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

ClinicalTrials.gov ID: NCT01872897

Final Statistical Analysis Plan, dated 25-Feb-2014

Changes to Planned Statistical Analyses Form, dated 19-Mar-2014

Changes to Planned Statistical Analyses Form, dated 08-May-2014

Changes to Planned Statistical Analyses Form, dated 17-Jul-2014

STATISTICAL ANALYSIS PLAN

GA1202

A MULTI-CENTRED, RANDOMISED, OPEN LABEL, PLACEBO-CONTROLLED, TWO-PERIOD CROSSOVER STUDY TO EVALUATE 4-HOUR ESOPHAGEAL pH CHANGE IN GERD PATIENTS AFTER ADMINISTRATION OF COMPOUND SODIUM ALGINATE DOUBLE ACTION CHEWABLE TABLETS OR MATCHING PLACEBO TABLETS

AUTHOR: [redacted]

VERSION NUMBER AND DATE: V5.1(FINAL), 25FEB2014

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Final V5.1 (Date 25Feb2014) for Protocol <<GA1202 >> Dated 01Mar2013

	Name	Signature	Date
Author:	[redacted]	[redacted]	
Position:	Manager, Biostatistics		
Company:	Quintiles		

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	16Apr2013	[redacted]	Not Applicable – First Version
0.2	30Jul2013		Update per internal comments
0.3	16Aug2013		Update per internal comments
0.4	19Aug2013		Update per internal comments
0.5	20Aug2013		Update per internal comments
1.0	20Aug2013		Update to draft version 1.0 and sent to sponsor for review
1.1	02SEP2013		Update per sponsor's comment
1.2	06Sep2013		Update per internal review comment
2.0	06Sep2013		Update to draft version 2.0 and sent to sponsor for review
3.0	21Oct2013		Update per sponsor's comment
3.1	23Oct2013		Update per sponsor's comment
4.0	25Oct2013		Update to final version 4.0
5.0	10Jan2014		Update to present the concomitant medication by ATC level.
5.1	25Feb2014		Update FAS definition Change listings (16.2.3.1-16.2.3.8) to be presented on FAS instead of all patients. Updated list of tables and listings per sponsor's comments.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BLQ	Below the lower limit of quantification
CI	Confidence Interval
CRF	Case report form
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
PP	Per protocol
PT	Preferred term
SAE	Serious adverse event
SOC	System organ class
SAP	Statistical analysis plan
SI	International System
ULQ	Upper limit of quantification
WHO	World Health Organization

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol GA1202. 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 protocol version 2, amendment 1, dated 4Jul2013.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

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

2.2. SECONDARY OBJECTIVES

The following secondary endpoints will also be evaluated:

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

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a multi-centre, randomised, open-label, placebo-controlled, two-period crossover study. Forty - four (44) patients are planned to be enrolled in this study to ensure that thirty six (36) patients complete it. After signing a written informed consent, patients will undergo a screening period up to 10 days. Patients who satisfy the study entry requirements within 10 days of consent, will be randomised to receive either four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets following placement of a pH electrode and a standardised refluxogenic meal.

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

3.2. SCHEDULE OF EVENTS

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

4. 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.

5. ANALYSIS SETS

Agreement and authorization of patients included/excluded from each analysis set will be conducted at data review meeting before database lock.

5.1. FULL ANALYSIS SET [FAS]

All patients enrolled (e.g. those assigned randomization number) in the study will be included in full analysis set (FAS).

5.2. SAFETY POPULATION

All patients who are subjected to any invasive procedures and/or take at least one dose of study medication will be included in safety population.

5.3. INTENT-TO-TREAT [ITT] POPULATION

All patients who take at least one dose of study medication and have evaluable pH monitoring data for at least 1 hour post-dosing will be included into intent-to-treat (ITT) population.

5.4. PER PROTOCOL [PP] POPULATION

The inclusion/exclusion from per protocol (PP) population will be confirmed during data review meeting, but will include patients who satisfied following criteria and did not experience any major protocol violations in ITT population: patients who adhered to the inclusive/exclusive criteria; did not take any prohibited medication which would interfere with evaluation of drugs in the study period; attended visits within the specified visit windows and had complete pH monitoring data for 4 hour post-dosing for both pH monitoring visits.

A major violation of the protocol is defined as any violation of the protocol that is considered to affect the efficacy results and may include the following:

- When a randomization error or administration of the wrong study medication occurred;
- When the patient did not satisfy the inclusion/exclusion criteria;
- When the patient had taken prohibited concomitant medications;
- When the patient failed to attend visit at specified visit windows;
- When the efficacy (4 hour post-dosing monitoring) evaluation was not completed for either monitoring visits.

Protocol violations will be categorized before database lock and will be summarized (by treatment sequence group and overall) and listed.

6. GENERAL CONSIDERATIONS

6.1. 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 first dose of study medication.

- 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.

6.2. 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). 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.

For patients randomized but not treated, baseline is defined as the last non-missing measurement taken on or before the baseline visit date.

6.3. 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 for by-visit summaries.

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

6.4. 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.

6.5. COMMON CALCULATIONS

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

- Test Value at Visit X – Baseline Value

Log transformed (natural logarithm) of efficacy data (or another transformation) might be used in the statistical models if after inspection of the data it is considered necessary. This decision will be undertaken in collaboration with the sponsor.

6.6. SOFTWARE VERSION

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

7. STATISTICAL CONSIDERATIONS

7.1 ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following factors are used in the analyses. For details of their inclusion in the models, see section 15.1.3.

- Treatment (Study medication and matching placebo tablets)
- Dose visit (Visit 2 and Visit 3)
- Subject
- Treatment sequence (Group A: Patients take study medication at Visit 2 and matching placebo tablets and Visit 3. Group B: Patients take study medication at Visit 3 and matching placebo tablets at Visit 2.

7.1. MULTICENTER STUDIES

This study will be conducted at two or more hospital sites. The 4-hour pH endpoints will be summarized separately for each center. Center will not be included as a factor in any of the statistical models because the study has a cross-over design

7.2. 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, i.e. patients with missing information will not be included in the denominator when calculating percentages. 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).

7.3. EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed for this study.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

Since there is only one primary analysis, no multiple comparison adjustments will be used.

8. OUTPUT PRESENTATIONS

The table and listing templates provided with this SAP describe the conventions for presentation of data in outputs, and presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by Quintiles Biostatistics.

9. DISPOSITION AND WITHDRAWALS

The number of patients who provided informed consent, as well as those who were eligible at Visit 1 and Visit 2 (met all inclusion criteria and not met all exclusion criteria) 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 FAS, Safety, ITT and PP population (see Section 4 for population definitions) will be summarized for each treatment sequence group and overall. Listings on patient completion/withdrawal information, as well as eligibility details will be reported

Major protocol violations will be summarized by treatment sequence 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 violations as well as population classification information will be listed.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be summarized by treatment sequence group and overall for all patients in FAS.

No statistical testing will be carried out for demographic or other baseline characteristics.

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

- Age (years) – calculated relative to date of consent
- Race
- Sex
- Height
- Weight

Counts and percentages will be displayed for patients with smoking habits (no, yes, former), alcohol/drug use (no, yes) and drugs of abuse history; summary statistics (mean, median, minimum, maximum and standard deviation) will be provided for the continuous variables including height, weight, age, smoking/drinking years and amount. These data will also be listed.

Summary statistics will be presented for patients' baseline Gastro-esophageal reflux disease (GERD) symptoms, including the severity and frequency of heartburn. In addition, 12 lead ECG and a standard hospital endoscopy examination will be conducted at baseline as part of the screening procedures. The following Information on ECG and endoscopy will be presented by summary statistics:

ECG:

Whether ECG is performed

Interpretation of ECG results

Endoscopy:

Whether endoscopy performed

Whether local anaesthetic throat spray administered

Whether a sedative administered

Any abnormalities presented in endoscopy

If the patient has erosive GERD

If the patient have hiatus hernia and diameter of the hernia

Other baseline characteristics such as laboratory evaluations, vital signs, and physical examination are specified in section 16.3, 16.5 and 16.6 respectively.

10.1. DERIVATIONS

Age = Date of Informed Consent – Date of Birth (rounded down to the nearest whole year)

11. MEDICAL HISTORY

Medical History conditions are defined as those conditions which stopped prior to or at screening visit. Medical history information will be coded using version 16.0 of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary and presented for all patients in FAS by system organ class (SOC) and preferred term (PT), for each treatment sequence group and overall.

12. CONCOMITANT ILLNESSES

Concomitant illnesses are conditions other than GERD which are ongoing before or on the day of last dose of Investigational Medicinal Product (IMP), or stopped after screening visit but before or on the day of last dose of IMP. Concomitant Illnesses will be captured from Medical History and Current Status form in CRF, and will be coded using MedDRA version 16.0 and presented for all patients in safety population by SOC and PT, for each treatment sequence 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 using the Anatomical Therapeutic Chemical (ATC) classification system, under Level 3 and Level 4 for the FAS (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

At each of the pH monitoring visits, patients will be administered four Compound Sodium Alginate Double Action Chewable Tablets or four matching placebo tablets under the supervision of the Investigator or his or her delegate. No measurement on medication compliance will be performed.

In addition, all patients will then receive Compound Sodium Alginate Double Action Chewable Tablets (two tablets four times daily) as Non-investigational Medicinal Product (NIMP) for symptomatic treatment. The number of tablets dispensed and returned will be recorded in CRF and presented by table and listing.

The following information regarding whether the patients fulfill each requirement prior to pH monitoring and the time interval from each procedure to taking treatment will be summarized by treatment sequence group:

Requirement prior to pH monitoring:

Not taken symptomatic treatment for GERD (antacids etc) in the 24 hours prior to pH monitoring

Abstain from alcohol 24 hours prior to the test meal

Fast for a minimum of 4 hours prior to insertion of manometry probe

Insert manometry probe to aid positioning of esophageal pH sensor prior to consuming test meal

Consume the entire reflux provoking meal

Record pH from 30 minutes prior to dosing to 4 hours post dosing

Time interval from each procedure to taking treatment:

Position pH electrode (90 mins before treatment)

Eat test meal (60 mins before treatment)

Activate pH monitoring data logger and Record (30 mins before treatment)

Stop pH monitoring (4 hour post dose)

The calculation of time interval is provided in section 14.1

14.1. DERIVATIONS

Time interval from each procedure to taking treatment (minutes) is calculated by

- Time of the procedure – Time when patient takes treatment

15. EFFICACY OUTCOMES

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY VARIABLE

The primary efficacy endpoint is the percentage of time during the 4 hour post dosing period with pH below pH 4 for Compound Sodium Alginate Double Action Chewable Tablets versus matching placebo tablets. This variable is collected on the "Results of 4-hour pH Monitoring" page in CRF.

15.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE

If less than 2 hours post-dosing monitoring result for this variable is available, for whatever reason, the derived variable will be considered missing. If 2 or more hours post-dosing monitoring data is available, the parameter will be derived by multiplying by the factor (4 hours / time with data available). Any data recorded more than 4 hours post-dosing will be ignored when deriving these parameter.

The table below shows the implementation of adjustment rules under different monitoring duration scenarios.

Monitoring Duration(End of pH monitoring – taking treatment)	Percentage of time with pH<4 during the monitoring period (data directly from database)	Number of hours with pH<4 during the monitoring period	Adjustment factor	Adjusted percentage with pH<4 over 4 hours
240 mins (4 hours)	80.0%	240 mins	1	80.0%
230 mins (<4 hours)	80.0%	230*80% mins	240/230	230*80%*240/230/240=80.0%
90 mins (<2 hours)	20.0%	90*20% mins	NA	missing

15.1.3 PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary endpoint will be analysed primarily using a linear mixed model with treatment, dosing visit and

treatment sequence as fixed effects and patient nested within treatment sequence as a random effect. 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 for each dosing visit and overall. The effects for dosing visit and treatment sequence will also be assessed.

The following SAS core code will be used.

```
proc mixed data=XXX method=REML;
  class treatment visit sequence subID;
  model Y= treatment visit sequence /ddfm=kenwardroger;
  random subID(sequence);
  lsmeans treatment/diff cl;
run;
```

SAS output from Mixed procedure will be sent to the sponsor to assist with the model assumptions review.

The linear mixed model for the primary endpoint is based on the assumption that the percentage of time with pH<4 within each treatment sequence group is normally distributed. To test this assumption, a qualitative residual analysis will be performed. If there is a major departure from the assumptions of normality or heteroscedasticity of residuals, then further analysis using transformed data might be performed if deemed necessary. If the analysis based on the transformed data still rises reasonable concerns about validity of the tests then the Wilcoxon Rank-Sum test will be used to compare the dosing visit difference (dosing visit 1 – dosing visit 2) between treatment sequence groups to represent the treatment comparison.

The primary efficacy analysis will be performed for the ITT population using adjusted 4-hour data based on the imputation rule specified in section 15.1.2.

15.1.4 Sensitivity Analysis of Primary Efficacy Variable

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

If the percentage of missing data for the primary endpoint is greater than 10% (data from > 10% patients is not recorded exactly at 4 hours (+/- 5 minutes), an additional complete case sensitivity analysis will be conducted, using only the observed 4-hour (+/- 5 minutes) data.

15.2. Secondary Efficacy

15.2.1 Secondary Efficacy Variables

The secondary endpoints are:

Percentage of time during the 4 hour post dosing period with pH below pH 5

Number of occasions during the 4 hour post dosing period when pH falls below pH 4

Number of occasions during the 4 hour post dosing period when pH falls below pH 5

Number of reflux episodes during the 4 hour post dosing period with pH below pH 4 for at least 5 minutes

Percentage of time during the first hour post dosing with pH below pH 4

Percentage of time during the first hour post dosing with pH below pH 5

Number of occasions during the first hour post dosing when pH falls below pH 4

Number of occasions during the first hour post dosing when pH falls below pH 5

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

The DeMeester scores during the 4 hour post dosing period.

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

15.2.2 Missing Data Methods for Secondary Efficacy Variables

Missing data for the percentage of time during the 4 hour post dosing period with pH below pH 5 due to early termination of recording will be derived in the same way as for the primary efficacy variable.

For the following secondary efficacy variables:

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

If less than 2 hours post-dosing monitoring result for these variables is available, for whatever reason, the derived variable will be considered missing. If 2 or more hours post-dosing pH data is available then the variable will be multiplied by 4 / (hours of post-dosing pH data available). Any data recorded more than 4 hours post-dosing will be ignored when deriving these parameters.

The table below shows the implementation of adjustment rules (take number of occasions as an example) under different monitoring duration scenarios.

Monitoring Duration(End of pH monitoring – taking treatment)	Number of occasions with pH<4 during the monitoring period (data directly from database)	Adjustment factor	Adjusted occasion with pH<4 over 4 hours
240 mins (4 hours)	2	1	2
230 mins (<4 hours)	2	240/230	2*240/230=2.09
90 mins (<2 hours)	1	NA	missing

Missing data for other secondary endpoints due to early termination of recording will not be derived.

15.2.3 Analyses of Secondary Efficacy Variables

The analysis methods for all secondary endpoints will be identically to those described for the primary endpoint in 15.1.3.

15.2.4 Sensitivity Analyses of Secondary Efficacy Variables

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

If the percentage of missing data for the secondary variables listed in section 15.2.2 is greater than 10% (data from > 10% patients is not recorded exactly at 4 hours +/- 5 minutes), an additional complete case sensitivity analysis will be conducted, using only the observed 4-hour (+/- 5 minutes) data.

16 Safety Outcomes

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

16.2 Adverse Events

Adverse Events (AEs) will be coded using MedDRA version 16.0. 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.

16.2.1 ADVERSE EVENTS

An overall AE summary presenting the number and percentage of patients within the following categories by treatment sequence 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 McNemar's test to compare the AE incidence during the 4-hour post dosing period between treatments will be presented for the following categories:

- Total number of AEs (note that for this item only the total numbers will be presented, no comparison on McNemar’s test will be performed)
- Patients with AEs
- Patients with SAEs
- Patients with AEs with a relationship to IMP as “Possible”, “Probable” and “Certain”
- Patients with severe AEs

In addition, following tables will be reported by treatment sequence group:

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

The tables above will be repeated for adverse events occur during the 4 hour post dosing period by treatment.

Individual listings on adverse events, related adverse events (see definition in section 16.1.1.2), serious adverse events, adverse events leading to dose change/study discontinuation and death will be reported.

16.2.1.1 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.

16.2.1.2 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.

16.2.2 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 AE page of the CRF 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 AE page of the CRF it will be considered as an AE leading to dose change. These will be summarized by SOC and PT by treatment sequence group and also listed.

16.2.3 Serious Adverse Events

SAEs are those events recorded as "Serious" on the Adverse Events page of the CRF. 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 sequence group. The tables will be repeated for serious adverse events during the 4 hour post doing period. Summaries will also be provided for SAEs leading to dose change as well as study discontinuation. These data will also be listed.

16.2.4 Adverse Events Leading to Death

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

16.3 Death

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

16.4 LABORATORY EVALUATIONS

Clinical assessments on hematology and clinical chemistry are to be measured at Visit 1 and Visit 3 (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 sequence group and overall. The significance of changes from baseline will be assessed using the Wilcoxon Signed-Rank Test within each sequence group and overall.

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

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 sequence 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 Visit 3 (Early Termination Visit) will be compared using the Wilcoxon Signed-Rank test within each treatment sequence group and overall. 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 CRF. The number and percentage of patients with abnormal or clinically significant results will be tabulated by treatment sequence 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.

16.5 ECG EVALUATIONS

A 12-lead ECG examination will be conducted at baseline. The results will be listed and summarised as per Section 10.

16.6 VITAL SIGNS

Vital signs will be conducted at baseline and final or early termination visits. The following Vital Signs measurements will be reported:
Systolic and diastolic blood pressure (after sitting for 5 minutes; mmHg)

Heart rate (radial pulse counted for 30 seconds after resting for 5 minutes; beats/minute)

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

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

16.7 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 screening

Incidence of clinically significant abnormalities at Visit 3 (early termination visit)

A shift table on clinically significant abnormalities between baseline and Visit 3 (Early Termination Vist) will be presented, and P- values from McNemar's test will be reported within each sequence group and overall.

A listing on clinical significant abnormalities will be reported.

16.8 REFERENCES

1. Reckitt Benckiser GA1202 Study Protocol Final Version 2.0, Amendment 1, 4Jun2013.

17 LIST OF TABLES

14.1.10.1 Prior Medications and Therapies - Full Analysis Set
14.1.10.2 Concomitant Medications and Therapies – Full Analysis Set
14.1.11 NIMP Accountability – Safety Population
14.1.12 4-Hour Monitoring Procedure – Intent-to-treat Population

14.2.1.1 Summary of 4-hour pH Monitoring Results based on Adjusted 4-hour Data – Intent-to-treat Population
14.2.1.2 Summary of 4-hour pH Monitoring Results based on Adjusted 4-hour Data by Center – Intent-to-treat Population

14.2.2.1 Analysis of Treatment Difference during the 4-hour Post Dosing Period based on Adjusted 4-hour Data – Intent-to-treat Population
14.2.2.2 Analysis of Treatment Difference during the 4-hour Post Dosing Period – Per protocol Population
14.2.2.3 Analysis of Treatment Difference during the 4-hour Post Dosing Period based on Log Transformed Adjusted 4-hour Data – Intent-to-treat Population

14.2.3.1 Analysis of Visit and Sequence Difference during the 4-hour Post Dosing Period – Intent-to-treat Population
14.2.3.2 Analysis of Visit and Sequence Difference during the 4-hour Post Dosing Period – Per Protocol Population

14.3.1.1 Summary of All Adverse Events – Safety Population
14.3.1.2 Comparison of Adverse Events during the 4-hour Post Dosing Period – Safety Population
14.3.2.1 Overall Adverse Events by System Organ Class, Preferred Term and Intensity – Safety Population
14.3.2.2 Overall Related Adverse Events by System Organ Class, Preferred Term and Intensity – Safety Population
14.3.2.3 Overall Serious Adverse Events by System Organ Class, Preferred Term and Intensity – Safety Population
14.3.2.4 Overall Related Serious Adverse Events by System Organ Class, Preferred Term and Intensity – Safety Population
14.3.2.5 Adverse Events during the 4-hour Post Dosing Period by System Organ Class, Preferred Term and Intensity – Safety Population
14.3.2.6 Related Adverse Events during the 4-hour Post Dosing Period by System Organ Class, Preferred Term and Intensity – Safety Population
14.3.2.7 Serious Adverse Events during the 4-hour Post Dosing Period by System Organ Class, Preferred Term and Intensity – Safety Population
14.3.2.8 Related Serious Adverse Events during the 4-hour Post Dosing Period by System Organ Class, Preferred Term and Intensity – Safety Population
14.3.2.9 Adverse Events Leading to Dose Change by System Organ Class and Preferred Term – Safety Population
14.3.2.10 Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Safety Population
14.3.2.11 Adverse Events Leading to Death - Safety Population
14.3.2.12 Serious Adverse Events Leading to Dose Change by System Organ Class and Preferred Term – Safety Population
14.3.2.13 Serious Adverse Events Leading to Study Discontinuation – Safety Population

14.3.3.1 Hematology: Observed Values – Safety Population
14.3.3.2 Hematology: Change from Baseline at Visit 3 – Safety Population
14.3.3.3 Clinical Chemistry: Observed Values – Safety Population
14.3.3.4 Clinical Chemistry: Change from Baseline at Visit 3 – Safety Population

14.3.3.5 Abnormal Results in Hematology – Safety Population
14.3.3.6 Abnormal Results in Clinical Chemistry – Safety Population
14.3.3.7 Clinically Significant Results in Hematology – Safety Population
14.3.3.8 Clinically Significant Results in Clinical Chemistry – Safety Population
14.3.3.9 Shift Table for Hematology – Safety Population
14.3.3.10 Shift Table for Clinical Chemistry – Safety Population

14.3.4.1 Vital Signs: Observed Values – Safety Population
14.3.4.2 Vital Signs: Change from Baseline at Visit 3 – Safety Population
14.3.5.1 Summary of Physical Examination Results – Safety Population
14.3.5.2 Shift Table for Physical Examination – Safety Population

18 LIST OF LISTINGS

16.2.1.1 Patient Completion Information - All Patients
16.2.1.2 Inclusion/Exclusion Criteria Eligibility - All Patients
16.2.1.3 Population Classification - Full Analysis Set

16.2.2. Major Protocol Deviations/Violations - Full Analysis Set
16.2.3.1 Demographic Data - Full Analysis Set
16.2.3.2 Medical History – Full Analysis Set
16.2.3.3 Concomitant Illnesses - Full Analysis Set
16.2.3.4 Smoking Habits and Alcohol/Drug Use - Full Analysis Set
16.2.3.5 GERD Status at Baseline - Full Analysis Set

16.2.3.6.1 Prior Medication and Therapies – Full Analysis Set
16.2.3.6.2 Concomitant Medications and Therapies – Full Analysis Set
16.2.3.7 Pregnancy Test Results - Full Analysis Set
16.2.3.8 12-lead ECG at Baseline – Full Analysis Set
16.2.3.9 Endoscopy Examination – Full Analysis Set
16.2.3.10 NIMP Accountability – Safety Population

16.2.4.1 4-hour pH Monitoring Procedure – Full Analysis Set
16.2.4.2 4-hour pH Monitoring Results – Full Analysis Set

16.2.5.1 Adverse Events - Safety Population
16.2.5.2 Related Adverse Events - Safety Population
16.2.5.3 Serious Adverse Events - Safety Population
16.2.5.4 Severe Adverse Events – Safety Population
16.2.5.5 Adverse Events Leading to Dose Change - Safety Population
16.2.5.6 Adverse Events Leading to Study Discontinuation – Safety Population
16.2.5.7 Serious Adverse Events Leading to Dose Change – Safety Population
16.2.5.8 Serious Adverse Events Leading to Study Discontinuation – Safety Population
16.2.5.9 Death – Safety Population

16.2.6.1 Hematology Results - Safety Population
16.2.6.2 Clinically Significant Hematology Results - Safety Population
16.2.6.3 Clinical Chemistry Results - Safety Population
16.2.6.4 Clinically Significant Chemistry Results – Safety Population

16.2.7.1 Vital Signs – Safety Population
16.2.7.2 Physical Examinations – Safety Population

APPENDIX 1 LIST OF LABORATORY ASSESSMENTS

Site 01

Assessment	Normal Range	SI Unit
Haematology		
Haemoglobin	113-151 for female, 131-172 for male	g/L
Red blood cells	3.68-5.13 for female, 4.09-5.74 for male	10^12/L
Mean cell haemoglobin concentration	322-362 for female, 320-355 for male	g/L
White blood cells	3.69-9.16 for female, 3.97-9.15 for male	10^9/L
Platelet count	101-320 for female, 85-303 for male	10^9/L
Clinical chemistry		
Sodium	130-147	mmol/L
Potassium	3.5-5.1	mmol/L
Calcium	2-2.75	mmol/L
Urea	2.5-7.1	mmol/L
Creatinine	53-97 for female, 62-115 for male	µmol/L
Uric Acid	160-430	µmol/L
Glucose	3.9-6.1	mmol/L
Inorganic phosphorous	0.8-1.6	mmol/L
Alanine transaminase	10-64	U/L
Aspartate transaminase	8-40	U/L

Site 02

Assessment	Normal Range	SI Unit

Haematology		
Haemoglobin	110-170	g/L
Red blood cells	4.09-5.74	10^12/L
Mean cell haemoglobin concentration	320-355	g/L
White blood cells	3.97-9.15	10^9/L
Platelet count	85-303	10^9/L
Clinical chemistry		
Sodium	135-145	mmol/L
Potassium	3.5-5.5	mmol/L
Calcium	2-2.5	mmol/L
Urea	1.7-8.3	mmol/L
Creatinine	40-110	µmol/L
Uric Acid	119-428	µmol/L
Glucose	3.6-6.1	mmol/L
Inorganic phosphorous	1-1.6	mmol/L
Alanine transaminase	0-75	U/L
Aspartate transaminase	0-40	U/L

Site 03

Assessment	Normal Range	SI Unit
Haematology		
Haemoglobin	110-150 for female, 120-160 for male	g/L
Red blood cells	3.5-5 for female, 4-5.5 for male	10^12/L
Mean cell haemoglobin concentration	310-350	g/L
White blood cells	4-10	10^9/L
Platelet count	100-300	10^9/L
Clinical chemistry		
Sodium	135-148	mmol/L
Potassium	3.5-5.5	mmol/L
Calcium	2.15-2.62	mmol/L
Urea	2.5-6.5	mmol/L
Creatinine	50-110	µmol/L
Uric Acid	150-420	µmol/L
Glucose	3.6-6.1	mmol/L
Inorganic phosphorous	0.82-1.62	mmol/L
Alanine transaminase	0-64	U/L
Aspartate transaminase	0-64	U/L

QUINTILES

Changes to Planned Statistical Analyses Form

Customer:	RB Healthcare
Protocol No.:	GA1202
Project Code:	QVA96908
Date:	19/MAR/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:

The term "Full Analysis Set" is to be renamed the "All Patient Population"

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

The RB Statistical Manager ([redacted]) was made aware of a comment made by the SFDA on a previous submitted RB study stating that RB had used the term Full Analysis Set (FAS) inappropriately.

According to the "Technical Guidelines of the Biostatistics for the Clinical Trials of Chemical Drugs and Biological Products" the FAS should be represented as follows: "The data set is obtained after excluding the examinees in the minimal and reasonable approach from all the randomized examinees". However the FAS in GA1202 represent **all** randomised patients. Therefore RB request that the Full Analysis Set (FAS) in this study is to be renamed the All Patient Population (APP). As listings currently including screen failures are headed 'All patients', this heading will now be headed 'All Screened Patients' to prevent confusion with the new definition.

In the final GA1202 SAP the FAS according to the guidance is represented by the Intent to Treat (ITT) population so no change is necessary for this population.

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 TFLs and ensuring appropriate documentation and explanation in the Statistical and Clinical Reports.

This change is purely a wording issue and does not affect the conduct or interpretation of the planned study analyses

Form completed by:

Title	Name	Signature	Date
Mgr, Biostatistics	[redacted]		

Form approved by:

Title	Name	Signature	Date
Dir, Biostatistics	[redacted]		

Form approved by Customer Representative (if applicable):

Title	Name	Signature	Date
Statistical Manager	[redacted]		

QUINTILES

Changes to Planned Statistical Analyses Form

Customer:	RB Healthcare
Protocol No.:	GA1202
Project Code:	QVA96908
Date:	08/MAY/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:

1. Additional analyses in which erosive/non-erosive GERD factor and its interaction with treatment are added to the primary analysis model.
2. Figure of the primary endpoint (ITT population) result showing the plot of DADA v placebo.

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

Requested by RB Statistical Manager ([redacted] to provide informative additional exploratory analyses not planned in the analyses and also a graphical representation of the primary endpoint result.

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 producing the requested output and ensuring appropriate documentation and explanation in the Statistical and Clinical Reports.

Form completed by:

Title	Name	Signature	Date
Mgr, Biostatistics	[redacted]		

Form approved by:

Title	Name	Signature	Date
Dir, Biostatistics	[redacted]		

Form approved by Customer Representative (if applicable):

Title	Name	Signature	Date
Statistical Manager	[redacted]		

QUINTILES

Changes to Planned Statistical Analyses Form

Customer:	RB Healthcare
Protocol No.:	GA1202
Project Code:	QVA96908
Date:	17/JUL/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:

Additional listing on minor protocol deviation is to be added.

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

During the preparation of the Clinical Study Report, the Quintiles Medical Writer ([redacted]) and team noticed that Table 14.1.2 includes an analysis of the minor protocol deviation, yet the listing referred to (Listing 16.2.2) only covers the major deviation.

According to the ICH GCP guidance, it was interpreted that only major deviation need to be reported hence only major protocol deviation listing was included in the SAP. However, to solve the anomaly in the CSR, RB Clinical Manager ([redacted]) and Statistical Manager ([redacted]) requested to have another listing added to display the minor deviation.

Thus, Listing 16.2.2 will become 16.2.2.1, and a new listing 16.2.2.2 will present all minor protocol deviation. Table 14.1.2 will reference both listings.

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

The RB Clinical Manager ([redacted]) and RB Statistical Manager ([redacted]) are responsible for requesting this change and Quintile Statisticians are responsible for providing the additional listing and ensuring appropriate documentation and explanation in the Statistical and Clinical Reports.

Form completed by:

Title: AD, Biostatistics — [redacted]

Form approved by:

Title: Dir, Biostatistics — Name / Signature / Date [redacted]

Form approved by Customer Representative (if applicable):

Title: Statistical Manager — [redacted]