Study Title: A Multi-centre, Randomised, Double-blind, Two Arm, Parallel Group, Placebo-controlled Study to Assess the Effect of Compound Sodium Alginate Double Action Chewable Tablets in Patients with Gastro-esophageal Reflux Disease

ClinicalTrials.gov ID: NCT01869491

Final Protocol, dated 28-Feb-2013

Reckitt Benckiser

1 STUDY PROTOCOL TITLE PAGE

CTA (China) Number:	2010L02452		
Study Number:	GA1210	**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-centre, randomised, double-blind, two arm, parallel group, placebo-controlled study to assess the effect of Compound Sodium Alginate Double Action Chewable Tablets in patients with gastro-esophageal reflux disease.		
Short Study Title:	Compound Sodium Alginate Double Action Chewable Tablet Symptomatic Relief Study.		
Protocol Date:	28 Feb 2013		
Protocol Version:	Final v 2.0		
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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3 PROTOCOL SYNOPSIS

3.1 Rationale

This study is being conducted to provide evidence for inclusion in applications to regulatory authorities that the Compound Sodium Alginate Double Action Chewable Tablets are effective in managing the symptoms of heartburn, acid regurgitation and dyspepsia in patients with GERD.

3.2 Objective(s)

The primary objective of this study is to assess the efficacy of Compound Sodium Alginate Double Action Chewable Tablets (mint-flavoured) compared with a matched placebo in reduction of the symptoms of GERD in patients with GERD as assessed using the Reflux Disease Questionnaire (RDQ).

The key secondary endpoint will compare between the two cohorts (Compound Sodium Alginate Double Action Chewable Tablets and matching placebo) for a 7-day treatment period for the following parameter:

- Change from baseline in RDQ scores for dyspepsia dimension

Other secondary endpoints will compare between the two cohorts (Compound Sodium Alginate Double Action Chewable Tablets and matching placebo) for a 7-day treatment period for the following parameters:

- OTE as a measure for patient's responsiveness/satisfaction
- Change from baseline in RDQ scores for heartburn dimension.
- Change from baseline in RDQ scores for regurgitation dimension.

Safety will be assessed in terms of the overall proportion of patients with adverse events (AEs).

3.3 Primary Endpoint

The primary study endpoint is to compare the change from baseline in RDQ symptom scores for the GERD dimension (heartburn and regurgitation) after a 7-day treatment period of a regimen of two Compound Sodium Alginate Double Action Chewable Tablets taken four times daily compared with a matched placebo.

3.4 Secondary Endpoints

The key secondary endpoint will compare between the two cohorts (Compound Sodium Alginate Double Action Chewable Tablets and matching placebo) for a 7-day treatment period for the following parameter:

- Change from baseline in RDQ scores for dyspepsia dimension

Other secondary endpoints will compare between the two cohorts (Compound Sodium Alginate Double Action Chewable Tablets and matching placebo) for a 7-day treatment period for the following parameters:

- OTE as a measure for patient's responsiveness/satisfaction
- Change from baseline in RDQ scores for heartburn dimension.
- Change from baseline in RDQ scores for regurgitation dimension.

Safety will be assessed in terms of the overall proportion of patients with adverse events (AEs).

3.5 Design Summary

This is a multi-centre, randomised, double blind, two arm, placebo-controlled, parallel group, study. After signing a written informed consent, patients will undergo a screening period of up to 7 days. Patients who satisfy the study entry requirements within 7 days of consent, will be randomised to receive either Compound Sodium Alginate Double Action Chewable Tablets (2 tablets four times daily) or matching placebo tablets (2 tablets four times daily), for a 7-day treatment period. At the beginning and end of the treatment period, patients will be required to complete the RDQ.

In addition, at the end of the 7-day treatment period, patients will be required to complete the overall treatment evaluation (OTE).

3.6 Sample Size

The sample size calculation, based on the UK pilot study date [10] and a previous pivotal China study, shows that 1054 evaluable patients need to complete the study (with the aim of having approximately 527 patients in each treatment group). An evaluable patient is defined as a randomised patient who completes the study treatment period and attends the end of treatment visit. In order to achieve this, it is estimated that approximately 1222 patients will have to be screened and approximately 1100 patients will have to be randomised.

Patients will receive a screening number on signing the informed consent. Patients will receive a separate randomisation number on being randomised to the study.

It is anticipated that between 25 and 50 sites will take part in the study. Each site will be asked to recruit between 10 and 200 patients.

3.7 Anticipated Study Timings

It is estimated that it will take 9 months to recruit the required number of patients.

The duration of each patient's participation in the study will be a maximum of 17 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 7 days will be allowed to screen a patient at Visit 1. If eligible, the patient will be randomised and will commence the 7-day treatment period at Visit 2 (Day 0).

The patients will be randomised to receive either Compound Sodium Alginate Double Action Chewable Tablets or matching placebo tablets for 7 days. Visit 3, the End of study visit, will occur on Day 8 (between Day 7 and Day 10).

The anticipated overall duration of study conduct is expected to be approximately one year.

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 to ≦ 65 years

3. Sex: male or female.

4. Primary diagnosis: Current evidence of symptomatic GERD in accord with the Montreal definition [1,14]. This evidence can be based solely on symptom characteristics. Patients should have a GERD history of frequent episodes of GERD-related symptoms during the last 3 months and also during 5 of the last 7 days prior to study screening.

5. GERD Status: Patients will be patients at the clinic or members of the public who respond to an advertisement or via their doctor. Patients must have had troublesome heartburn and/or regurgitation (with or without dyspepsia symptoms) of at least mild or moderate intensity* on at least five days during the week before the start of screening. If the patient also has other symptoms, the heartburn, regurgitation or dyspepsia should be the predominant symptoms.

   *Symptom intensity should be assessed using the following scale;

   - Mild: awareness of symptom but easily tolerated
   - Moderate: discomforting symptom sufficient to cause interference with normal activities including sleep
   - Severe: incapacitating symptom with inability to perform normal activities, including sleep

6. Patients who have not taken any antacids within 24 hours before randomisation (Visit 2) and be instructed not to take antacids 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 must be sufficiently literate to be able to complete the RDQ unaided.

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 and/or discovered on endoscopy 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 were observed on endoscopy 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 diseases 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

Patients will be recruited by the investigator from out-patient clinics, from the hospital database or those patients who respond to advertising. Patients suffering from mild to

moderate symptoms of GERD and who meet all eligibility criteria will be given the opportunity by the investigator to participate in the study.

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 the patient may have. If the patient feels fully informed and happy 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 subject for their personal records.

All patients will be given a 5-digit screening number once they have provided consent. The first two digits will refer to the centre number and the second three digits to the number of patients screened at that centre. For example, screening numbers at centre 01 will start 01001, 01002 etc.

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

The following baseline assessments (Visit 1, screening) will be conducted: demographics, laboratory safety data (haematology & biochemistry), vital signs (blood pressure and heart rate), 12-lead ECG, endoscopy, medical history and current status, medication and therapy history, physical examination and pregnancy testing (women of child-bearing potential will undergo urine pregnancy testing).

At the end of the screening period, patients will return to the clinic (Visit 2, Randomisation) to complete the RDQ questionnaire and have any adverse events and concomitant medications recorded. If the subject fulfils the eligibility criteria for randomisation, a unique 4-digit randomisation number will be allocated and study medication dispensed (0001, 0002 etc.). The numbers available at a site have to be allocated to the subjects in consecutive order. Patients will be instructed to start taking their medication the following day for seven days (two tablets taken four times a day: 30 minutes after breakfast, 30 minutes after lunch, 30 minutes after dinner and immediately before lying down for bed).

Visit 3 will take place preferably on the day following completion of 7-days of study treatment, ie, Day 8, or if necessary up to one day before and 2 days after (Day 7 to Day 10). At this visit, the patient will complete the RDQ questionnaire and answer questions relating to overall satisfaction with the trial therapy (OTE) over the previous seven days. All unused and empty study medication containers will be returned for assessment of compliance with treatment. The following will be completed: vital signs (blood pressure and heart rate) concomitant medication, adverse events, physical examination, laboratory

investigations (haematology and biochemistry) and pregnancy testing (women of child-bearing potential will undergo urine pregnancy testing).

The patient will be instructed to return to the investigator before the end of treatment if they require further treatment for their GERD symptoms or have unacceptable adverse events. If the investigator withdraws the patient from the study for these or any other reasons the patient will complete the study at this early termination visit and the following will be completed.

The patient will complete the RDQ questionnaire and answer questions relating to overall satisfaction with the trial therapy (OTE) over the study treatment period. All unused and empty study medication containers will be returned for assessment of compliance with treatment. The following will also be completed: vital signs (blood pressure and heart rate), concomitant medication, adverse events, physical examination, laboratory investigations (haematology and biochemistry), pregnancy testing (women of child-bearing potential will undergo urine pregnancy testing) and reason for early study termination.

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

Schedule	FLOW CHART OF STUDY			
Study period	Visit 1 Screening (up to 7 days)	Visit 2 Randomisation (Day 0)	Visit 3 End of study (Day 8) (between Day 7 and Day 10)	Visit ET Replaces Visit 3 if early termination (Day 1 to 6)
Informed consent	X			
Assess inclusion-/exclusion criteria and suitability for study	X	X		
Record demographics, assess concomitant medication and relevant medical history	X	X		
Physical exam, collection of blood samples for haematology & biochemistry, vital signs	X		X	X
Urine pregnancy test	X		X	X
12-lead ECG	X			
Endoscopy	X			
Investigator's assessment of GERD status	X			
Make appointment for next visit	X	X		
Randomisation		X		
Dispense study medication & emergency card provided		X		
Patient completes RDQ questionnaire.		X	X	X
Record AEs and concomitant medication		X	X	X
Collect returned medication, assess compliance with study medication.			X	X
Complete OTE			X	X

3.11 Statistics

Sample size

In a previous pilot study conducted in the UK (GA1203), a least square mean difference (Gaviscon – Placebo) of -0.61 was obtained from the ANCOVA model comparing the change in the GERD dimension score from the RDQ after 1 week. The root mean squared error (RMSE) from the ANCOVA model, which included treatment as a fixed effect and the day 0 RDQ GERD dimension score as a covariate, was 0.9735.

In the same study, a least square mean difference (Gaviscon – Placebo) of -0.43 was obtained from the ANCOVA model comparing the change in the Dyspepsia dimension score from the RDQ after 1 week. The root mean squared error (RMSE) from the ANCOVA model, which included treatment as a fixed effect and the day 0 RDQ Dyspepsia dimension score as a covariate, was 1.121.

For the purposes of sample size estimation using the module for a two-group t-test between equal means in NQuery Advisor 7.0, the least square means difference and RMSE from GA1203 will be used to estimate the effect sizes. The effect sizes using these results would be estimated as 0.627 for the GERD dimension and 0.384 for the Dyspepsia dimension.

In other previous studies, different endpoints to the RDQ were used to demonstrate the efficacy of Gaviscon Original Liquid compared to Placebo Liquid. The percentage of patients that rated a positive improvement in symptoms were reported. In a study conducted in the UK (0900901), 74% of Gaviscon Original patients had a positive improvement of symptoms compared to only 44% of Placebo patients. When a similar study was conducted in China (GA0917), the corresponding results were 77% for Gaviscon Original and 67% for Placebo, thus suggesting an increased Placebo effect in the Chinese population compared to the UK population.

Assuming a reduced effect size of 0.2 for the Dyspepsia dimension, this would require a total of 1054 patients with evaluable dyspepsia data from the RDQ to have 90% power to show a statistical significant difference at the 5% level using a two-group t-test. The actual analysis method to be used would be an ANCOVA model with treatment as a fixed effect, centre as a random effect and the day 0 RDQ Dyspepsia dimension score as a covariate.

If an effect size of 0.4 is assumed for the GERD dimension, a sample size of 1054 patients would give more than 99% power to show a statistical significant difference at the 5% level using a two-group t-test. The actual analysis method to be used would be an ANCOVA model with treatment as a fixed effect, centre as a random effect and the day 0 RDQ GERD dimension score as a covariate.

To allow for 5% drop outs, 1100 patients will be randomised to ensure that 1054 patients have evaluable data for the Dyspepsia dimension score.

Statistical analysis

All statistical tests performed will be 2-tailed with significance assessed at the 5% significance level. The null hypothesis at all times will be the equality of the treatments being compared.

The primary endpoint (change in RDQ GERD dimension score) will be analysed using an analysis of covariance (ANCOVA) model with a fixed effect term for treatment, centre as a random effect and the day 0 RDQ GERD dimension score as a covariate. Treatment group differences will be estimated using the least square means and presented with 95% confidence intervals and p-values to make inferences.

The change in symptom score for each dimension seperately will be analysed identically to the primary endpoint although the included covariate will be the relevant dimension day 0 score rather than the GERD dimension score.

To preserve the type 1 error rate of 5% for the key secondary endpoint (change from day 0 in RDQ scores for dyspepsia dimension), a closed testing procedure will be applied. A significant comparison at the 5% level ($p<0.05$) for this key secondary endpoint will only be deemed as confirmatory evidence if the primary endpoint is also significant at the 5% significance level ($p<0.05$). All other secondary endpoints and/or any further sensitivity or alternate analyses for the primary and key secondary endpoint will serve as supportive evidence only and therefore no further adjustment for multiple comparisons will be made.

The change scores in frequency and intensity for each dimension as well as the two OTE responses will be compared between treatments using a Wilcoxon Rank Sum Test stratified by centre.

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 Fisher's Exact Test for all AEs, for those AEs classified by the Investigator as possibly or probably related to IMP and for severe AEs.

4 TABLE OF CONTENTS

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

4.2 List of 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
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
GERD	Gastro-esophageal reflux disease
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GVG	Global Vigilance Group
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
ITT	Intent-to-Treat
NIMP	Non-investigational Medicinal Product
NSAIDs	Non Steroidal Anti-Inflammatory Drugs
OTC	Over-the-counter
OTE	Overall Treatment Evaluation

Abbreviation	Abbreviation in Full
PFDA	Provincial Food and Drug Administration (China)
PPI	Proton pump inhibitor
PRO	Patient Reported Outcome
QA	Quality Assurance
QC	Quality Control
RDQ	Reflux Disease Questionnaire
R&D	Research and Development
RB	Reckitt Benckiser
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SFDA	State Food and Drug Administration (China)
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]
[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]

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. It is anticipated that approximately 30 hospital centres will participate in this study.

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 include antacids, proton pump inhibitors (PPIs) and histamine H2-receptor antagonists. While PPIs are effective in acid-related conditions, they offer limited benefit for patients whose symptoms are more related to regurgitation [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 medicinal 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 dyspepsia and heartburn. This effect is increased by the addition of sodium bicarbonate which also has a neutralising action. The total neutralising capacity of the product at the lowest dose of two tablets is approximately 10 mEqH+. Compound Sodium Alginate Double Action Chewable Tablets are given as two to four tablets four times daily; the minimum dose of two tablets four times daily has been selected to be studied.

No pivotal clinical studies have previously been performed with Compound Sodium Alginate Double Action Chewable Tablets to demonstrate relief of symptoms of reflux and dyspepsia in patients with GERD. A symptom relief pilot study in 110 patients with GERD was conducted in the UK to provide sufficient data to inform the protocol for this study. The pilot study demonstrated the study design was suitable and robust, and that the Reflux Disease Questionnaire (RDQ) [9] was a suitable Patient Reported Outcome (PRO) for use in assessing symptom relief in GERD and dyspepsia. No safety signals or issues were identified in the pilot study [10].

This study design is based on the pilot study and will examine the efficacy of Compound Sodium Alginate Double Action Chewable Tablets compared with matching placebo in treating the symptoms of reflux and dyspepsia in patients with GERD.

The potential risks to patients taking part in the present study are considered to be low. The adverse reactions that occur very rarely (<1/10,000) as a result of taking Compound Sodium Alginate Double Action Chewable Tablets and other 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 provide evidence for inclusion in applications to regulatory authorities that the Compound Sodium Alginate Double Action Chewable Tablets are effective in managing the symptoms of heartburn, acid regurgitation and dyspepsia in patients with GERD.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of this study is to assess the efficacy of Compound Sodium Alginate Double Action Chewable Tablets (mint-flavoured) compared with a matched placebo in reduction of the symptoms of GERD in patients with GERD as assessed using the Reflux Disease Questionnaire (RDQ).

8.2 Secondary Objective(s)

The secondary objectives of this study are to assess the efficacy of Compound Sodium Alginate Double Action Chewable Tablets compared with matching placebo in reduction of the symptoms of heartburn, acid regurgitation and dyspepsia in patients with GERD. Other secondary objectives include the efficacy of Compound Sodium Alginate Double Action Chewable Tablets compared with placebo in patient responsiveness / satisfaction and comparison of safety in terms of adverse events.

9 STUDY DESIGN

9.1 Study Endpoints

9.1.1 Primary Endpoint

The primary study endpoint is to compare the change from baseline in RDQ symptom scores for the GERD dimension (heartburn and regurgitation) after a 7-day treatment period of a regimen of two Compound Sodium Alginate Double Action Chewable Tablets taken four times daily compared with a matched placebo.

9.1.2 Secondary Endpoints

The key secondary endpoint will compare between the two cohorts (Compound Sodium Alginate Double Action Chewable Tablets and matching placebo) for a 7-day treatment period for the following parameter:

- Change from baseline in RDQ scores for dyspepsia dimension

Other secondary endpoints will compare between the two cohorts (Compound Sodium Alginate Double Action Chewable Tablets and matching placebo) for a 7-day treatment period for the following parameters:

- OTE as a measure for patient's responsiveness/satisfaction
- Change from baseline in RDQ scores for heartburn dimension.
- Change from baseline in RDQ scores for regurgitation dimension.

Safety will be assessed in terms of the overall proportion of patients with adverse events (AEs).

9.2 Design Summary

This is a multi-centre, randomised, double blind, two arm, placebo-controlled, parallel group, study. After signing a written informed consent, patients will undergo a screening period of up to 7 days. Patients who satisfy the study entry requirements within 7 days of consent, will be randomised to receive either Compound Sodium Alginate Double Action Chewable Tablets (2 tablets four times daily) or matching placebo tablets (2 tablets four times daily), for

a 7-day treatment period. At the beginning and end of the treatment period, patients will be required to complete the RDQ.

In addition, at the end of the 7-day treatment period, patients will be required to complete the overall treatment evaluation (OTE).

9.3 Discussion of Study Design

The primary endpoint and some of the secondary endpoints are assessed using information collected in the Reflux Disease Questionnaire (RDQ). The choice of the RDQ is based on this being a validated questionnaire which collects patient assessments of their heartburn, acid regurgitation and dyspepsia. The RDQ is validated in English (Appendix 1) and Chinese Mandarin (Appendix 2). It comprises a 12-item self-administered questionnaire which was designed to assess the frequency and severity of heartburn, acid regurgitation and dyspepsia symptoms. The heartburn and acid regurgitation subscales can be combined into a GERD dimension [9]. Response options are scaled as Likert-type with scores ranging from 0 to 5 for frequency (not present to daily) and severity (not present to severe).

Other secondary endpoints are assessed using the Overall Evaluation of Treatment (OTE). The OTE is a validated scale that rates the overall change in clinical status on a 15-point scale (-7 to -1 = worse; 0 = no change or about the same; and +1 to +7 = better). It then categorises the change with a second question asking how patients perceive the importance of the change on a 7-point scale from: 1 = not important, 2 = slightly important, 3 = somewhat important, 4 = moderately important, 5 = important, 6 = very important, 7 = extremely important [11-13].

9.4 Number of Patients

The sample size calculation, based on the UK pilot study date [10] and a previous pivotal China study, shows that 1054 evaluable patients need to complete the study (with the aim of having approximately 527 patients in each treatment group). An evaluable patient is defined as a randomised patient who completes the study treatment period and attends the end of treatment visit. In order to achieve this, it is estimated that approximately 1222 patients will have to be screened and approximately 1100 patients will have to be randomised.

Patients will receive a screening number on signing the informed consent. Patients will receive a separate randomisation number on being randomised to the study.

It is anticipated that between 25 and 50 sites will take part in the study. Each site will be asked to recruit between 10 and 200 patients.

Further details are provided in Section 14.1.

9.5 Study Duration

It is estimated that it will take 9 months to recruit the required number of patients.

The duration of each patient's participation in the study will be a maximum of 17 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 7 days will be allowed to screen a patient at Visit 1. If eligible, the patient will be randomised and will commence the 7-day treatment period at Visit 2 (Day 0).

The patients will be randomised to receive either Compound Sodium Alginate Double Action Chewable Tablets or matching placebo tablets for 7 days. Visit 3, the End of study visit, will occur on Day 8 (between Day 7 and Day 10).

The anticipated overall duration of study conduct is expected to be approximately one year.

9.6 Patient Commitment to the Study

9.6.1 Duration of Patient Participation

Up to 7 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, endoscopy, 12-lead ECG, haematology and biochemistry 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 7 days after Visit 1. Patients will be required to complete a baseline RDQ which will ask the patient to rate their symptoms over the previous 7 days and have any adverse events and concomitant medications recorded. Patients meeting the entry criteria will be randomised and then issued with either Compound Sodium Alginate Double Action Chewable Tablets or matching placebo tablets to take for 7 days.

At Visit 3, End of treatment period (Day 8, between Day 7 and day 10), unused investigational medicinal product (IMP) will be collected. Patients will be required to complete the RDQ questionnaire and OTE (overall treatment evaluation) as a measure of the responsiveness to the study therapy and undergo assessment by the Investigator for

compliance and safety (AEs, haematology and clinical biochemistry and urine pregnancy test for female patients).

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 biochemistry at Visit 1 and Visit 3. The volume of blood samples for a patient will not exceed 30 ml in total for all visits.

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.

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.

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 to ≦ 65 years
3. Sex: male or female.
4. Primary diagnosis: Current evidence of symptomatic GERD in accord with the Montreal definition [1,14]. This evidence can be based solely on symptom characteristics. Patients should have a GERD history of frequent episodes of GERD-related symptoms during the last 3 months and also during 5 of the last 7 days prior to study screening.
5. GERD Status: Patients will be patients at the clinic or members of the public who respond to an advertisement or via their doctor. Patients must have had troublesome heartburn and/or regurgitation (with or without dyspepsia symptoms) of at least mild or moderate intensity* on at least five days during the week before the start of screening. If the patient also has other symptoms, the heartburn, regurgitation or dyspepsia should be the predominant symptoms.

   *Symptom intensity should be assessed using the following scale;

   - Mild: awareness of symptom but easily tolerated
   - Moderate: discomforting symptom sufficient to cause interference with normal activities including sleep
   - Severe: incapacitating symptom with inability to perform normal activities, including sleep
6. Patients who have not taken any antacids within 24 hours before randomisation (Visit 2) and be instructed not to take antacids 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 must be sufficiently literate to be able to complete the RDQ unaided.

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 and/or discovered on endoscopy 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 on endoscopy 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 diseases 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.

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 by the investigator from out-patient clinics, from the hospital database or those patients who respond to advertising. Patients suffering from mild to moderate symptoms of GERD and who meet all eligibility criteria will be given the opportunity by the investigator to participate in the study.

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.

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

Table 11-1 Schedule of Assessments

Schedule	FLOW CHART OF STUDY			
Study period	Visit 1 Screening (up to 7 days)	Visit 2 Randomisation (Day 0)	Visit 3 End of study (Day 8) (between Day 7 and Day 10)	Visit ET Replaces Visit 3 if early termination (Day 1 to 6)
Informed consent	X			
Assess inclusion-/exclusion criteria and suitability for study	X	X		
Record demographics, assess concomitant medication and relevant medical history	X	X		
Physical exam, collection of blood samples for haematology & biochemistry, vital signs	X		X	X
Urine pregnancy test	X		X	X
12-lead ECG	X			
Endoscopy	X			
Investigator's assessment of GERD status	X			
Make appointment for next visit	X	X		
Randomisation		X		
Dispense study medication & emergency card provided		X		
Patient completes RDQ questionnaire.		X	X	X
Record AEs and concomitant medication		X	X	X
Collect returned medication, assess compliance with study medication.			X	X
Complete OTE			X	X

* Previous endoscopy results may be used if conducted prior to consent within 28 days of giving consent and if the examination was conducted at the same hospital

** OTE: Overall Treatment Evaluation.

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 the patient may have. If the patient feels fully informed and happy to participate in the study then 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 5-digit screening number once they have provided consent. The first two digits will refer to the centre number and the second three digits to the number of patients screened at that centre. For example, screening numbers at centre 01 will start 01001, 01002 etc.

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

11.3.1.1 Clinical Assessments Performed at Baseline

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

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
- Biochemistry
- Details are listed in section 13.4

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
- GERD status as assessed by the investigator

Medication and therapy history:

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

Physical examination

- A standard physical examination will be conducted

Pregnancy testing

- Women of child-bearing potential will undergo urine pregnancy testing. Pregnancy tests will be performed with urine pregnancy kits using standard urine pregnancy testing methods.

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.

11.3.2 Clinical Assessments Performed After Baseline

11.3.2.1 Clinical Assessments at Visit 2

At the end of the screening period, within 7 days of consent, patients will return to the clinic to complete the RDQ questionnaire and have any changes in medical history and concomitant medications recorded.

If the patient fulfils the eligibility criteria (check inclusion / exclusion criteria) for randomisation, a unique 4-digit randomisation number will be allocated and study medication dispensed (0001, 0002 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 will be allocated to the patients in consecutive order. Patients will be instructed to start taking their medication the following day for seven days (two tablets taken four times a day: 30 minutes after breakfast, 30 minutes after lunch, 30 minutes after dinner and immediately before lying down for bed). Patients will be instructed to chew tablets thoroughly and swallow. 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.

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 either two Compound Sodium Alginate Double Action Chewable Tablets or two matching placebo tablets four times per day.
- Instructions to non-investigator staff to ring a 24-hour telephone number in case of emergency. This will be the number of the investigator site.

11.3.2.2 Clinical Assessments at Visit 3, End of Treatment

Visit 3 will take place preferably on the day following completion of 7-days of study treatment, ie, Day 8, or if necessary up to 1 day before and 2 days after that (Day 7 to Day 10). At this visit, the patient will complete the RDQ questionnaire and answer questions relating to overall satisfaction with the trial therapy (OTE) over the previous seven days. All unused and empty study medication containers will be returned for assessment of compliance with treatment. 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 medicines will be recorded.

Adverse Events

- All adverse events will be recorded.

Physical examination

- A standard physical examination will be conducted.

Laboratory investigations

- Haematology
- Biochemistry

- 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)

The patient will be instructed to return to the investigator before the end of treatment if they require further treatment for their GERD symptoms or have unacceptable adverse events. Early termination applies to study Days 1 to 6. If the investigator withdraws the patient from the study for these or any other reasons the patient will complete the study at this early termination visit and the following will be completed.

The patient will complete the RDQ questionnaire and answer questions relating to overall satisfaction with the trial therapy (OTE) over the study treatment period. All unused and empty study medication containers will be returned for assessment of compliance with treatment. 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 medicines will be recorded.

Adverse Events

- All adverse events will be recorded.

Physical examination

- A standard physical examination will be conducted.

Laboratory investigations

- Haematology
- Biochemistry
- 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.

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 RDQ. OTE is also a secondary efficacy variable.

11.4.1.2 Methods of Assessment of Efficacy Variables

The following assessments of symptoms will be used:

- RDQ (Appendix 1 & 2) is a self-assessed patient questionnaire which is designed to measure and evaluate specific GERD symptoms of heartburn, regurgitation and dyspepsia. The items that constitute the three dimensions of heartburn, regurgitation and dyspepsia are listed in Table 1 (Sub-dimensions of the symptoms). The Scoring system of the RDQ is shown in the Table 2 (Scoring system of RDQ).

Table 1. Sub-dimensions of the symptoms		
Regurgitation	Heartburn	Dyspepsia
Acid in the mouth.	Burning behind the breastbone.	Burning in the upper stomach.
Unpleasant movement of material upwards from the stomach.	Pain behind the breastbone.	Pain in the upper stomach.

Table 2. Scoring system of RDQ		
Score	Frequency	Intensity/Severity
0	None	None
1	Less than one day a week	Very mild
2	Once day a week	Mild
3	2-3 days a week	Moderate
4	4-6 days a week	Moderately severe
5	Daily	Severe

The Overall Treatment Evaluation (OTE): patients will be prompted by the question “Thinking over the last 7 days and the medication you received, how would you rate the change in your symptoms?” and “How important was the change in the symptoms to you?”.

11.4.2 Appropriateness of Measurements

The RDQ is an accepted reflux disease questionnaire that also assesses dyspepsia and is therefore an appropriate method of assessing the efficacy of Compound Sodium Alginate Double Action Chewable Tablets on symptoms of GERD and dyspepsia in this study. It has been validated in Chinese Mandarin and is therefore appropriate for use in this study.

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 medication and 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.
- Randomisation code is broken.

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; 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.

If a patient is withdrawn prematurely from the study, the assessments listed in section 11.3.2.3 will be carried out.

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

Treatment compliance will be assessed on the basis of tablet counts. Patients will be instructed to bring their unused IMP and any empty containers with them at each visit. For the time period between each visit, the number of unused tablets returned will be recorded. For the entire treatment period of the study, the proportion of tablets taken relative to the expected number of tablets that should have been taken will be calculated. A compliance to IMP intake of less than 75% will be considered a major protocol deviation. Patients with compliance of less than 75% will be excluded from the per protocol population.

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 in writing and provide a copy to RB for filing in the TMF. [redacted] inform the SFDA within 15 days of the date of termination of the study 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 treatments will be shipped to [redacted] where both 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.

Labels and all packaging will be matching for both active and placebo packs and will not identify which of the two treatments (active or placebo) the patient's pack contains.

12.2 Identity of Non-Investigational Medicinal Products

NIMPs are not used in this study.

12.3 Randomisation and Treatment Allocation

12.3.1 Randomisation

Drug supplies will be randomised by the RB Investigational Material Supply Unit, according to a computer-produced randomisation schedule. On entry, patients will be allocated a unique patient number in numerical sequence based on the patient numbers supplied to that site. Issue of the IMP at the site in this numerical sequence will ensure correct randomisation.

The IMSU will hold the master code for the randomisation schedule and will supply the Investigator with the randomisation code for each patient as individually sealed envelopes. The code will only be broken for an individual patient in an emergency such as a serious AE (SAE) for which it is necessary to know the study treatment in order that the SAE be treated appropriately. If the code for a patient is broken, the Investigator should withdraw the patient from the study, document the details of the event in the patient's CRF and promptly inform

the RB/[redacted] Clinical Project Manager. If, for any reason, the code is broken the patient will be withdrawn from the study.

The [redacted] study monitor will check the randomisation code-break envelopes on a regular basis at monitoring visits, to ensure the above procedures are being followed. All code-break envelopes, whether sealed or opened, will be returned to RB at the end of the study.

[redacted] will break the code for all patients only after all data queries have been answered and the database has been locked.

12.3.2 Blinding

The study is blinded using matching placebo and active tablets, identically packaged and labelled.

12.3.3 Emergency Unblinding Procedures

The randomisation code envelopes will be provided to the unit providing a 24 hour blind breaking service (either Investigator Unit or Pharmacy).

The randomisation code will only be broken for an individual patient in an emergency such as an SAE that requires knowledge of which IMP was taken so that the SAE can be treated appropriately. If the code for a patient is broken, the Investigator must withdraw the patient from the study, document the details of the event in the patient's CRF, and promptly inform the RB and [redacted] Clinical Project Managers.

12.3.4 IMP allocation for Replacement Patients

Patients will not be replaced.

12.4 Dosage Instructions

Each patient will be instructed to thoroughly chew and swallow Compound Sodium Alginate Double Action Chewable Tablets or matching placebo tablets as a multiple dose regimen. Prior to dosing, all patients will be instructed by the Investigator on how they will take the

medication, ie, on each occasion take two tablets simultaneously, thoroughly chew and swallow both tablets. Patients will be instructed to start taking their medication the day after their randomisation visit for seven days (two tablets taken four times a day: 30 minutes after breakfast, 30 minutes after lunch, 30 minutes after dinner and immediately before lying down for bed).

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

- Medication errors involving subject 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 subject.

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 Packaging

Sufficient IMP supplies will be packaged and labelled initially for 2000 patients (1000 patients per treatment group). This will allow for the initial allocation of 60 patients to each site. Each patient pack will contain 64 tablets (allowing 7 days study treatment and one days' overage).

12.6 Labelling

12.6.1 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 will be labelled and each blister pack in the patient pack will be labelled.

12.6.2 Non-Investigational Medicinal Products

NIMPs are not used in this study.

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

The Investigator will keep all IMPs 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 IMPs 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 IMPs to any person except study personnel and patients enrolled in this study.

The study drug 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 a daily basis on working days. The temperature log will be reviewed by the study monitor.

12.8 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).

12.9 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) 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.

12.10 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 / symptoms, 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.

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 IMP 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 AR's. 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 AR's 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's 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's 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

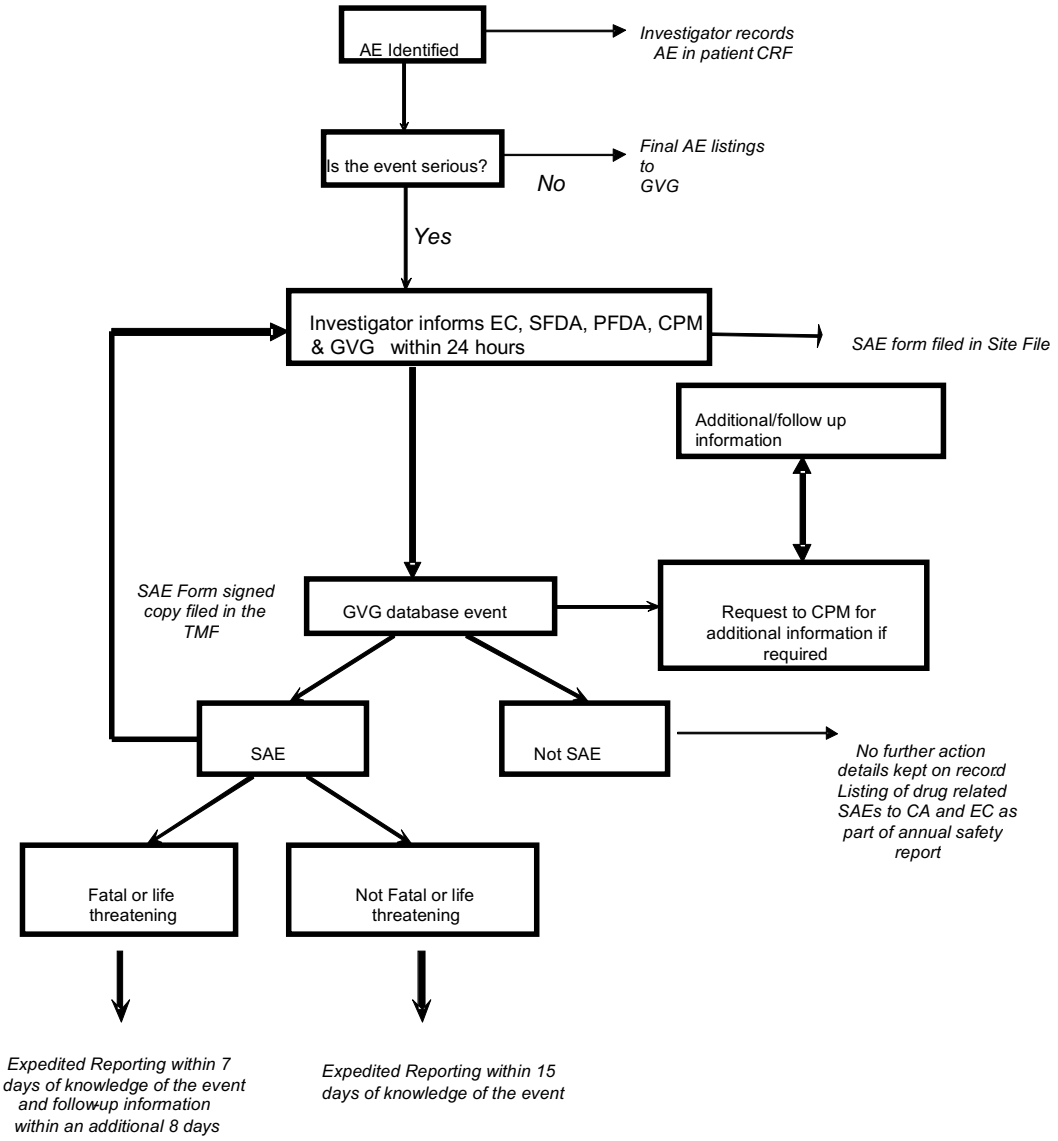
2. All other investigators participating in the study will be informed by the CPM

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 (refer to Adverse Event Reporting section 13.1.4 for further details).

13.2 Overdose

In the event of an overdose of the trial medication, symptomatic treatment should be given. The patient may notice abdominal distension.

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 an 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 screening 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 screening 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 code for all patients is broken 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

In a previous pilot study conducted in the UK (GA1203), a least square mean difference (Gaviscon – Placebo) of -0.61 was obtained from the ANCOVA model comparing the change in the GERD dimension score from the RDQ after 1 week. The root mean squared error (RMSE) from the ANCOVA model, which included treatment as a fixed effect and the day 0 RDQ GERD dimension score as a covariate, was 0.9735.

In the same study, a least square mean difference (Gaviscon – Placebo) of -0.43 was obtained from the ANCOVA model comparing the change in the Dyspepsia dimension score from the RDQ after 1 week. The root mean squared error (RMSE) from the ANCOVA model, which included treatment as a fixed effect and the day 0 RDQ Dyspepsia dimension score as a covariate, was 1.121.

For the purposes of sample size estimation using the module for a two-group t-test between equal means in NQuery Advisor 7.0, the least square means difference and RMSE from GA1203 will be used to estimate the effect sizes. The effect sizes using these results would be estimated as 0.627 for the GERD dimension and 0.384 for the Dyspepsia dimension.

In other previous studies, different endpoints to the RDQ were used to demonstrate the efficacy of Gaviscon Original Liquid compared to Placebo Liquid. The percentage of patients that rated a positive improvement in symptoms were reported. In a study conducted in the UK (0900901), 74% of Gaviscon Original patients had a positive improvement of symptoms compared to only 44% of Placebo patients. When a similar study was conducted in China (GA0917), the corresponding results were 77% for Gaviscon Original and 67% for Placebo, thus suggesting an increased Placebo effect in the Chinese population compared to the UK population.

Assuming a reduced effect size of 0.2 for the Dyspepsia dimension, this would require a total of 1054 patients with evaluable dyspepsia data from the RDQ to have 90% power to show a statistical significant difference at the 5% level using a two-group t-test. The actual analysis method to be used would be an ANCOVA model with treatment as a fixed effect, centre as a random effect and the day 0 RDQ Dyspepsia dimension score as a covariate.

If an effect size of 0.4 is assumed for the GERD dimension, a sample size of 1054 patients would give more than 99% power to show a statistical significant difference at the 5% level using a two-group t-test. The actual analysis method to be used would be an ANCOVA model with treatment as a fixed effect, centre as a random effect and the day 0 RDQ GERD dimension score as a covariate.

To allow for 5% drop outs, 1100 patients will be randomised to ensure that 1054 patients have evaluable data for the Dyspepsia dimension score.

14.2 Data to be Analysed

The following defined populations will be used for the analysis of the study data.

All patient population: includes all patients recruited into the study. Data presentation will comprise information on patient disposition, withdrawals and protocol deviations as well as baseline data.

Safety population: includes those recruited into the study and receive at least one dose of the study medication. Summaries and analyses for all safety endpoints will be conducted on this population.

Intent to treat (ITT) population: includes those recruited into the study and have at least partially completed RDQ questionnaire for the trial therapy period or are known to have withdrawn from the study due to poor efficacy. Summaries and analyses for all primary and secondary endpoints will be conducted on this population.

Per protocol (PP) population: includes all patients from the ITT population who have adequate compliance with the treatment during the study (defined as $\geq$ 75% study medication used from return tablet count) and no major protocol deviations. This PP population will be defined based upon a review of blinded data prior to database lock. All summaries and analyses for all primary and secondary endpoints will be additionally conducted using this population to support the corresponding ITT results.

If there is a discrepancy in patient numbers between the all patient population and any other population, then baseline data will be summarised additionally for that population and for those patients that are excluded from that population.

14.3 Patient Disposition and Characteristics

Descriptive summary statistics will be provided for demographic characteristics for each treatment 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 demographic category will be provided.

14.4 Efficacy Analyses

Efficacy data will be recorded from the RDQ questionnaire and the patient overall treatment evaluation (OTE).

All efficacy data will be listed in the appendices of the study report and summarised for the ITT and PP populations by treatment group (n as the number of observations, mean, median, SD, minimum and maximum). Categorical variables will be summarised by treatment group using frequency distributions (showing cell frequencies and percentages).

For those patients that do not return for Visit 3 because of confirmed poor efficacy from the treatment between Day 1 and Day 6, all efficacy data at Visit 3 will be imputed as no change from the day 0 values (BOCF). All other withdrawn patients that do not have the reason of withdrawal confirmed as poor efficacy and do not complete the Visit 3 assessments will be treated as missing. If the number of such patients is high, a sensitivity analysis will be conducted to assess the robustness of this imputation and the effect on results.

14.4.1 Primary Efficacy Analysis Endpoint

The primary study endpoints are to compare the change from day 0 in RDQ symptom scores for the GERD dimension (heartburn and regurgitation) after a 7-day treatment period of a regimen of two Compound Sodium Alginate Double Action Chewable Tablets taken four times daily compared with a matched placebo.

14.4.2 Secondary Efficacy Endpoints

The key secondary endpoint will compare between the two cohorts (Compound Sodium Alginate Double Action Chewable Tablets and placebo) for a 7-days treatment period for the following parameter:

- Change from day 0 in RDQ scores for dyspepsia dimension

Other secondary endpoints will compare between the two cohorts (Compound Sodium Alginate Double Action Chewable Tablets and placebo) for a 7-days treatment period for the following parameters:

- OTE as a measure for patient's responsiveness/satisfaction

- Change from day 0 in RDQ scores for heartburn dimension.
- Change from day 0 in RDQ scores for regurgitation dimension.

14.4.3 Statistical Methods for Efficacy Analyses

All statistical tests performed will be 2-tailed with significance assessed at the 5% significance level. The null hypothesis at all times will be the equality of the treatments being compared.

Normality assumptions will be evaluated by an examination of the residual plots. Depending on the degree of departure from these assumptions, an alternate nonparametric approach may be used for supportive purposes.

The primary endpoint (change in RDQ GERD dimension score) will be analysed using an analysis of covariance (ANCOVA) model with a fixed effect term for treatment, centre as a random effect and the day 0 RDQ GERD dimension score as a covariate. Treatment group differences will be estimated using the least square means and presented with 95% confidence intervals and p-values to make inferences.

The change in symptom score for each dimension seperately will be analysed identically to the primary endpoint although the included covariate will be the relevant dimension day 0 score rather than the GERD dimension score.

To preserve the type 1 error rate of 5% for the key secondary endpoint (change from day 0 in RDQ scores for dyspepsia dimension), a closed testing procedure will be applied. A significant comparison at the 5% level ($p<0.05$) for this key secondary endpoint will only be deemed as confirmatory evidence if the primary endpoint is also significant at the 5% significance level ($p<0.05$). All other secondary endpoints and/or any further sensitivity or alternate analyses for the primary and key secondary endpoint will serve as supportive evidence only and therefore no further adjustment for multiple comparisons will be made.

For the primary and key secondary endpoint, two additional separate exploratory ANOVA models will be conducted identical to those stated above but with one additional interaction term for the treatment by centre interaction (random effect) and treatment by baseline covariate interaction respectively.

The change scores in frequency and intensity for each dimension as well as the two OTE responses will be compared between treatments using a Wilcoxon Rank Sum Test stratified by centre.

14.5 Safety Analyses

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 Fisher's Exact Test for all AEs, for those AEs classified by the Investigator as possibly or probably 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 within-treatment changes from baseline will be assessed using the Wilcoxon Signed-Rank Test. The significance of between treatment changes from baseline will be assessed using the Wilcoxon Rank-Sum Test. Statistical testing will be performed at last visit.

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 within-treatment changes from baseline will be assessed at the last visit, using the Wilcoxon Signed-Rank Test. The significance of between treatment changes from baseline will be assessed at the last visit using the Wilcoxon Rank-Sum.

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 SDV 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 consent must be verified from source documents as a minimum. In addition the following will be verified:
    - Endoscopy results
    - 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 be used in this study. The Investigator is responsible for the quality of the data recorded in the eCRF. 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 into the eCRF such that the eCRF 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 eCRFs before the first patient at that site is enrolled. The Investigator must review all entries for completeness and correctness. Data management will be conducted by Quintiles. The eCRF system will keep an audit trail of all changes made after the eCRF pages are initially completed and submitted.

The Investigator agrees to complete and sign the eCRFs 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 eCRF has been completed should be answered promptly. Following monitoring of each patient's eCRF, the investigator will electronically sign the eCRF. 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 eCRFs for completeness and adherence to the protocol..Following completion of the study, the Investigator will no longer be able to access the eCRFs. They will therefore be provided with a CD with all of the eCRFs from their site by the data management group.

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.

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23 APPENDICES

23.1 Appendix 1 English version Reflux Disease Questionnaire

Reflux Disease Questionnaire (RDQ)

Please answer each question by ticking one box per row.

1. Thinking about your symptoms over the past 7 days, how often did you have the following?

	Did not have	1 day	2 days	3-4 days	5-6 days	Daily
a. A burning feeling behind your breastbone	☐	☐	☐	☐	☐	☐
b. Pain behind your breastbone	☐	☐	☐	☐	☐	☐
c. A burning feeling in the centre of the upper stomach	☐	☐	☐	☐	☐	☐
d. A pain in the centre of the upper stomach	☐	☐	☐	☐	☐	☐
e. An acid taste in your mouth	☐	☐	☐	☐	☐	☐
f. Unpleasant movement of material upwards from the stomach	☐	☐	☐	☐	☐	☐

2. Thinking about your symptoms over the past 7 days, how would you rate the following?

	Did not have	Very mild	Mild	Moderate	Moderately severe	Severe
a. A burning feeling behind your breastbone	☐	☐	☐	☐	☐	☐
b. Pain behind your breastbone	☐	☐	☐	☐	☐	☐
c. A burning feeling in the centre of the upper stomach	☐	☐	☐	☐	☐	☐
d. A pain in the centre of the upper stomach	☐	☐	☐	☐	☐	☐
e. An acid taste in your mouth	☐	☐	☐	☐	☐	☐
f. Unpleasant movement of material upwards from the stomach	☐	☐	☐	☐	☐	☐

RDQ - UK-English. 051208

23.2 Appendix 2 Chinese Mandarin version Reflux Disease Questionnaire

Version B

反流性疾病问卷调查(RDQ)

回答每条问题时，请在每行其中一个空格内加上「✓」号。

1. 回想过去 7 天，你出现以下症状有多频繁?

	无	1 星期少于 1 天	1 星期 1 天	1 星期 2-3 天	1 星期 4-6 天	每天
a. 胸骨后感到灼热	☐	☐	☐	☐	☐	☐
b. 胸骨后感到疼痛	☐	☐	☐	☐	☐	☐
c. 上腹中心感到灼热	☐	☐	☐	☐	☐	☐
d. 上腹中心感到疼痛	☐	☐	☐	☐	☐	☐
e. 口腔内有酸味	☐	☐	☐	☐	☐	☐
f. 有东西从胃部向上移动而感到不适	☐	☐	☐	☐	☐	☐

2. 回想过去 7 天，你认为以下症状出现时的程度如何?

	无	很轻微	轻微	中度	较严重	严重
a. 胸骨后感到灼热	☐	☐	☐	☐	☐	☐
b. 胸骨后感到疼痛	☐	☐	☐	☐	☐	☐
c. 上腹中心感到灼热	☐	☐	☐	☐	☐	☐
d. 上腹中心感到疼痛	☐	☐	☐	☐	☐	☐
e. 口腔内有酸味	☐	☐	☐	☐	☐	☐
f. 有东西从胃部向上移动而感到不适	☐	☐	☐	☐	☐	☐

RDQ (Mainland China) 051208