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 Statistical Analysis Plan, dated 29-Jul-2014

Changes to Planned Statistical Analyses Form, dated 01-Sep-2014

STATISTICAL ANALYSIS PLAN

GA1210

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

AUTHOR: [redacted]

VERSION NUMBER AND DATE: V2.0, 29JUL2014

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Final V2.0 (Date 29Jul2014) for Protocol Version Final v 2.0 Amendment 1, Dated 04Jun2013

	Name	Signature	Date
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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	[redacted]	[redacted]	
Position:	Statistical Manager		
Company:	Reckitt Benckiser Brands Limited		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
0.1	30Dec2013	[redacted]	Not Applicable – First Version
0.2	08Apr2014		Updated per sponsor's comments
1.0	24Apr2014		Updated per sponsor's comments and version up.
1.1	12May2014		Updated per new sensible findings.
1.2	18Jun2014		Updated per Dry run 1's comments and findings. 1. Updated compliance section for clarity. 2. Concomitant medications are to be presented by indication and ATC class in addition to by preferred term. 3. Added subgroup analyses for GERD status and Endoscopy Findings.
1.3	23Jul2014		Updated per Dry run 2's comments and findings. 1. Revised the definition of PP population. 2. Updated time on treatment derivation to account for missing visit date. 3. Further clarified on missing data imputation. 4. Refined subgroup analysis to only include by GERD status.
2.0	29Jul2014		Version up to 2.0 for finalization

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ANOVA	Analysis of Variance
BLQ	Below the lower limit of quantification
CI	Confidence Interval
CRF	Case report form
CSP	Clinical Study Protocol
FAS	Full analysis set
GERD	Gastro-esophageal reflux disease
IMP	Investigational medicinal product
ITT	Intention-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NIMP	Non-investigational medicinal product
OTE	Overall treatment evaluation
PP	Per protocol
PT	Preferred term
RDQ	Reflux Disease Questionnaire
SAE	Serious adverse event
SOC	System organ class
SAP	Statistical analysis plan
SI	International System
ULQ	Upper limit of quantification
WHO	World Health Organization

2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol GA1210. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on clinical study protocol (CSP) version Final v 2.0 Amendment 1, dated 04Jun2013.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

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

3.2. SECONDARY OBJECTIVES

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.

3.3. SAFETY OBJECTIVES

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

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

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).

The sample size calculation, based on the UK pilot study 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 randomized.

Patients can enter the study, if eligible, 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) to receive either Compound Sodium Alginate Double Action Chewable Tablets or matching placebo tablets. Visit 3, the End of study visit, will occur on Day 8 (between Day 7 and Day 10).

4.2. SCHEDULE OF EVENTS

Schedule of assessments can be found in Section 3.10 of the protocol.

5. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by Quintiles Biostatistics following Reckitt Benckiser's Authorization of this SAP, Database Lock and Sponsor Authorization of Analysis Sets.

6. ANALYSIS SETS

Agreement and authorization of patients included/excluded from each analysis set was conducted at a blind data review meeting on 23rd July 2014, prior to database lock.

6.1. ALL PATIENT [AP] POPULATION

All patients recruited (e.g. those with eligibility confirmed at screening visit and assigned randomization number) into the study will be included in the All Patient Population.

6.2. SAFETY POPULATION [SAF]

All patients who are recruited into the study and receive at least one dose of study medication will be included in safety population.

6.3. INTENT-TO-TREAT [ITT] POPULATION

All patients who are 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 will be included into intent-to-treat (ITT) population.

6.4. PER PROTOCOL [PP] POPULATION

The inclusion/exclusion from per protocol (PP) population was confirmed during a blind data review meeting on 23rd July 2014, and will include all patients from the ITT population who have no major protocol deviations or other circumstances that may be relevant to efficacy assessment during the study.

A major protocol deviation that affects efficacy assessment is defined as any deviation of the protocol that is considered to affect the efficacy results and will include the following:

- Patient did not satisfy an inclusive/exclusive criteria that was deemed to have potential to affect efficacy;
- Patient took prohibited medication which would interfere with evaluation of drugs in the study period;
- Patient had inadequate treatment compliance. Adequate compliance with the treatment is defined as ≥ 75% of study medication used from return tablet count.

Additionally, a patient will be excluded from the PP population if they returned for Visit 3/Early termination visit outside the 7 – 10 day window and did not withdraw for lack of efficacy

7. GENERAL CONSIDERATIONS

7.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date, and will be used to show start/stop day of assessments and events.

Reference start date (Day 0) is defined as the day of randomisation.

- Study Day = (date of event – reference start date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

Randomization date will be considered as the same date of randomization visit, that is, visit 2.

7.2. BASELINE

Unless otherwise specified, baseline value refers to the tests or measurements recorded at Visit 1, screening

visit. If a particular test or measurement was repeated after Visit 1, screening visit, then the baseline value is defined as the last non-missing measurement taken prior to Visit 2, Day 0 (including unscheduled assessments). Baseline for RDQ scores are collected on Day 0. In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

7.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries. In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries.

Early termination data will be mapped to the next available visit number, i.e., Visit 3, for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

7.4. STATISTICAL TESTS

The default significant level will be (5%); confidence intervals (CIs) will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

7.5. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

7.6. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.2 or higher.

8. STATISTICAL CONSIDERATIONS

8.1. MULTICENTER STUDIES

This study will be conducted at multiple hospital sites. Allocation to treatment arms is stratified by centre.

Centre pooling will be carried out across all centres for use in statistical summaries for this study. Centre will be

included in the statistical models to adjust for centre effect. Treatment by centre interaction may also be explored using additional analyses. Refer to Section 15 for more details.

8.2. MISSING DATA

Patients who withdraw from the study will not be replaced.

Unless otherwise specified, all analysis will be based on the number of non-missing observations. If relevant for categorical tabulations, missing values will be treated as another category, so that all tabulations involving this variable will also include a row or column as appropriate to indicate the number of patients for whom the variable was recorded as a missing value.

For AEs, partial or missing dates and times will not be imputed, and this will be listed as originally reported in the Case Report Form (CRF).

8.3. EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed for this study.

8.4. MULTIPLE COMPARISONS/ MULTIPLICITY

To preserve the type 1 error rate of 5% for the key secondary endpoint (change from baseline 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 exploratory 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.

9. OUTPUT PRESENTATIONS

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by Quintiles Biostatistics.

Continuous variables will be summarized using descriptive statistics, i.e., number of subjects (n), mean, median, standard deviation, minimum and maximum.

Qualitative variables will be summarized by counts and percentages. Unless otherwise stated, the calculation of proportions will be based on the sample size of the population of interest.

10. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study. The number of patients who provided informed consent, as well as those who were eligible will be summarized overall.

The number of patients who completed the study, the number of patients who withdrew prematurely from the study, the reasons for withdrawals and the number of patients in the AP, Safety, ITT and PP population will be summarized for each treatment group and overall.

Listings on patient completion/withdrawal information, as well as eligibility details will be reported.

Major protocol deviation will be summarized by treatment group and overall. Furthermore the number of patients to be excluded from each population together with reasons of exclusion will be summarized. Details on major protocol deviation as well as population classification information will be listed.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be summarized by treatment group and overall for all patients in AP. If there is a discrepancy in patient numbers between the AP and any other population, then baseline data will be summarised additionally for that population.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) –relative to date of consent
- Race
- Sex
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- Smoking status – Yes, No, Former smoker
- Smoking years and amount (cigarettes per day)
- Alcohol use – Yes, No
- Drinking years and amount (gram per day)
- Drug of abuse history – Yes, No

Summary statistics will be presented for Investigator's assessment of patients' baseline GERD-related symptoms, including the severity of heartburn, regurgitation and dyspepsia.

In addition, interpretation of the 12-lead ECG results and abnormalities present in a standard hospital endoscopy examination will be reported at baseline as part of the screening procedures.

12. MEDICAL HISTORY AND CONCOMITANT ILLNESS

Medical History conditions are defined as those conditions which stopped prior to or at screening visit. Medical history information will be coded using version 17.0 of Medical Dictionary for Regulatory Activities (MedDRA) and presented for all patients in safety population by system organ class (SOC) and preferred term (PT), by treatment group and overall.

Concomitant illnesses are conditions other than GERD which are ongoing before or on the day of last dose of study drug, or stopped after screening visit but before or on the day of last dose of study drug. Concomitant illnesses will be captured from "Medical History and Current Status (excluding GERD)" form in eCRF, and will be coded using MedDRA version 17.0 and presented for all patients in safety population by SOC and PT, by treatment group and overall.

13. PRIOR AND CONCOMITANT MEDICATION AND THERAPIES

Medications will be coded using World Health Organization (WHO) Drug Dictionary Enhanced version dated 01Mar2013 and tabulated by indication collected on the eCRF(AE, Medical History, GERD, Endoscopy Related, Other), Anatomical Therapeutic Chemical (ATC) class and Standardized Medication Name for the safety population (for prior and concomitant medications separately)

- 'Prior' medications are medications which started and stopped prior to first dose of study medication.
- 'Concomitant' medications are medications which:
  - started prior to, on or after first dose of study medication
  - AND ended on or after first dose of study medication or were ongoing at the end of the study.

14. STUDY MEDICATION EXPOSURE & COMPLIANCE

The extent of exposure and compliance with study treatment will be presented for the safety population. Patients will receive Compound Sodium Alginate Double Action Chewable Tablets (two tablets four times daily) or matching placebo tablets for a period of 7 days.

14.1. DERIVATIONS

The date of first treatment administration will be the day after "date of dispense" on the eCRF "Drug Dispense" at Visit 2. The date of last treatment administration will be the day before the date of Visit 3 or Early Termination; for patients who do not have a Visit 3 or Early Termination date, the drug return date on the eCRF "Drug Return" will be used. Time on treatment in days will be derived from the following formula:

Time on treatment (days) = (date of Visit 3 or Early Termination or drug return date-1) – (date of dispense at Visit 2 +1) + 1

Compliance with study treatment is based on the drug accountability data recorded on the eCFR "Drug Dispense" and "Drug Return" forms and will be calculated as the number of tablets taken (total dispensed – total returned) divided by the prescribed number of tablets expressed as a percentage, see calculations below:

Θ = Prescribed number of tablets required to be taken per day, i.e., 8 tablets in this study.

$$\text{Compliance (\%)} = \frac{[\text{N of tablets dispensed at Visit2}]-[\text{N of tablets returned at Visit3 or Early Termination}]}{\text{Time treatment(days)}*\Theta} \text{x } 100$$

15. EFFICACY OUTCOMES

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY VARIABLE

The primary efficacy endpoint is the change from baseline 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. This variable is derived from the data collected on the "Reflux Disease Questionnaire" form in eCRF.

The RDQ is a self-administered questionnaire in which subjects are asked to report the frequency and severity of their upper gastrointestinal symptoms (refer to Appendix 1 and 2 of the Protocol). There are three subscales that evaluate regurgitation, heartburn and dyspepsia. The heartburn and regurgitation subscales can be combined into a GERD dimension. Refer to Appendix 2 for RDQ scoring instructions for deriving the RDQ symptom scores for the GERD dimension.

15.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE

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) if Early Termination visit is missing. If there is missing data for a patient in the RDQ questionnaire at an occasion and the missing data is less than or equal to 50% of the item scores within a dimension, the missing items will be imputed using the mean score of the non-missing item scores. If more than 50% of the item scores are missing, no imputation will be performed and the dimension score will be excluded from the analysis.

15.1.3. Primary Analysis of Primary Efficacy Variable

The primary endpoint will be performed for the ITT population primarily using a linear mixed model with a fixed effect term for treatment, centre as a random effect and the baseline RDQ GERD dimension score as a covariate. The primary analysis is to test the null hypothesis that there is no difference between treatment, least square means (with 95% CI) corresponding to the two treatments will be presented. Descriptive statistics will also be presented for the primary endpoint by treatment.

The following SAS core code will be used:

```
proc mixed data=XXX method=REML;
  class treatment center;
  model chg = base treatment / DDFM=KR;
  random center;
  lsmeans treatment/diff cl;
run;
```

15.1.4. Sensitivity Analysis of Primary Efficacy Variable

A sensitivity analysis will be conducted on the primary endpoint using the PP population.

15.1.5. Exploratory Analysis of Primary Efficacy Variable

Two additional separate exploratory mixed models will be conducted identical to those stated above but with additional interaction terms for the treatment by centre interaction (random effect) and treatment by baseline covariate interaction respectively.

15.1.6. Subgroup Analysis of Primary Efficacy Variable

The analysis will be repeated within each of the subgroups separately as indicated below:

GERD status: Erosive vs Non-erosive.

15.2. Secondary Efficacy

15.2.1 Secondary Efficacy Variables

The key secondary endpoint is:

- Change from baseline in RDQ scores for dyspepsia dimension

Other secondary endpoints are:

- Overall treatment evaluation (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.

The secondary efficacy analyses will be performed for the ITT population.

Refer to Appendix B for RDQ scoring instructions for deriving the RDQ symptom scores for the dyspepsia, heartburn and regurgitation dimension.

The two OTE responses are collected on the "Overall Treatment Evaluation" form in eCRF as responses to questions 1) thinking over the last 7 days and the medication you received, how would you rate the change in your symptoms; and 2) how important was the change in the symptoms to you.

15.2.2 Missing Data Methods for Secondary Efficacy Variables

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 concerning RDQ scores at Visit 3 will be imputed as no change from the day 0 values (BOCF) if Early Termination visit is missing. If there is missing data for a patient in the RDQ questionnaire at an occasion and the missing data is less than 50% of the item scores within a dimension, the missing items will be imputed using the mean score of the non-missing item scores. If more than 50% of the item scores are missing, no imputation will be performed and the dimension score will be excluded from the analysis.

15.2.3 Analyses of Secondary Efficacy Variables

The analysis methods for the key secondary endpoint will be identically to those described for the primary endpoint in 15.1.3, 15.1.4 and 15.1.5 except that the included covariate will be the baseline RDQ score for the relevant dimension.

The difference in the two OTE responses will be compared between treatment groups using a Wilcoxon Rank Sum Test stratified by centre.

The following SAS core code will be used:

```
proc freq data=XXX;
  tables center*treatment*ote_resp/cmh2 scores=modridit ;
run;
```

The second OTE response (i.e., how important was the change in symptoms) will also be examined in the subgroup of patients who have reported an improvement in the first OTE response.

The change scores in frequency and intensity for each dimension, i.e., the 12 items asked on the RDQ questionnaire, will be compared between treatment groups using a Wilcoxon Rank Sum Test stratified by centre.

The analysis methods for the other two secondary endpoints (heartburn and regurgitation dimensions) will be

identical to those described for the primary endpoint in 15.1.3 and 15.1.4 except that the included covariate will be the baseline RDQ score for the relevant dimension.

15.2.4 Sensitivity Analyses of Secondary Efficacy Variables

Sensitivity analyses will be conducted on the secondary endpoints using the PP population.

15.2.5 Exploratory Analysis of Key Secondary Efficacy Variables

Two additional separate exploratory mixed models will be conducted identical to those stated above but with additional interaction terms for the treatment by centre interaction (random effect) and treatment by baseline covariate interaction respectively.

16 Safety Outcomes

All outputs for safety outcomes will be based on the Safety population.

16.1 Adverse Events

Adverse Events (AEs) will be coded using MedDRA version 17.0. For an individual patient, only adverse events commencing after first dose of IMP and no later than last dose of IMP+1day will be included in the AE and serious adverse event (SAE) summaries. 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. Where an AE start date is partially or completely missing, and it is unclear using partial dates as to whether the AE is treatment-emergent, it will be assumed that it is.

16.1.1 ADVERSE EVENTS

An overall AE summary presenting the number and percentage of patients within the following categories by treatment group and total will be provided.

- Total number of AEs (each patient might be counted more than once within this item)
- Patients with AEs
- Patients with SAEs
- Patients with AEs with a relationship to IMP as “Possible”, “Probable” and “Certain”
- Patients with severe AEs
- Patients with AEs leading to IMP dose change
- Patient with AEs leading to IMP permanently discontinued

In addition, an analysis using Fisher's exact test to compare the AE incidence between treatment groups will be presented for the following categories:

- Patients with AEs
- Patients with AEs with a relationship to IMP as “Possible”, “Probable” and “Certain”
- Patients with severe AEs

In addition, the following tables will be reported by treatment groups:

- AEs, by SOC, PT and severity
- Related AEs, by SOC, PT and severity

16.1.1.1 Severity

Severity is classified as mild/ moderate/ severe. AEs with a missing severity will be counted in a separate missing category. If a patient reports an AE more than once within that SOC/ PT, the AE with the worst case severity will be used in the corresponding severity summaries.

16.1.1.2 Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as “Unassessable/Unclassified”, “Conditional/Unclassified”, “Unrelated”, “Unlikely”, “Possible”, “Probable”, and “Certain”. Adverse events with a relationship of “Possible”, “Probable” and “Certain” to IMP will be considered as related to study medication. AEs with a missing relationship to study medication will be counted in a separate missing category. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

16.1.2 ADVERSE EVENTS LEADING TO DOSE CHANGE OR DISCONTINUATION OF STUDY MEDICATION

If the action taken for an AE is recorded as “IMP permanently discontinued” on the “Adverse Events” form of the eCRF, it will be considered as an AE leading to permanent discontinuation. If the action taken for an AE is recorded as “IMP dose changed” on the “Adverse Events” form of the eCRF, it will be considered as an AE leading to dose change. These will be summarized by SOC and PT by treatment group and also listed.

16.1.3 SERIOUS ADVERSE EVENTS

SAEs are those events a response of "Yes" for the item "Is the Adverse Event serious?" on the "Adverse Events" form of the eCRF. A summary of SAEs by SOC, PT and severity, as well as a summary of related SAEs by SOC, PT, and severity will be reported by treatment group. Summaries will also be provided for SAEs leading to dose change as well as study discontinuation. These data will also be listed.

16.1.4 ADVERSE EVENTS LEADING TO DEATH

AEs leading to Death are those events with outcome reported as "Fatal" on the "Adverse Events" form of the eCRF. A summary of AEs leading to death by SOC and PT will be prepared. This information will also be listed.

16.2 DEATH

Only AEs leading to death are recorded for this study, please refer to Section 16.1.4.

16.3 LABORATORY EVALUATIONS

Clinical assessments on hematology and clinical chemistry are to be measured at Visit 1 and Visit 3 or Early Termination Visit. A list of laboratory assessments to be included in the outputs is provided in appendix 1. Local laboratories will be used for the assessment of hematology and clinical chemistry data and these data will be converted to the International System (SI) of units by Data Management Team using standard conversion factors. Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

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.

Each pre-study baseline laboratory value will be categorised as low, normal, or high based on the reference range of the local laboratories:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory 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 (Visit 3

or Early Termination Visit) will be compared using the Wilcoxon Signed-Rank test within each treatment group. Statistical testing will be performed at last visit.

In addition to the high and low quantitative laboratory assignments (as identified by means of the laboratory reference ranges), clinically significant quantitative laboratory assessments will be identified by investigator and the result will be recorded in the eCRF. The number and percentage of patients with abnormal or clinically significant results will be tabulated by treatment groups by visit. The results will also be listed.

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

16.4 VITAL SIGNS

Vital signs including systolic/diastolic blood pressure (mmHg) and heart rate (beats/min) will be conducted at Visit 1 and Visit 3 or early termination visit.

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 Test.

A complete listing on all patients' vital sign result will be presented.

16.5 PHYSICAL EXAMINATION

A physical examination is to be performed at Visit 1 and Visit 3 or Early Termination Visit. The following summaries will be provided for physical examination data:

Incidence of clinically significant abnormalities at each visit will be presented and a shift table on clinically significant abnormalities between baseline and Visit 3 (or early termination visit) will be presented by treatment group.

A listing on clinical significant abnormalities will be reported.

17 REFERENCE

Reckitt Benckiser GA1210 Study Protocol Final Version 2.0, Amendment 1, 4Jun2013

Reckitt Benckiser GA1210 Annotated Study Book_Version 04_ 28Mar2014

APPENDIX 1 LIST OF LABORATORY ASSESSMENTS

Assessment	SI Unit
Haematology	
Haemoglobin	g/L
Red blood cells	10^12/L
Mean cell haemoglobin concentration	g/L
White blood cells	10^9/L
Platelet count	10^9/L
Clinical chemistry	
Sodium	mmol/L
Potassium	mmol/L
Calcium	mmol/L
Urea	mmol/L
Creatinine	µmol/L
Uric Acid	µmol/L
Glucose	mmol/L
Inorganic phosphorous	mmol/L
Alanine transaminase	U/L
Aspartate transaminase	U/L

APPENDIX 2 REFLUX DISEASE QUESTIONNAIRE (RDQ)

Description

The RDQ is a self-administered questionnaire. It has been used to assess treatment induced changes over time and will be validated as a diagnostic tool of gastroesophageal reflux disease for use in primary care.

Scoring

The questionnaire, which contains 12 items, uses a six-graded Likert scale, where 0 represents the most positive option and 5 the most negative one. A raw score is calculated.

A mean value for the items in each dimension should be calculated:

Heartburn: 1a. A burning feeling behind your breastbone
1b. Pain behind your breastbone
2a. A burning feeling behind your breastbone
2b. Pain behind your breastbone

Regurgitation: 1e. An acid taste in your mouth
1f. Unpleasant movement of material upwards from the stomach
2e. An acid taste in your mouth
2f. Unpleasant movement of material upwards from the stomach

GERD dimension: 1a. A burning feeling behind your breastbone
1b. Pain behind your breastbone
2a. A burning feeling behind your breastbone
2b. Pain behind your breastbone
1e. An acid taste in your mouth
1f. Unpleasant movement of material upwards from the stomach
2e. An acid taste in your mouth
2f. Unpleasant movement of material upwards from the stomach

Dyspepsia: 1c. A burning feeling in the centre of the upper stomach
1d. A pain in the centre of the upper stomach
2c. A burning feeling in the centre of the upper stomach
2d. A pain in the centre of the upper stomach

References:

- Shaw MJ, Talley NJ, Beebe TJ, Rockwood T, Carlsson R, Adlis S, Fendrick M, Jones R, Dent J, Bytzer P. Initial validation of a diagnostic questionnaire for gastroesophageal reflux disease. Am J Gastroenterol 2001;96:52-57.
- Shaw MJ, Crawley JA. Improving health-related quality of life in gastro-oesophageal reflux disease. Drugs 2003;63:2307-2316.
- Ofman JJ, Shaw M, Sadik K, Grogg A, Emery K, Lee J, Reyes E, Fullerton S. Identifying patients with gastroesophageal reflux disease – Validation of a practical screening tool. Dig Dis Sci 2002;47:1863-1869.
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QUINTILES

Changes to Planned Statistical Analyses Form

Customer:	RB Healthcare
Protocol No.:	GA1210
Project Code:	QVA96909
Date:	01/SEP/2014

The timing of the change(s) was:

- ☒ After unblinding (or database lock for an open-label study) but before completion of the final Statistical Report/Clinical Study Report
- ☐ After completion of the final Statistical Report/Clinical Study Report

Describe the change(s) required:

Table 14.2.3.3, the site and site*treatment interaction initially entered the model as random effect. During review of the final unblinded output, it was found that the p-value for the site*treatment interaction term was not calculated due to non positive definite variance matrix. Thus for this table, the analysis will be updated with site, and site*treatment entered into the model as fixed effects.

Describe the process used to decide on the change(s) and who was involved:

As the key intention of this analysis was to test the null hypothesis of equal treatment differences across centres, it was decided by the RB Statistical Manager ([redacted]) to change the analysis presented because this could not be assessed from the planned analysis using random effects. Although this change may not have the same level of power to detect a significant treatment by centre interaction as the previously planned analysis and relies on different assumptions about the centre effect, it at least provides some unbiased information on the homogeneity of the treatment difference across centres. Due to negative variance components in the planned analysis (and setting the centre x treatment variance as zero), in the assessment of the treatment effect the calculated degrees of freedom are not valid.

The group(s) responsible for the change(s) and implications for the study:

The RB Statistical Manager ([redacted]) is responsible for requesting this change and Quintile Statisticians are responsible for updating the affected output and ensuring appropriate documentation and explanation in the Statistical and Clinical Reports.

Form completed by:

Title	Name	Signature	Date
AD, Biostatistics	[redacted]		

Form approved by:

Title	Name	Signature	Date
Dir, Biostatistics [redacted]	[redacted]		

Form approved by Customer Representative (if applicable):

Title	Name	Signature	Date
Statistical Manager	[redacted]	[redacted]	