIMP	Non-investigational Medicinal Product
NSAID	Non Steroidal Anti-Inflammatory Drug
OTC	Over-the-counter
PFDA	Provincial Food and Drug Administration in China
PPI	Proton pump inhibitor
QA	Quality Assurance
R&D	Research and Development
RB	Reckitt Benckiser
SAE	Serious Adverse Event
SDV	Source Data Verification
SFDA	State Food and Drug Administration in China
SOP	Standard Operating Procedure
UK	United Kingdom (of Great Britain and Northern Ireland)

5 INVESTIGATORS AND ADMINISTRATIVE STUCTURE

5.1 Reckitt Benckiser Details

The following RB personnel are responsible for the conduct of the study:

Table 5-1 Reckitt Benckiser Details

Name	Position	Address and Contact Number
[redacted]	Clinical Project Manager	Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS. UK.
[redacted]	Global Medical Director	[redacted] Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS. UK.
[redacted]	Senior Statistician	[redacted] Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS. UK. [redacted]

The names and addresses of the [redacted] Study Monitors will be provided in the Initiation Visit Report.

5.2 Investigational Sites

This is a multi-centre, hospital based study in China. This study will be conducted at two or more hospital sites.

The Co-ordinating Principal Investigator is [redacted] China.

5.3 Laboratories

Local hospital site laboratories will be used for this study. The names and addresses of all laboratories involved in the study for safety analyses will be documented in the Initiation Visit Reports for each site.

6 INTRODUCTION

Gastro-esophageal reflux disease (GERD) is a condition that develops when the backward movement of stomach contents into the esophagus causes troublesome symptoms and/or complications. The troublesome symptoms of GERD can have significant impact on health-related quality of life and work productivity [1-4]. GERD is believed to be the most common upper gastro-intestinal condition, affecting between 10% and 20% of the Chinese population and the prevalence of GERD in Asia is reported to be approximately 5% [5].

Dyspepsia (sometimes referred to by the non-medical term indigestion) is defined as pain or discomfort centred in the upper abdomen. It is often described as a feeling of fullness, bloating, nausea, heartburn or gassy discomfort in the chest or abdomen.

Heartburn and regurgitation are the two most predominant clinical manifestations of GERD [6]. The pain is usually burning in character and felt retrosternally, rising from the epigastrium towards or into the throat.

The over-the-counter (OTC) preparations for treatment of heartburn in China include antacids, proton pump inhibitors (PPIs) and histamine H2-receptor antagonists as well as traditional Chinese medicines. While PPIs are effective in acid-related conditions, they offer limited benefit for patients with functional dyspepsia and/or functional heartburn [6-8].

Compound Sodium Alginate Double Action Chewable Tablets (also known as Gaviscon® Double Action Tablets) are a combination of two antacids (calcium carbonate and sodium bicarbonate) and an alginate. On ingestion, the product reacts rapidly with gastric acid to form a raft of alginic acid gel having a near neutral pH and which floats on the stomach contents effectively impeding gastro-esophageal reflux.

Calcium carbonate neutralises gastric acid to provide fast relief from indigestion and heartburn. This effect is increased by the addition of sodium bicarbonate which also has a neutralising action. The total neutralising capacity of four tablets is approximately 20 mEqH+.

A similar study was previously conducted in China to demonstrate the effect of Gaviscon® Original Liquid on esophageal pH in GERD patients [9]. No clinical studies have been performed with Compound Sodium Alginate Double Action Chewable Tablets to demonstrate the effect on esophageal pH in patients with GERD. This study is being conducted to provide evidence for inclusion in applications to regulatory authorities that Compound Sodium Alginate Double Action Chewable Tablets are effective for the treatment of reflux in patients diagnosed with GERD.

The potential risks to patients taking part in the present study are considered to be low. Endoscopy and placement of the pH catheter can cause discomfort but the risks associated with these procedures are 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 patient being sensitive to any of the active substances (sodium alginate, sodium bicarbonate and calcium carbonate) or any of the excipients. Other adverse reactions include:

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

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

For this reason, the risk benefit balance for the current study is considered to be acceptable.

This study will be conducted in accordance with the principles set out in the Declaration of Helsinki. It will comply with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

7 STUDY RATIONALE

This study is being conducted to assess the effectiveness of the Compound Sodium Alginate Double Action Chewable Tablets compared to placebo on acidic reflux events into the esophagus in patients diagnosed with GERD.

8 STUDY OBJECTIVES

The objective of this study is to demonstrate that Compound Sodium Alginate Double Action Chewable Tablets are statistically significantly superior to matching placebo tablets in the suppression of gastric reflux provoked by a standard refluxogenic meal in GERD patients. Gastric reflux will be assessed by ambulatory esophageal pH monitoring over 4 hours.

The purpose of this study is to compare esophageal pH profiles monitored during the 4-hours after ingestion of a refluxogenic test meal, followed by a single dose of study medication. Patients recruited to the study will attend the clinic on two occasions separated by 7 days, and at each visit they will consume a refluxogenic meal; 30 minutes later the patient will be randomised to receive either a dose of either four Compound Sodium Alginate

Double Action Chewable Tablets or four matching placebo tablets. On each occasion esophageal pH will be monitored for 4 hours post dosing. Each patient will be his/her own control. Between the pH monitoring visits, patients will take Compound Sodium Alginate Double Action Chewable Tablets, two tablets 4 times daily for 7 days, to provide ongoing symptom relief.

8.1 Primary Objective

The primary objective of this study is to compare the time during the 4 hour post dosing period where the pH is below pH 4 for Compound Sodium Alginate Double Action Chewable Tablets versus matching placebo tablets.

8.2 Secondary Objective(s)

The secondary objectives of this study are to determine and compare the number of occasions and percentage of time during the 1 and 4 hour post dosing period when pH falls below pH 4 and pH 5. Other secondary objectives include comparing the longest reflux time and DeMeester scores during the 4 hour period.

9 STUDY DESIGN

9.1 Study Endpoints

9.1.1 Primary Endpoint

The primary efficacy endpoint will be the percentage of time during the 4 hour post dosing period with pH below pH 4 for Compound Sodium Alginate Double Action Chewable Tablets versus matching placebo tablets.

9.1.2 Secondary Endpoints

The following secondary endpoints will also be evaluated:

- Percentage of time during the 4 hour post dosing period with pH below pH 5
- Number of occasions during the 4 hour post dosing period when pH falls below pH 4

- Number of occasions during the 4 hour post dosing period when pH falls below pH 5
- Number of reflux episodes during the 4 hour post dosing period with pH below pH 4 for at least 5 minutes
- Percentage of time during the first hour post dosing with pH below pH 4
- Percentage of time during the first hour post dosing with pH below pH 5
- Number of occasions during the first hour post dosing when pH falls below pH 4
- Number of occasions during the first hour post dosing when pH falls below pH 5
- The longest reflux time during the 4 hour post dosing period (i.e. the longest period with pH below pH 4)
- The DeMeester scores during the 4 hour post dosing period

9.2 Design Summary

This is a multi-centre, randomised, open-label, placebo-controlled, two-period crossover study. After signing a written informed consent, patients will undergo a screening period of up to 10 days. Patients who satisfy the study entry requirements within 10 days of consent, will be randomised to receive either four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets following placement of a pH electrode and a standardised refluxogenic meal.

Upon completion of the 4-hour post-dose pH monitoring period patients will be instructed to begin taking supplied Compound Sodium Alginate Double Action Chewable Tablets (two tablets four times daily) for 7 days. Patients will return after the 7 day period for repeat catheter insertion and pH monitoring, receiving the alternative randomised treatment.

9.3 Discussion of Study Design

Esophageal pH monitoring is a well validated and accepted technique for diagnosis of gastro-esophageal reflux disease (GERD). It provides direct physiologic measurement of acid in the esophagus and can assess the response of the disease to treatment. In this study it is being used to assess and compare the effects of Compound Sodium Alginate Double Action Chewable Tablets and matching placebo tablets on pH over a 4 hour post-dose period 30 minutes after a refluxogenic meal.

A crossover design is used for this study where the patient has pH measurement for four hours after four Compound Sodium Alginate Double Action Chewable Tablets and four matching placebo tablets on two separate occasions. A 7-day washout period occurs between each pH monitoring visit; all patients will receive standardised treatment consisting of Compound Sodium Alginate Double Action Chewable Tablets (two tablets four times daily) for their symptoms of GERD during during this washout period between pH monitoring visits.

9.4 Number of Patients

The number of patients enrolled for this study has been derived from experience of previous pH monitoring studies conducted with other Gaviscon formulations. It is anticipated that 36 evaluable patients will be required to complete the study. In order to achieve this, 44 patients will be enrolled in this study.

Further details are provided in Section 14.1.

9.5 Study Duration

It is estimated that the clinical phase of this study will commence in May 2013 and last a period of 6-9 months.

The duration of each patient's participation in the study will be a maximum of 19 days (from screening visit to end of treatment visit) and involve 3 visits.

Patients can enter the study, if eligible, as soon as all screening results are available following informed consent at Visit 1. A maximum of 10 days will be allowed to screen a patient at Visit 1. If eligible, the patient will be randomised and will commence the first pH monitoring period at Visit 2 (Day 0). The patients will be randomised to receive either four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets 30 minutes after a refluxogenic meal with pH monitored and recorded for a 4-hour period post-dose.

All patients will then receive Compound Sodium Alginate Double Action Chewable Tablets (two tablets four times daily) as Non-investigational Medicinal Product (NIMP) for symptomatic treatment. Patients will stop Compound Sodium Alginate Double Action Chewable Tablets 24 hours prior to returning for Visit 3 which occurs 7 ± 2 days later. The patient will receive the alternate treatment after a refluxogenic meal with pH monitored and recorded for a 4-hour period post-dose.

The anticipated overall duration of study conduct will be between 6 and 9 months.

9.6 Patient Commitment to the Study

The duration of each patient's participation in the study will be up to 19 days (from screening visit to final visit). The initial screening visit (Visit 1) will be followed by two visits (Visits 2 and 3) at which the patient will consume a refluxogenic meal, followed 30 minutes later by a dose of either four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets (as randomised); esophageal pH will be monitored continuously from 30 minutes prior to dosing to 4 hours post dosing. The study will be completed with post-study assessments after the second pH monitoring visit.

9.6.1 Duration of Patient Participation

Up to 10 days will be allowed to screen a patient at Visit 1 following informed consent. The pre-study procedures will consist of a medical history and physical examination, 12-lead ECG, endoscopy diagnostic examination (endoscopy's conducted prior to consent may be used if patients were examined within 28 days of giving consent if the examination was conducted at the same hospital), haematology and clinical chemistry and urine pregnancy test for female patients of child-bearing potential.

Visit 2 (Day 0) will take place immediately after all screening results are available and within 10 days after Visit 1. Patients meeting the entry criteria will be randomised to receive either four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets administered following placement of a pH electrode (using manometry to position the pH electrode) and 30 minutes after a standardised refluxogenic meal. pH will be measured for 4 hours post-dose.

The patient will then be issued with Compound Sodium Alginate Double Action Chewable Tablets (two tablets four times daily) to take for 7 $\pm$ 2 days, stopping dosing at least 24 hours prior to Visit 3.

At Visit 3, End of treatment period (Day 7 ± 2 days), unused investigational medicinal product (IMP) will be collected. The patient will receive the alternate treatment following placement of a pH electrode and 30 minutes after a standardised refluxogenic meal. pH will be measured for 4 hours post-dose followed by a final assessment for safety (AEs, haematology and clinical chemistry with urine pregnancy test for female patients and physical examination).

Further details on the timing of study visits are provided in Section 11.2.

9.6.2 Invasive Procedures

Blood samples will be taken for haematology and clinical chemistry at Visit 1 and Visit 3. The total volume of blood samples will not exceed 30 ml.

An endoscopy will be performed at screening or results may be used if conducted prior to consent within 28 days of giving consent if the examination was conducted at the same hospital.

pH reflux monitoring for a period of 4.5 hours will take place on two occasions. This requires placement of the pH monitoring probe via one nostril, down the back of the throat, and into the esophagus as the patient swallows. Esophageal manometry is used to guide the accurate placement of the pH electrodes.

Further details on the study assessments are provided in Section 11.2.

9.6.3 General and Dietary Restrictions

Patients will be instructed to follow their routine meal pattern, avoiding food not normally consumed, such as excessively spicy food. There should be an interval of at least three hours between meals.

The patient will be asked to abstain from alcohol 24 hours prior to each test meal and to fast for a minimum of 4 hours prior to placement of the pH electrodes.

The patient will be asked not to take any treatment for GERD symptoms for 24 hours prior to each test meal.

9.7 End of Study

The end of the study is defined as the last visit of the last patient undergoing the study.

[redacted] will notify SFDA within 90 days of the end of the study (within 15 days if the study is terminated prematurely).

The Investigator will notify the IEC within 90 days of the end of the study (within 15 days if the study is terminated prematurely).

10 STUDY POPULATION

10.1 Inclusion Criteria

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

1. Informed consent has been obtained.
2. Age: ≥ 18 years to ≤ 65 years.
3. Sex: male or female.
4. Primary diagnosis: meet the diagnostic criteria for GERD with a GERD history of frequent episodes of GERD-related symptoms during the last 2 months prior to study screening. The patient must also meet the following criteria:
    a. The only or main symptom is heartburn (burning feeling back of breast bone) and/or acid reflux. Symptoms persists or have occurred repeatedly for more than 2 months;
    b. As assessed by the Investigator at screening by questioning of the patient, the frequency of occurrence of heartburn is ≥ 3 days/week and the score of severity of heartburn in general is ≥ Level 2 within 3 weeks before screening;

The severity of heartburn will be evaluated as follows:

Level 0	no heartburn
Level 1	heartburn is mild in severity and is not obvious
Level 2	heartburn is moderate, or it is obvious when it occurs, the patient experiences discomfort
Level 3	heartburn is severe and significant, seriously interferes with daily activities

The frequency of heartburn will be evaluated as number of days /week that heartburn is suffered (0, 1, 2, 3, 4, 5, 6 or 7 days).

5. Status: Patients will be patients at the clinic or members of the public who respond to an advertisement or via their doctor.

6. Patients who have not taken any antacids within 24 hours before randomisation (Visit 2) and be instructed not to take antacids, other than the Compound Sodium Alginate Double Action Chewable Tablets provided, throughout the remainder of the study.

7. Patients taking mucous membrane protection drugs or prokinetics may enter the study provided that these are discontinued for at least 5 days before screening and throughout the remainder of the study.

8. Systemic glucocorticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs, except for low dose aspirin which can be given for cardioprotection) can only be taken for up to 3 consecutive days in the 28 days prior to screening.

9. Absence of relevant abnormalities in the physical examination, endoscopy, ECG and laboratory safety results.

10. Patients who are willing to consume the entire standard refluxogenic test meal. Patients cannot be vegetarian.

10.2 Exclusion Criteria

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

1. Patients who have a history of drug, solvent or alcohol abuse (weekly alcohol intake ≥ 140g).

2. Patients who have suffered cardiac chest pain within the last year.

3. Patients who have suffered a recent, significant unexplained weight loss of more than 6 Kg in the last 6 months.

4. Female patients of childbearing potential who, for the duration of the study, are either unwilling or unable to take adequate contraceptive precautions (as defined in Section 10.3) or are unwilling to be sexually abstinent (as defined in Section 10.3).

5. Pregnancy or lactating mother.

6. Patients with a history and/or symptom profile suggestive of the following: any other gastrointestinal (GI) disease, erosive GERD (Los Angeles [LA] classification grades C-D), Barrett's esophagus, acute peptic ulcer and/or ulcer complications, Zollinger-Ellison syndrome, gastric carcinoma, pyloric stenosis, oesophageal or gastric surgery, intestinal obstruction, current pernicious anaemia, indication for H-pylori eradication therapy, known gastro-intestinal bleeding (hematochezia or hematemesis) within the last 3 months, and severe diseases of other major body systems.

7. Patients who are observed at screening to have a hiatus hernia with a diameter which exceeds 3cm.

8. Patients who have taken anti-cholinesterase drugs, traditional Chinese medicines for treating gastrointestinal disease, ulcerlmin or misoprostol preparations within 7 days prior to screening or throughout the study.

9. Patients who have taken PPIs during the 10 days prior to screening, prokinetics or H2 antagonists during the 5 days prior to screening or systemic glucocorticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs, except for low dose aspirin which can be given for cardioprotection) on more than 3 consecutive days or PPI-based triple or quadruple therapy for eradication of H-pylori during the last 28 days.

10. Patients taking or requiring to take macrolide antibiotics, such as erythromycin, azithromycin, from the day before screening.

11. Patients with difficulty in swallowing.

12. Patients with known hypophosphataemia, phenylketonuria or hypercalcaemia.

13. Patients with severe constipation, or history of intestinal obstruction.

14. In the opinion of the Investigator, patients with damaged heart or kidney function and patients who require a low sodium diet.

15. Patients either with any co-existing condition which, in the opinion of the Investigator, would be likely to compromise patient safety or interfere with assessment of efficacy; or with any clinically significant abnormal laboratory values; or in the Investigator's view to unable to comply fully with the study requirements.

16. Any previous history of allergy or known intolerance to any of the IMP's or following formulation constituents: macrogol 20,000, mannitol (E421), copovidone, acesulfame K, aspartame (E951), mint flavour, carmoisine lake (E122), magnesium stearate, xylitol DC (contains carmellose sodium) or the following formulation constituents: sodium alginate, calcium carbonate, sodium bicarbonate.

17. Previously randomised into the study.

18. Employee at study site.

19. Partner or first-degree relative of the Investigator.

20. Patients who failed screening will not be allowed to re-enter the study.

21. Participation in a clinical study in the previous 6 months or participation in a previous Gaviscon study.

22. Unable in the opinion of the Investigator to comply fully with the study requirements.

10.3 Patients of Reproductive Potential

Woman of childbearing potential must take adequate contraceptive precautions for the entire duration of study participation. Adequate contraceptive precautions include 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 is in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g., calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception. Should the patient become sexually active while participating in the study, she must agree to use a double barrier method or condoms/diaphragms with spermicidal foam/gel/film/cream/suppository). Patients are to be informed that a female condom and male condom should not be used together as friction between the two can result in either product failing. A woman of childbearing potential is defined as any female who is less than 2 years post-menopausal or who has not undergone a hysterectomy or surgical sterilisation, e.g. bilateral tubal ligation, bilateral ovariectomy (oophorectomy).

The procedures to be followed if a patient becomes pregnant while enrolled in the study are described in Section 13.3.

11 STUDY METHODOLOGY

11.1 Recruitment of Study Patients

Patients will be recruited from the hospital clinics, hospital database or by advertisement. Patients suffering from mild to moderate symptoms of GERD will be given the opportunity by the investigator to participate in the study. Patients will be recruited according to the Investigator's standard procedures at the study site.

11.2 Study Visits/Assessments

A patient is enrolled into a study when he or she (or a legal representative as defined in Section 16.2) has signed the informed consent form, i.e. prior to any study-specific assessments being performed.

Table 11-1 Schedule of Assessments

Items	Visit 1 (Screening Visit)	Visit 2 0-10 days after Visit 1	Visit 3 7 ± 2 days after Visit 2	Early Termination (ET) Visit
Assess patient's suitability to enter study	X	X		
Issue patient information sheet and obtain informed consent	X			
Assess concomitant medications	X	X	X	X
Medical history	X	X		
Physical examination	X		X	X
Blood samples for haematology & clinical chemistry, urine pregnancy tests	X		X	X
Vital signs	X		X	X
12-lead ECG	X			
Endoscopy	X			
Assess Adverse Events		X	X	X
Administer refluxogenic test meal (after fast)		X	X	
Administer single randomised dose of four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets 30 min after completion of test meal		X	X	
4-hour pH monitoring (from 30 min prior to dosing to 4 hours post dosing)		X	X	
Collect and record time pH data obtained		X	X	
Dispense one week NIMP Compound Sodium Alginate Double Action Chewable Tablets (2 tablets 4 times daily)		X		
Make appointment for next visit	X	X		
Collect returned unused & used medication (IMP & NIMP)			X	X
End of study Assessments			X	X

pH Monitoring

The time course for pH monitoring is summarised in the following table:

Table 11-2 Schedule for pH monitoring

Visit	Time	First Dosing Visit Procedures
2	• Ensure patient has not taken symptomatic treatment for GERD (antacids etc) in the 24 hours prior to pH monitoring • Ensure the patient has abstained from alcohol for 24 hours prior to the test meal. • Ensure the patient has fasted for a minimum of 4 hours prior to insertion of manometry probe. • Insert manometry probe to aid positioning of esophageal pH sensor (prior to consuming test meal). • Record pH from 30 minutes prior to dosing to 4 hours post dosing.	
2	-4 hours	Abstain from food.
	-60 min	Eat test meal.
	-30 min	End of test meal. Start recording pH measurement.
	0	Administer four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets (as randomised).
	4 hours	End of esophageal pH measurement.
	Prior to departure	Question for adverse events. Leave Unit.
Visit	**Time**	**Second Dosing Visit Procedures**
3	• Ensure patient has not taken symptomatic treatment for GERD (antacids etc), including Compound Sodium Alginate Double Action Chewable Tablets, in the 24 hours prior to pH monitoring • Ensure the patient has abstained from alcohol for 24 hours prior to the test meal. • Ensure the patient has fasted for a minimum of 4 hours prior to insertion of manometry probe. • Insert manometry probe to aid positioning of esophageal pH sensor (prior to consuming test meal). • Record pH from 30 minutes prior to dosing to 4 hours post dosing.	
3	-4 hours	Abstain from food.
	-60 min	Eat test meal.
	-30 min	End of test meal. Start recording pH measurement.
	0	Administer four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets (as randomised).

	4 hours	End of esophageal pH measurement.
	Prior to departure	Question for adverse events. Follow-up assessments. Leave Unit.

11.3 Baseline Visit

11.3.1 Screening/Enrolment Procedures

Potential patients will be provided with the patient information sheets and given ample time to read and decide whether they are interested in taking part in the study. If the patient is interested, she/he will speak to the investigator or person delegated by the investigator to take consent who will explain more about the study and answer any questions. If the patient feels fully informed and willing to participate in the study they will complete, sign and date the informed consent form (ICF). The ICF will then be counter signed and dated by the investigator or person delegated by the investigator to take consent. A copy of the ICF and patient information sheet will be provided to the patient for their personal records.

All patients will be given a 4-digit screening number once they have provided consent. The first two digits will refer to the centre number and the second two digits to the number of patients screened at that centre. For example, screening numbers at centre 01 will start 0101, 0102 etc.

The screening process can take up to a maximum of ten days after informed consent.

11.3.1.1 Clinical Assessments Performed at Baseline (Visit 1, Screening Visit)

The following baseline assessments (Visit 1, screening visit) will be conducted:

Review of primary inclusion and exclusion criteria

<u>Assessment of symptoms</u>

The severity of heartburn will be evaluated as follows:

Level 0 no heartburn

Level 1 heartburn is mild in severity and is not obvious

Level 2 heartburn is moderate, or it is obvious when it occurs, the patient experiences discomfort

Level 3 heartburn is severe and significant, seriously interferes with daily activities

The frequency of heartburn will be evaluated as number of days / week that heartburn is suffered (0, 1, 2, 3, 4, 5, 6 or 7 days)

The primary inclusion criteria will be based on the symptom of heartburn only.

Demographic data:

- Sex
- Race (categorised as: Caucasian, Asian, Afro-Caribbean and Other)
- Date of birth
- Height (cm)
- Weight (kg)
- Smoking/alcohol/drugs of abuse history/use

Laboratory safety data:

- Haematology
- Clinical chemistry

Vital signs:

- Blood pressure (after sitting for 5 minutes; mmHg)
- Heart rate (radial pulse counted for 30 seconds after resting for 5 minutes; beats/minute)

12-lead ECG

Medical history and current status:

- Primary diagnosis
- Duration of disease

- Medical history and current status

Medication and therapy history:

- Current therapy (including any OTC or traditional Chinese medicines)
- Therapy in the previous 30 days (including any OTC or traditional Chinese medicines)

Endoscopy examination:

- A standard hospital endoscopy examination will be conducted to indicate whether the patient meets inclusion/exclusion criteria.
- Endoscopy diagnosis examinations conducted prior to consent may be used if patients were examined within 28 days of giving consent, only if the examination was conducted at the same hospital and if the endoscopy results are available for study monitoring purposes.

Physical examination

- A standard physical examination

Pregnancy testing

- Women of child-bearing potential will undergo urine pregnancy testing.

11.3.2 Clinical Assessments Performed After Baseline

11.3.2.1 Clinical Assessments at Visit 2

Visit 2 will take place up to 10 days after Visit 1. It can be the same day as Visit 1 but will only occur on the same day as Visit 1 if the patient meets all criteria with respect to use of concomitant medication, abstention from alcohol, fasting etc.

At Visit 2 patients will return to the clinic to have any medical history changes during the screening period and concomitant medications recorded; any adverse events noted during the pH monitoring session will be recorded. If the patient fulfils the eligibility criteria for randomisation, a unique 3-digit randomisation number will be allocated and study medication dispensed (001, 002 etc.). The randomisation number will be pre-printed on the medication assigned to that patient. Randomisation numbers will not be site-specific. The numbers available at a site have to be allocated to the patients in consecutive order.

Eligible patients will undergo the following pH monitoring procedure:

4-hour pH monitoring

1) Patients will be required to fast for a minimum period of 4 hours prior to insertion of the manometric probe used to transfer the pH electrode.
2) The basic equipment requirements for ambulatory esophageal pH studies are a portable data logger for data storage, a pH electrode, a computer and software for analysis of pH data.
3) The probe and pH electrode will be passed through a nostril; manometry will be used to ensure the pH electrode is correctly positioned 5 cm above the superior margin of the lower esophageal sphincter (LES) and then taped to the face to hold it in place.
4) 30 minutes after the procedure patients will receive a standardised reflux provoking meal (Section 12.5); patients will be allowed 30 minutes to consume the entire meal. After consumption of the meal the pH monitoring data logger will be activated and recording will continue until 4 hours post-dose.
5) 30 minutes after completing the meal patients will receive their randomised single dose of study medication, either four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets.
6) Patients will remain in the clinic for the duration of the pH monitoring period, under supervision. They will be allowed to sit or stand during the pH monitoring period but will be encouraged not to lie down.
7) Volunteers will not be permitted to eat or drink anything other than the test meal from the start of the fasting period until the end of the first dosing visit.
8) Upon completion of the monitoring period patients will be given a prescribing card which they will use to collect their symptom control medication, Compound Sodium Alginate Double Action Chewable Tablets, from a dispensing unit. Sufficient medication will be dispensed to allow 8 days usage. Patients will be instructed to begin taking their Compound Sodium Alginate Double Action Chewable Tablets later that same day (typically the evening of Visit 2) and continue until their last dose 24 hours prior to their next visit. Patients will be instructed to follow their routine meal pattern, avoiding food not normally consumed, such as excessively spicy food. There should be an interval of at least three hours between meals. They will be instructed to take bring all medication with them to the clinic when they return for Visit 3.
9) Patients will be questioned about adverse events ("How have you been feeling today?"). Any adverse events reported in response to this question or otherwise spontaneously reported by the volunteer or observed by the study personnel at any point during study procedures will be recorded in the patient's CRF.

On completion of the visit, an appointment will be made for the next visit, 7 ± 2 days later. Patients will be instructed to stop taking Compound Sodium Alginate Double Action Chewable Tablets 24 hours prior to the next visit and fast from food and liquids for 4 hours prior to the next visit.

Emergency cards will be issued to patients before they leave the centre. The emergency card will be the size of a credit card and will contain the following information:

- Study number.
- Patient (randomisation) number.
- Statement that patient is participating in a clinical trial.
- Statement that the patient is taking two Compound Sodium Alginate Double Action Chewable Tablets four times per day.
- Instructions to non-investigator staff to ring a 24-hour telephone number in case of emergency.

11.3.2.2 Clinical Assessments at Visit 3

Patients will arrive at the hospital 7 ± 2 days after the last visit. At Visit 3 the Investigator will:

1) Record any concomitant medications and adverse events occurring since the last visit;

2) The Investigator will conduct 4-hour pH monitoring (see section 11.3.2.1 4-hour pH monitoring for procedure and fasting requirements). At this second dosing visit, the patient will receive the alternate randomised study treatment (four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets).

3) 4-hour pH monitoring data will be collected from Visit 3. The Investigator will record any additional adverse events and concomitant medications at the end of the visit.

4) All medication, used and unused blister packs, will be returned to the drug dispensing unit.

Post study Follow Up Assessments (visit 3)

The following examinations and investigations will be conducted after the pH monitoring data has been collected (on the same day as the pH monitoring visit):

Vital Signs

- Blood pressure (after sitting for 5 minutes; mmHg).
- Heart rate (radial pulse counted for 30 seconds after resting for 5 minutes; beats/minute).

Concomitant Medication

- All concomitant medication usage including any OTC medications and tradional Chinese medications will be recorded.

Adverse Events

- All adverse events will be recorded.

Physical examination

- A standard physical examination will be conducted.

Laboratory investigations (haematology and clinical chemistry)

- Details are listed in section 13.4.

Pregnancy testing

- Women of child-bearing potential will undergo urine pregnancy testing.

11.3.2.3 Clinical Assessments at Early Termination (ET) Visit (only if required for patient early terminations)

If the investigator withdraws the patient from the study for any reason after Visit 2 the patient will complete the study at this early termination visit and the following will be completed.

Vital Signs

- Blood pressure (after sitting for 5 minutes; mmHg).
- Heart rate (radial pulse counted for 30 seconds after resting for 5 minutes; beats/minute).

Concomitant Medication

- All concomitant medication usage including any OTC medications and traditional Chinese medications will be recorded.

Adverse Events

- All adverse events will be recorded.

Physical examination

- A standard physical examination will be conducted.

Laboratory investigations (haematology and clinical chemistry)

- Details are listed in section 13.4.

Pregnancy testing

- Women of child-bearing potential will undergo urine pregnancy testing

Early Study Termination

- The investigator will assess the reason for early termination: AE; lack of efficacy; lost to follow-up; no further need for IMP; protocol violation; death; withdrawal of consent; other.
- The patient will return unused NIMP

11.4 Study Variables and Methods of Assessment

11.4.1 Efficacy Variables

11.4.1.1 Overview of Efficacy Variables

The primary and some secondary efficacy variables are derived from the 4-hour pH monitoring sessions following four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets.

11.4.1.2 Methods of Assessment of Efficacy Variables

Efficacy is assessed by esophageal pH monitoring following a standard refluxogenic test meal. A single dose of the study treatment is administered 30 minutes after completion of the meal and pH measurements recorded for 4 hours post-dose. Patients will be randomised to receive four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets and one week later will receive the alternate treatment.

11.4.2 Appropriateness of Measurements

Esophageal pH monitoring is a well validated and accepted technique for diagnosis of gastro-esophageal reflux disease (GERD). It provides direct physiologic measurement of acid in the esophagus and can assess the response of the disease to treatment. In this study it is being used to assess and compare the effects of four Compound Sodium Alginate Double Action Chewable Tablets and four matching placebo tablets on pH over a 4 hour post-dose period 30 minutes after a refluxogenic meal.

A crossover design is used for this study where the patient has pH measurement after Compound Sodium Alginate Double Action Chewable Tablets and matching placebo tablets on two separate occasions. A 7-day washout period occurs between each pH monitoring visit; all patients will receive standard treatment, Compound Sodium Alginate Double Action Chewable Tablets (two tablets four times daily), for their symptoms of GERD during this washout period between pH monitoring visits.

11.5 Study Specific Supplies

Not applicable

11.6 Unscheduled Visits

If unscheduled visits occur, the Investigator must record the following in the patient's CRF:

- Reason for unscheduled visit
- Any AEs.
- Concomitant therapy changes.
- Withdrawal (if deemed appropriate).
- Any clinical assessments deemed appropriate for the clinical care of the patient.

If the dosage regimen of study medication has been changed, the Investigator must contact the RB Clinical Project Manager in order to determine if the patient should be withdrawn from the study or may be allowed to continue. The Clinical Project Manager will advise the Investigator of how information should be recorded on the CRF.

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

11.7 Patient Withdrawal and Replacement Criteria

11.7.1 Patient Withdrawal

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

- AEs that in the judgement of the Investigator may cause severe or permanent harm (significant clinical deterioration is an AE).
- Violation of the study protocol.
- In the Investigator's judgement, it is in the patient's best interest.

- Patient declines further study participation.

The primary reason for withdrawal will be documented as one of the following: AE; lack of efficacy; lost to follow-up; no further need for IMP (unless this is a study endpoint); protocol violation; death; withdrawal of consent; other. The Investigator must make reasonable attempts to contact patients who are lost to follow-up - a minimum of 2 documented telephone calls or a letter is considered reasonable.

In the event of early withdrawal the patient should have the assessments listed in Section 11.3.2.3 completed.

11.7.2 Replacement of Patients

Patients who withdraw from the study will not be replaced.

11.8 Additional Care of Study Patients Following Completion of the Study

Patients who experience AEs at the end of the study, or experience the onset of an AE after the end of the study, will be followed up as described in Sections 13.1.7 and 13.1.8.

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

11.9 Treatment Compliance

The IMP will be administered at the study site under the supervision of the Investigator or his or her delegate.

11.10 Premature Termination of the Study

RB may prematurely terminate the conduct of the study specific study sites or the entire study. Reasons for early termination include, but are not limited to:

- Inability to recruit or slow recruitment of patients

- Unacceptable data quality
- Concerns regarding the risk/benefit ratio
- Withdrawal of CA or IEC approval
- Recall of a batch of IMP where replacement medication will not be provided
- Results from an interim statistical or safety analysis
- Inability to remedy a clinical hold or suspension
- Unresolved non-compliance with GCP or the protocol that compromises patient rights or safety or the study data

The CPM will inform all investigators in writing at specific study sites relevant to the decision. A suitable course of action will be agreed for existing patients. The investigator will inform the IEC/IRB in writing and provide a copy to RB for filing in the TMF. [redacted] will inform the SFDA within 15 days of the date of termination and file a copy of the correspondence in TMF.

12 STUDY TREATMENTS

12.1 Identity of Investigational Medicinal Products

The following medication will be supplied.

- Compound Sodium Alginate Double Action Chewable Tablets.
- Matching placebo tablets.

Compound Sodium Alginate Double Action Chewable Tablets will be manufactured to Good Manufacturing Practice (GMP) by Reckitt Benckiser Healthcare (UK) Limited, Dansom Lane, Hull, HU8 7DS, UK (Product Licence 00063/0157). The matching placebo tablets will be manufactured to Good Manufacturing Practice (GMP) by [redacted] for RB.

The active and placebo treatment will be shipped to [redacted] where both active and placebo will be blister packed. The blister packs will be shipped to the Investigational Material Supplies Unit (IMSU), Reckitt Benckiser Healthcare UK Ltd, Dansom Lane, Hull, HU8 7DS UK.

The supplies will be assembled and labelled to GMP standards by the Investigational Material Supplies Unit (IMSU), Reckitt Benckiser Healthcare UK Ltd, Dansom Lane, Hull, HU8 7DS. They will be shipped directly from IMSU to be distributed to the investigator sites from a distribution centre in China.

For the open-label single dose treatments, labels will identify which of the two treatments (active or placebo) the patient's pack contains.

12.2 Identity of Non-Investigational Medicinal Products

Each patient will be instructed to take Compound Sodium Alginate Double Action Chewable Tablets as a multiple dose regimen for the 7-day period between each pH monitoring visit. Prior to dosing, all patients will be instructed by the Investigator on how they will take the medication, ie, chew and swallow two tablets on each dosing occasion. Patients will be instructed to start taking their medication on the same day following the first pH monitoring visit (usually the evening dose). Two tablets will be chewed and swallowed four times a day: 30 minutes after breakfast, 30 minutes after lunch, 30 minutes after dinner and immediately before lying down for bed.

Compound Sodium Alginate Double Action Chewable Tablets will be used for treatment of the symptoms of GERD between the pH monitoring visits and not for experimental purposes.

Compound Sodium Alginate Double Action Chewable Tablets will be manufactured to Good Manufacturing Practice (GMP) by Reckitt Benckiser Healthcare (UK) Limited, Dansom Lane, Hull, HU8 7DS, UK (Product Licence 00063/0157).

The active treatment will be shipped to [redacted], where the Compound Sodium Alginate Double Action Chewable Tablets will be blister packed. The blister packs will be shipped to the Investigational Material Supplies Unit (IMSU), Reckitt Benckiser Healthcare UK Ltd, Dansom Lane, Hull, HU8 7DS UK.

The supplies will be assembled and labelled to GMP standards by the Investigational Material Supplies Unit (IMSU), Reckitt Benckiser Healthcare UK Ltd, Dansom Lane, Hull, HU8 7DS. They will be shipped directly from IMSU to be distributed to the investigator sites from a distribution centre in China.

12.3 Randomisation and Treatment Allocation

12.3.1 Randomisation

Drug supplies for the two single doses per patient will be randomised by the RB IMSU, according to a computer-produced randomisation schedule. On randomisation, patients will be allocated a unique patient number in numerical sequence. Issue of the IMP in this sequence will ensure randomisation.

The IMSU will hold the master code for the randomisation schedule.

This study is not blinded.

12.3.2 Blinding

This study is not blinded.

12.3.3 Emergency Unblinding Procedures

This study is not blinded.

12.3.4 IMP allocation for Replacement Patients

Patients will not be replaced.

12.4 Dosage Instructions

For the open-label, single dose treatment at each of the pH monitoring visits, patients will be administered four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets.

All patients will be instructed by the Investigator on how they will take the medication, ie, thoroughly chew then swallow each tablet.

Medication errors may result in this study, from the administration or consumption of the wrong drug, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such

medication errors occurring to a study participant will be captured on the adverse event (AE) page of the CRF and on a SAE form as appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable to RB irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to a medicinal product
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE/SAE, as determined by the investigator, the medication error and any associated AE/SAEs will be captured on an AE CRF page /SAE form (refer to Adverse Event Reporting section 13.1 for further details).

12.5 Standard Test Meal

In addition to the study medications, during the pH monitoring period, all the patients are required to consume a standard test meal on two separate occasions. This will comprise the following from McDonalds:

The Standardised Meal will consist of the following:

Medium sized McDonalds Big Mac

Portion of Medium size fries

Medium sized Fanta Orange Drink

This meal has a total calorific value of 990 kcal and contains protein 31 g, fat 40 g and carbohydrate 124 g.

12.6 Packaging

Sufficient drug supplies will be packaged and labelled for 100 patients for the single dose crossover.

Each patient's open-label, single dose pack will contain two blister packs each pack containing 4 tablets. Four tablets are to be taken from the first blister pack at the first pH monitoring visit and four tablets are to be taken from the second blister pack at the second pH monitoring visit.

Each patient's complete pack for the study will consist of:

- One blister pack containing 4 Compound Sodium Alginate Double Action Chewable Tablets
- One blister pack containing 4 matching placebo tablets

12.7 Labelling

12.7.1 Investigational Medicinal Product(s)

Supplied IMP(s) will be labelled according to GCP and GMP requirements and any other applicable national/state legislation.

Each patient pack and each patient carton will be labelled and each blister pack will be labelled.

12.7.2 Patient Carton

The blister packs containing the single dose study treatments will be contained in an outer carton.

12.7.3 Patient Pack

The patient pack will contain one open label treatment carton containing 8 blister packs of NIMP Compound Sodium Alginate Double Action Chewable Tablets and one single dose IMP carton containing the two single dose, open-label packs for to be administered at pH monitoring visits.

12.7.4 Non-Investigational Medicinal Products

Supplied NIMP will be labelled according to GCP and GMP requirements and any other applicable national/state legislation.

Each blister pack, patient pack and each patient carton will be labelled.

The patient will be asked to complete a NIMP return form noting the number of tablets returned.

12.8 Accountability of Investigational and Non-Investigational Medicinal Product(s)

The Investigator will keep all IMP(s) and NIMP(s) in a pharmacy or a secure storage facility, accessible only to those individuals authorised by the Investigator to dispense the medication.

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

The Investigator agrees not to supply IMP(s) and NIMP(s) to any person except study personnel and patients enrolled in this study.

All IMP(s) and NIMP(s) should be stored between 4°C and 30°C. Temperatures must be monitored using a minimum / maximum thermometer and recorded in a temperature log on working days.

12.9 Disposal of Unused Investigational and Non-Investigational Medicinal Product(s)

The Investigator agrees to conduct a drug supply inventory, to record the results of this inventory ("IMP/NIMP Removal from Site" form) and to return it and all original IMP/NIMP containers, whether empty or containing IMP or NIMP, to [redacted] at the end of the study or in stages during the course of the study.

[redacted] and RB will arrange for the appropriate and timely destruction of all returned IMP(s) and NIMP(s) following the end of the study (on finalisation of the study report).

12.10 Concomitant Therapies

Concomitant therapies are defined as prescribed medications, physical therapies, and over-the-counter preparations, including herbal preparations licensed for medicinal use, other than IMP(s) and NIMP(s) that the patient receives during the course of the study.

The Investigator will record any medications given for treatment of AEs on the concomitant medication page in the patient's CRF. Any medication taken by the patient from the time of giving informed consent through to the end of the study should also be recorded in the CRF. Any changes in concomitant therapy during the study will be documented, including cessation of therapy, initiation of therapy, and dose changes.

12.11 Prohibited Therapies

The use of the following therapies will not be permitted:

- PPIs during the 10 days prior to screening and throughout the study.
- Prokinetics or H2 antagonists during the 5 days prior to screening and throughout the study.
- Systemic glucocorticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs except low dose aspirin given for cardioprotection) on more than 3 consecutive days in the 28 days prior to screening and are not allowed throughout the study.
- PPI-based triple or quadruple therapy for eradication of H-pylori during the 28 days prior to screening and throughout the study.
- Mucous membrane protection drugs for 5 days prior to screening and throughout the study.
- Patients who have taken anti-cholinesterase drugs, traditional Chinese medicines for treating gastrointestinal disease, ulcerlmin or misoprostol preparations within 7 days prior to screening or throughout the study.
- Macrolide antibiotics, such as erythromycin, azithromycin, from the day before screening and throughout the study.
- Any antacids within 24 hours before randomisation (Visit 2) and throughout the remainder of the study. Compound Sodium Alginate Double Action Chewable Tablets will be provided for symptom relief at the end of Visit 2 but must be stopped 24 hours prior to Visit 3.

Patients who use any of these above medications during the study will be withdrawn.

The Investigator Brochure indicates that due to the presence of calcium carbonate which acts as an antacid, a time-interval of 2 hours should be considered between Compound Sodium Alginate Double Action Chewable Tablet intake and the administration of other medicinal products, especially H2-antihistaminics, tetracyclines, digoxine, fluoroquinolone, iron salt, ketoconazole, neuroleptics, thyroxine, penicilamine, beta-blockers (atenolol, metoprolol, propranolol), glucocorticoid, chloroquine and diphosphonates.

13 SAFETY ASSESSMENTS

13.1 Adverse Events

13.1.1 Adverse Event Definitions

Adverse Event (AE): Any untoward medical occurrence in a patient participating in a clinical study administered an IMP, which does not necessarily have a causal relationship with administration of the IMP.

Comment: An AE can 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.

AEs do not include the following:

- Medical or surgical procedures; the condition requiring a medical or surgical procedure is an AE.
- Elective surgery or pre-existing conditions requiring planned procedures outside the scope of the study.

Adverse Reaction (AR) to an IMP: All untoward and unintended responses to an IMP related to any dose administered.

Comment: All AEs judged by either the Investigator or the sponsor as having a reasonable causal relationship to an IMP qualify as ARs. The expression “reasonable causal relationship” means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event (SAE): Any untoward medical occurrence (i.e. AE) that at any dose:

- Results in death.
- Is life-threatening.
- Requires hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is otherwise considered to be medically significant.

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

Medical judgement should be exercised in deciding whether an AE or AR is otherwise considered to be medically significant. Important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above should also be considered serious.

Examples of such medically significant events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias or convulsions that do not result in hospitalisation.
- Development of drug dependency or drug abuse.

Unexpected Adverse Reaction: An AR, the nature or intensity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unauthorised IMP or SmPC for an authorised IMP).

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

Suspected Unexpected Serious Adverse Reaction (SUSAR): An SAE considered to have a causal relationship with administration of the IMP, and the nature or intensity of which is not consistent with the applicable product information (e.g. Investigator brochure for an unauthorised IMP or SmPC for an authorised IMP).

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

13.1.2 Observation Period for Adverse Event Reporting

The observation period for an individual patient will start after giving informed consent and will finish at the last visit defining the end of the study for the given individual patient.

Any SAEs occurring after Informed Consent must be reported.

Any untoward medical events occurring after Informed Consent but prior to IMP administration should be recorded in the patient’s medical history and not reported as an AE.

13.1.3 Information to be Collected on Adverse Events

Each AE will be recorded according to the criteria given below. “Relationship to IMP” must be determined by the Investigator (if medically qualified) or by a medically qualified Co-Investigator.

Table 13-1 Table of Information to be Collected on Adverse Events

Variable	Category	Definition
AE reported term		Any untoward medical occurrence in a patient administered an IMP and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the IMP.
Date AE started		The date on which the AE started.
Date of change in severity of AE		The date on which the AE changed in severity. This date equates to the finish date of the old severity and the onset date of the new severity.
Intensity		Intensity will be determined by the Investigator. For symptomatic AEs the following definitions will be applied, but medical experience and judgement should also be used in the assessment of intensity.
	Mild	The AE does not limit usual activities; the patient may experience slight discomfort.
	Moderate	The AE results in some limitation of usual activities; the patient may experience significant discomfort.
	Severe	The AE results in an inability to carry out usual activities; the patient may experience intolerable discomfort or pain.
Actions taken	None	No action was taken in relation to this AE.
	IMP dose changed	The dose of IMP was changed due to this AE, i.e. increase, decrease, or temporary discontinuation.
	IMP permanently discontinued	The IMP was permanently discontinued due to this AE.
	Symptomatic therapy	Symptomatic therapy was added or changed due to this AE.
	Patient hospitalised or hospitalisation prolonged	The patient was hospitalised or hospitalisation was prolonged due to this AE.
	Other action (specify)	Other action was taken due to this AE, e.g. diagnostic tests, laboratories and procedures.
Relationship to IMP	Unassessable/ Unclassifiable	Insufficient information to be able to make an assessment.

Variable	Category	Definition
	Conditional/ Unclassified	Insufficient information to make an assessment at present (causality is conditional on additional information).
	Unrelated	No possibility that the AE was caused by the IMP.
	Unlikely	Slight, but remote, chance that the AE was caused by the IMP, but the balance of judgment is that it was most likely not due to the IMP.
	Possible	Reasonable suspicion that the AE was caused by the IMP.
	Probable	Most likely that the AE was caused by the IMP.
	Certain	The AE was definitely caused by the IMP.
Is the AE serious?	Results in death Life-threatening Requires or prolongs hospitalisation Results in persistent or significant disability/incapacity Congenital anomaly/birth defect Otherwise considered to be medically significant	See Section 13.1.1.
Date resolved		The date on which the AE ceased to be present.
Outcome	Not recovered/not resolved	The AE still persists.
	Recovered/resolved	The AE is resolved.
	Recovered/resolved with sequelae	The patient is stabilised, but with sequelae from this AE.
	Recovering/resolving	The patient is recovering from this AE/this AE is resolving.
	Fatal	The patient died whilst this AE was ongoing or as a result of it.
	Unknown	The outcome of this AE is not known.
Has the patient ever experienced this AE before?	Yes/No	A query confirming whether the patient has a previous medical history of the AE at any time before entering into the study. If the patient has experienced this AE before, brief details should be given under additional information.
Additional information		Additional information regarding the AE.

13.1.4 Procedure for Reporting Adverse Events

All AEs that arise after the patient has had IMP administered will be recorded in the patient's CRF. AEs can be reported spontaneously by the patient or in response to non-leading questioning or observation by the Investigator, or be a significant laboratory abnormality.

The Investigator will ask the patient: "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.

Assessments of the relationship of AEs to IMP must be made by the Investigator (if medically qualified) or by a medically qualified Co-Investigator.

13.1.5 Procedure for Reporting Serious Adverse Events

In the event of a Serious Adverse Event (SAE), the Investigator should telephone the Clinical Project Manager (CPM) within 24 hours of knowledge of the event. The name and contact number of the CPM will be provided to the Investigator in the study protocol and/or at the Study Initiation Visit. To allow timelines to be met the Investigator can report the event to the Global Vigilance Group (GVG) simultaneously by contacting GVG by email: [redacted]. The CPM will also forward any SAE information/forms to the RB Global Vigilance Group within the same day using the email address: [redacted]

Out of hours emergency contacts will be provided to the Investigator in the study protocol and/or at the Study Initiation Visit. If notification is via telephone the CPM will ensure that a SAE Form is completed but the Investigator will be requested to make a detailed written report by sending a follow-up SAE Form as soon as possible. The CPM will be responsible for reporting the event to the Global Vigilance Group ([redacted]). All the SAE forms will be provided to the CPM function via email, and a copy filed in the TMF. Any inconsistencies in the information received from the Investigator will be clarified using the Adverse Event Data Clarification Form.

If the case does require reporting, a CIOMS (Council for International Organizations of Medical Sciences) form will be produced. A copy of this will be sent to the RB Drug Safety Officer (DSO) in China who will complete the SFDA SAE Form in Chinese and submit to the SFDA within 7 days for fatal or life-threatening events, or 15 days for all events.

If the event requires expedited reporting (event classified as a SAE):

1. The IEC/IRB, SFDA and PFDA will be notified by the Investigator within 24 hours of awareness

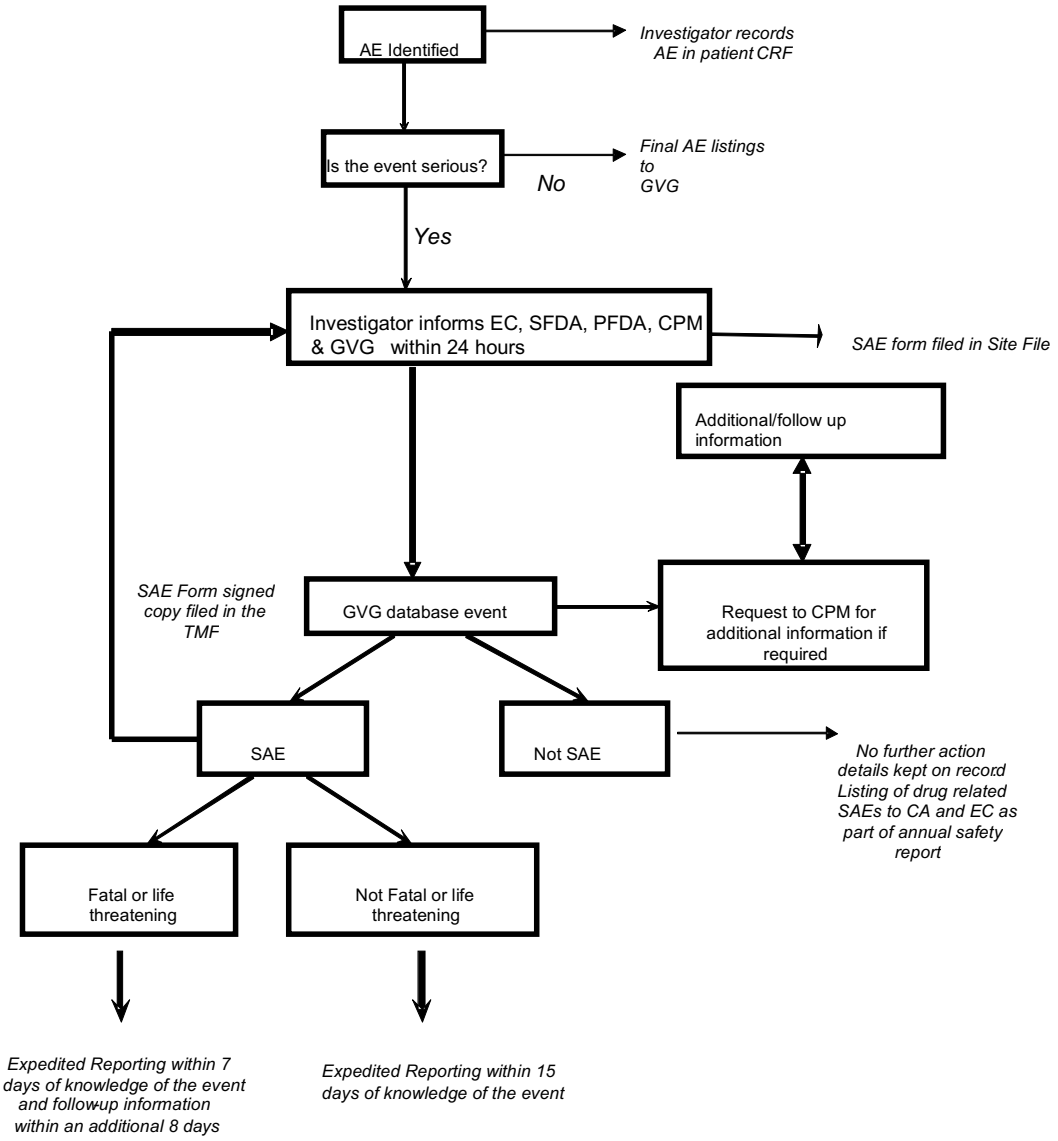
2. All other investigators participating in the study will be informed by the CPM

The Investigator will be instructed to retain a copy of all the SAE Forms in the Investigator Site File, and must inform his/her local ethics committee/institutional review board of all SAEs occurring in the study.

The Investigator should not break the randomisation code except when it is necessary to do so in order to ensure the patient receives appropriate medical care (see Section 12.2).

The overall procedure for reporting SAEs is illustrated in the flowchart below.

Figure 13-1 Procedure for Reporting SAEs



13.1.6 Reporting to Regulatory Authorities

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

13.1.7 Follow-up of Patients Experiencing Adverse Events upon Completion of the Study or Withdrawal from the Study

All SAEs, and all AEs that cause premature withdrawal of the patient from the study, that have not resolved by the end of the study will be followed up by the Investigator until resolution or until the Investigator believes there will be no further change. This may involve the patient making additional visits to the site.

All other AEs will be followed up where possible to resolution or until the Investigator believes there will be no further change, whichever is the earlier.

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

13.1.8 Procedures for Patients Experiencing Onset of Adverse Events after End of the Study

As the active study drug in this study is not absorbed, a serious adverse event that occurs within a day of the final dose of study medication should be reported and followed to resolution or until the Investigator believes there will be no further change.

13.2 Overdose

Overdoses are reportable to RB irrespective of the presence of an associated AE/SAE. The overdose and any associated AE/SAE will be captured on an AE CRF page/SAE form.

13.3 Pregnancy

If a patient is found to be pregnant after being dosed with IMP:

- Promptly notify RB (i.e. Clinical Project Manager) or CRO monitor (if CRO is Investigator's first port of call for reporting SAEs).
- Withdraw the patient from the study.

- Perform study completion assessments.
- Collect details of due date, etc.

Pregnancy follow-up will be conducted by RB GVG personnel as part of their drug safety monitoring responsibilities and will not form part of the study dataset.

Pregnancy should be reported to RB as AE.

13.4 Clinical Laboratory Investigations

All blood samples will be collected and prepared according to the standard procedures of the hospital laboratory conducting the analyses at each of the study sites. Laboratory safety parameters will be analysed using standard validated methods.

The following investigations will be made:

Haematology

- Haemoglobin
- Red blood cells
- Mean cell haemoglobin concentration
- White blood cells
- Platelet count

Biochemistry

- Electrolytes: sodium, potassium, calcium
- Urea
- Creatinine
- Uric acid
- Glucose
- Inorganic phosphorous
- Alanine transaminase
- Aspartate transaminase

Pregnancy testing

- Women of child-bearing potential will undergo urine pregnancy testing (positive or negative).

The total volume of blood expected to be sampled for clinical laboratory safety investigations from an individual patient in the course of the study is not expected to exceed 30 ml.

13.4.1 Collection of Laboratory Samples

Blood samples will be collected and labelled in tubes provided by the local laboratory.

Urine samples will be collected mid-stream.

13.4.2 Labelling of Laboratory Samples

The site's standard labels will be used.

13.4.3 Reference Ranges

Up-to-date reference ranges for the above investigations must be obtained for each site performing analyses prior to the start of the study and be updated as appropriate during the course of the study.

13.4.4 Laboratory Results Review

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

A copy of these results will be provided to the [redacted] monitor.

13.4.5 Good Clinical Laboratory Practice (GCLP) Compliance

Confirmation of compliance with GCLP will be required from the laboratories involved prior to the start of the study.

The laboratories will be requested to provide documented evidence of GCLP compliance. This may be a statement of compliance issued by the appropriate national authority, or details of accreditation by a recognised organisation.

An independent inspection of the laboratories by [redacted] or RB may be conducted.

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

Vital signs and physical examinations will be conducted at baseline and final or early termination visits. A 12-lead ECG and endoscopy will be conducted and the results will be reviewed by the investigator at baseline as part of the screening procedures. Patients will be asked about adverse events at follow-up visits.

14 STATISTICAL CONSIDERATIONS

The statistical analysis will be undertaken in collaboration with Quintiles.

A detailed Statistical Analysis Plan will be finalised before the database is locked and prior to analysis of the study being carried out.

Any deviations from the analyses described below will be included in the Statistical Analysis Plan, which will form Appendix 16.1.9 of the clinical study report.

14.1 Sample Size Justification

No statistical justification for the sample size in this study was performed because the variance of the response is not known for Compound Sodium Alginate Double Action Chewable Tablets.

The number of patients enrolled for this study has been derived from experience of previous pH monitoring studies conducted with other Gaviscon® formulations.. It is anticipated that 36

evaluable patients will be required to complete the study. In order to achieve this, 44 patients will be enrolled in this study.

14.2 Data to be Analysed

Definition of the analysis populations:

- Full Analysis Set (FAS): All patients enrolled in the study;
- Safety (Safety) population: All patients who are subjected to any invasive procedures and/or take at least one dose of study medication;
- Intention to treat (ITT) population: All patients who take at least one dose of study medication and have evaluable pH monitoring data for at least 1 hour post-dosing;
- Per protocol (PP) population: The criteria for inclusion in the PP population will be confirmed during data checking, but will at least include the following: patients who adhered to the inclusive/exclusive criteria; did not take any prohibited medication which would interfere with evaluation of drugs in the study period; attended visits within the specified visit windows and had complete pH monitoring data for 4 hour post-dosing for both pH monitoring visits.

The ITT population and safety population are the primary populations for evaluation of efficacy and safety, respectively. The PP population will be used for a secondary evaluation of the primary endpoint only.

14.3 Patient Disposition and Characteristics

Descriptive summary statistics will be provided for demographic characteristics and baseline data for each treatment sequence group and all patients. For continuous parameters, mean, standard deviation, median, minimum, and maximum will be provided. For categorical parameters, the cell frequencies and percentage of patients in each category will be provided.

14.4 Efficacy Analyses

Results will be summarised by treatment for each dosing visit and overall (Compound Sodium Alginate Double Action Chewable Tablets, matching placebo tablets) using n, mean, standard deviation, median, minimum and maximum values.

If less than 2 hours post-dosing monitoring data is available, for whatever reason, (or less than 1 hour post-dosing data within the first hour for parameters based on the first hour post-dosing) the derived parameters will be considered missing. If 2 or more hours post-dosing monitoring data is available, the parameters will be derived using the data available, and will be adjusted, where necessary, by multiplying by the factor (4 hours / time with data available). Any data recorded more than 4 hours post-dosing will be ignored when deriving these parameters.

14.4.1 Primary Efficacy Analysis Endpoint

The primary efficacy parameter will be the percentage of time during the 4 hour post dosing period with pH below pH 4.

14.4.2 Secondary Efficacy Endpoints

The secondary endpoints will be:

- Percentage of time during the 4 hour post dosing period with pH below pH 5
- Number of occasions during the 4 hour post dosing period when pH falls below pH 4
- Number of occasions during the 4 hour post dosing period when pH falls below pH 5
- Number of reflux episodes during the 4 hour post dosing period with pH below pH 4 for at least 5 minutes
- Percentage of time during the first hour post dosing with pH below pH 4
- Percentage of time during the first hour post dosing with pH below pH 5
- Number of occasions during the first hour post dosing when pH falls below pH 4
- Number of occasions during the first hour post dosing when pH falls below pH 5

- The longest reflux time during the 4 hour post dosing period (i.e. the longest period with pH below pH 4)
- The DeMeester scores during the 4 hour post dosing period.

14.4.3 Statistical Methods for Efficacy Analyses

SAS 9.1 (or later) will be used for statistical analysis.

All statistical tests will be conducted using two-tailed tests at the 5% significance level.

The null hypothesis at all times will be the equality of the fixed effect being compared from the model.

The primary endpoint will be analysed primarily using an ANOVA of variance model with treatment, dosing visit treatment sequence as fixed effects and patient nested within treatment sequence as a random effect. The difference between treatment least square means will be used to represent the treatment differences. The effects for dosing visit and treatment sequence will also be assessed. A residual analysis will be performed. If there is a major departure from the assumptions of normality, independence or heteroscedasticity of residuals, then further analysis using transformed data will be used to support the original model results. If such assumptions still do not hold following an appropriate transformation then Wilcoxon Rank-Sum test will be used to compare the dosing visit difference (dosing visit 1 – dosing visit 2) between treatment sequence groups to represent the treatment comparison.

All secondary endpoints will be analysed identically to the primary endpoint.

All secondary endpoints and sensitivity or alternate analyses for the primary endpoint will serve as supportive evidence for the primary analysis only and therefore no adjustment for multiple comparisons will be made.

14.5 Safety Analyses

Withdrawals will be listed in the Clinical Study Report (CSR) Appendices and summarised by reason for withdrawal.

Adverse events will be listed on a patient by patient basis in the CSR Appendices. The number of adverse events will be summarised by body system and preferred term, relationship to study medication and severity. The number of patients experiencing adverse events will also be summarised in the same manner.

14.5.1 Adverse Events

All AEs will be coded using the most up-to-date version of MedDRA. For an individual patient, AEs that began prior to the first dose of IMP or more than one day after the final dose of IMP will not be included in the analysis.

The incidence of AEs (number and percent of patients reporting each type of AE at least once during the study) will be summarised for all AEs, by investigator attribution of relationship to IMP and by severity. The incidence of AEs will be compared among (between) treatment groups using McNemar's Test for all AEs, for those AEs classified by the Investigator as possibly, probably or certainly related to IMP and for severe AEs.

14.5.2 Laboratory Data

For the purpose of analysing laboratory data, "baseline" is defined as the baseline assessments at Visit 1, screening and "last visit" is defined as the final visit, Visit 3 or the Early Termination Visit.

Each pre-study baseline laboratory value will be categorised as low, normal, or high based on the reference range. Each post-baseline value will be classified in a similar manner, producing a 3 x 3 table for each treatment group at each post-baseline visit. Scores of "1" will be assigned to low values, "2" to normal values, and "3" to high values. Using these scores, shifts from baseline will also be assigned a score. For example, a laboratory value that shifts from low to high will be assigned a score of 2, whilst a laboratory value that remains at a low value will be assigned a score of 0. Shifts between these categories between baseline and subsequent timepoints will be compared using the Wilcoxon Signed-Rank test within each treatment group. Statistical testing will be performed at last visit.

At each visit, summary statistics for the absolute laboratory value and the changes from baseline will be presented by treatment group. The significance of changes from baseline will be assessed using the Wilcoxon Signed-Rank Test.

Scatter plots of end of treatment values versus baseline values will be provided for all laboratory tests.

14.5.3 Vital Signs

At each visit, summary statistics for the absolute vital sign value and the changes from baseline will be presented by treatment group. The significance of changes from baseline will be assessed at the last visit, using the Wilcoxon Signed-Rank Test.

14.5.4 Other Variables Related to Safety

No further variables related to safety will be analysed.

14.6 Interim Analyses

No interim analysis is planned for this study.

15 QUALITY CONTROL AND QUALITY ASSURANCE AUDIT

15.1 Monitoring

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

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

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

15.2 Source Document Verification

On-site monitoring will also include source document verification (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, ECG tracings, laboratory results) contained in the patient records held at the investigational site, and thereby verified as accurate.

The Investigator must be aware that:

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

- Details of SAEs.

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

- Study number, brief description or title of study.
- Date that the patient gave written consent.
- All visit dates.
- All SAEs.
- All concomitant medications.

15.3 Audit

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

15.4 RB Policy on Fraud in Clinical Studies

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

16 ETHICS

16.1 Independent Ethics Committee/Institutional Review Board Review

Written approval of the study by an independent and appropriately constituted IEC/IRB must be obtained and a copy provided to RB before any protocol-related procedures that do not form part of the patient's normal clinical treatment are performed.

The approval letter must contain:

- Name and address of the IEC/IRB.
- Date of meeting.
- Sufficient information to identify the version of both the protocol and patient information/informed consent.
- Sufficient information to identify the version of other documents reviewed.

The investigator must also provide RB with a list of IEC/IRB members that includes each member's name, sex, and institutional affiliation.

The Investigator must submit all protocol amendments to the IEC/IRB for approval and notify them of any administrative changes.

16.2 Patient Information and Consent

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

16.3 Informing General Practitioners

Not applicable.

17 REGULATORY REQUIREMENTS

17.1 Competent Authority Authorisation

This study proposal was submitted to the SFDA and approved on 4 June 2010. The approval number is 2010L02452.

17.2 Curriculum Vitae

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

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

The Investigator and individuals to whom the Investigator has delegated some of his or her responsibilities as an investigator will be asked to provide sample signatures. The duties delegated to them will also be recorded on the signature and delegation of duties forms.

18 DATA HANDLING AND RECORD KEEPING

18.1 Case Report Forms (CRFs)

Electronic CRFs (eCRFs) will not be used in this study. The Investigator is responsible for the quality of the data recorded in the CRF. The data recorded should be a complete and accurate account of the patient's record collected during the study. The Investigator and study monitor will identify any data that will be recorded directly on the CRF such that the CRF will be considered the source document (i.e. no prior written or electronic record of the data). The study monitor will document this on the Initiation Visit Report.

The Investigator 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/No carbon required (NCR) CRFs before the first patient at that site is enrolled. The Investigator must review all entries for completeness and correctness. When changes or corrections are made on any paper/NCR CRF, the Investigator or authorised persons must draw a single line through the error then initial and date the correction, as well as stating the reason for the error, except

when due to a transcription error. The original entry should not be obscured. Data management will be conducted by Quintiles. The paper CRF / NCR CRF system will keep an audit trail of all changes made after the CRF pages are initially completed and submitted.

The Investigator agrees to complete and sign the CRFs in a timely fashion after completion of each patient and make them available to the study monitor for full inspection. In addition, any data queries prepared after the original CRF has been completed should be answered promptly. Following monitoring of each patient's paper CRF / NCR 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.

Before acceptance, the study monitor will review the CRFs for completeness and adherence to the protocol. If a paper CRF is being used, the top copy will be submitted to the organisation responsible for data management and a second copy will be retained by the Investigator in the Study Site File.

18.2 Retention of Essential Documentation

The Investigator should retain all essential documents (as defined in ICH E6 or according to other national and international regulations) until at least 5 years after the completion of the study. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with RB. It is the responsibility of RB to inform the Investigator when these documents no longer need to be retained.

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

18.3 Protocol Amendments

The investigator must abide by the agreed protocol as approved by the IEC/IRB.

No change will be made to the agreed protocol without the prior written approval of the Investigator, the Clinical Project Manager, the R&D Manager Clinical (Healthcare) and the Global Medical Director, except in circumstances where the immediate safety of the patient is at risk. Written approval will also be obtained from other functions if appropriate, for example the Statistician if the amendment relates to a change in endpoints.

All substantial protocol amendments require IEC/IRB and regulatory approval. Protocol amendments will be submitted to the same IEC/IRB and regulatory authority as the study protocol.

19 CLINICAL TRIAL AGREEMENT

Before the study commences, a Clinical Trial Agreement be will signed in which financial aspects of the study (including financial disclosure) as well as responsibilities and obligations are described. This will take the form of:

- A contract between [redacted] and the Investigator/healthcare organisation.

20 COMPENSATION, INDEMNITY AND INSURANCE

20.1 Compensation

Appropriate treatment and/or compensation will only be provided and/or paid to the patient by the Sponsor to the extent that a patient suffers injury or death directly attributable to participation in the study without:

- Fault on the part of the investigator or the CRO or its employees or agents.
- The investigator or the CRO failing to comply with the protocol.
- The investigator or the CRO failing to notify the Sponsor of the claim or denying the Sponsor full conduct of the claim.

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

20.2 Indemnity

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

20.3 Insurance

If required, and in accordance with applicable regulatory and legal requirements, RB will take out appropriate insurance policies on behalf of the Investigator and staff who conduct part or all of this study, and/or on behalf of the patients participating in the study.

21 REPORTING, PUBLICATION AND PRESENTATION

A clinical study report will be prepared according to ICH E3 (Structure and Content of Clinical Study Reports) as part of RB's commitment to Good Clinical Practice. The report will be a record of the total study conduct and findings, and will be subject to approval by the Co-ordinating Investigator who will sign the final report.

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

Any publication must state that it is a part of a multicentre study. Where it would be impractical to send the manuscript to every Investigator in a multicentre study, a copy will be sent to the Co-ordinating Investigator. In such a study, RB may wish to publish the results of the study and this may be done without all participants having the opportunity to review the manuscript.

22 REFERENCES

1. Vakil N, Veldhuyzen van Zanten S, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastro-esophageal reflux disease (GERD)- a global evidence-based concensus. Am J Gastrolenterol 2006, 101: 1900-1920.
2. Armstrong D. Systematic review: persistence and severity in gastroesophageal reflux disease. Aliment Pharmacol Ther 2008, 28: 841-853.
3. Liker H, Hungin AP, Wiklund I. Management of reflux disease in primary care: the subject perspective. J Am Boar Fam Pract 2005, 18: 393-400.
4. Wahqvist P, Reilly M, Barkun AN. Systematic review: the impact of gastro-oesophageal reflux disease on work productivity. Aliment Pharmacol Ther 2006, 24: 259-272.

5. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2005, 54: 710-717.

6. Kahrilas PJ, Howden CW, Hughes, N. Response of Regurgitation to Proton Pump Inhibitor Therapy in Clinical Trials of Gastroesophageal Reflux Disease. Am J Gastroenterol 2011, 106:1419–1425.

7. Moayyedi P, Delaney BC, Vakil N, Forman D, Talley NJ. The efficary of proton pump inhibitors in nonulcer dyspepsia: A systematic review and economic analysis. Gastroenterology 2004, 127: 1329-1337.

8. Fass R, Tougas G. Functional heartburn: The stimulus, the pain, and the brain. Gut 2002, 51: 885-892.

9. GA0916 data on file

23 APPENDICES

There are no appendices.

Reckitt Benckiser

PROTOCOL NON SUBSTANTIAL AMENDMENT NUMBER [1]

PRINCIPAL INVESTIGATOR:

[redacted]

China

DETAILS OF PROTOCOL AMENDMENT:

1. Section(s) to be Changed:

Section 5.1, Table 5.1 – Reckitt Benckiser Details, page 18

From:

Name	Position	Address and Contact Number
[redacted]	Clinical Project Manager	Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS. UK. [redacted]
[redacted]	Global Medical Director	Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS. UK. [redacted]
[redacted]	Senior Statistician	Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS. UK. [redacted]

Revised Paragraphs:

Name	Position	Address and Contact Number
[redacted]	Clinical Project Manager	Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS, UK, Telephone No: [redacted]
[redacted]	Reckitt Benckiser **Medical Officer**	Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull HU8 7DS. [redacted]
[redacted]	**Statistical Manager**	Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull HU8 7DS. Tel [redacted]

Reason for Change:

Change of the person responsible at the Sponsor Company for medical cover of the study.

2. Section(s) to be Changed:

pH Monitoring table footnote in Section 3.10, page 8 and Section 11.2, page 34

From:

Revised Paragraphs:

Addition of the following words "The timings in this table are for guidance only. For full details see GA1202 pH Monitoring Guidelines" as a footnote to the pH monitoring table.

Reason for Change:

Clarification that the timings for pH monitoring procedures are only used for guidance. The pH monitoring guidelines provide full details of the methods.

3. Section(s) to be Changed:

Section 12.2, Identity of Non-Investigational Medicinal Products, page 45

From:

Compound Sodium Alginate Double Action Chewable Tablets will be manufactured to Good Manufacturing Practice (GMP) by Reckitt Benckiser Healthcare (UK) Limited, Dansom Lane, Hull, HU8 7DS, UK (Product Licence 00063/0157).

The active treatment will be shipped to [redacted], where the Compound Sodium Alginate Double Action Chewable Tablets will be blister packed. The blister packs will be shipped to the Investigational Material Supplies Unit (IMSU), Reckitt Benckiser Healthcare UK Ltd, Dansom Lane, Hull, HU8 7DS UK.

Revised Paragraphs:

Compound Sodium Alginate Double Action Chewable Tablets will be manufactured and blister packed to Good Manufacturing Practice (GMP) by Reckitt Benckiser Healthcare (UK) Limited, Dansom Lane, Hull, HU8 7DS, UK (Product Licence 00063/0157).

The blister packs will be shipped to the Investigational Material Supplies Unit (IMSU), Reckitt Benckiser Healthcare UK Ltd, Dansom Lane, Hull, HU8 7DS UK.

Reason for Change:

The NIMP was to be manufactured at [redacted] but this was switched to Reckitt Benckiser Healthcare (UK) Ltd to utilise standard Gaviscon blister packs.

CTA (China) Number:	2010L02452
Trial Number:	GA1202
Protocol Title:	A multi-centred, randomised, open label, placebo-controlled, two-period crossover study to evaluate 4-hour esophageal pH change in GERD patients after administration of Compound Sodium Alginate Double Action Chewable Tablets or matching placebo tablets
Protocol Amendment Date:	4 Jun 2013
Version:	Final Version 2, Amendment 1
Phase:	III

Reviewed and Agreed by:

[redacted]

Clinical Project Manager
Reckitt Benckiser
Healthcare (UK) Limited

Statistical Manager
Reckitt Benckiser Healthcare
(UK) Limited

Reviewed and Approved by:

R&D Senior Manager (Health), Clinical:

Global Medical Director:

[redacted]

Reckitt Benckiser Medical Officer:

[redacted]

Reviewed and Accepted by:

Co-ordinating Principal Investigator:

[redacted]

China