STATISTICAL ANALYSIS PLAN

Final 1.0 dated 28th June 2017

Randomized, Double-blind, Placebo-controlled, Phase 2 Trial of RHB-102 (Ondansetron 12 mg Bimodal Release Tablets) for Diarrhea Predominant Irritable Bowel Syndrome (IBS-D)

Protocol number: RHB-102-02
Protocol Date: Amendment 4 dated 16th February 2017

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Signatures

1 REVISION HISTORY

Date	Version	Description	Author
28th June 2017	Final 1.0	Final Version	[redacted]

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2 LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviation	Description of abbreviations
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under Curve
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CO_2	Bicarbonate
CRF	Case Report Form
CRP	C-reactive Protein
CSR	Clinical Study Report
ER	Exposure-response
FDA	Food and Drug Administration
IBS	Irritable Bowel Syndrome
IBS-D	Irritable Bowel Syndrome – Diarrhea predominant
ICH	International Committee on Harmonisation
kg	kilogram
LS	Least Square
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mITT	Modified Intent-To-Treat
MMRM	Mixed Model Repeated Measures
NCI-CTCAE v 4	National Cancer Institute common terminology criteria for adverse events, version 4
OR	Odds Ratio
oz	US Fluid Ounce
PD	Protocol Deviation
PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Analysis
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TLF	Tables, Listings, and Figures
TSH	Thyroid Stimulating Hormone
USA	United States of America
vs	Versus

Abbreviation	Description of abbreviations
WBC	White Blood Cells
WHO	World Health Organization
WHO-DD	World Health Organization – Drug Dictionary

List of Key Terms

Terms	Definition of terms
Adverse Event	An adverse event is as any untoward medical occurrence in a patient administered a study drug and that does not necessarily have a causal relationship with this treatment.
Baseline	The baseline value is defined as the measurement before the first dose of double-blind study drug.
Discontinuation	The act of concluding participation, prior to completion of all protocol required elements, in a trial by an enrolled patient.
End of Study	The time of the last patient's last protocol-defined assessment.
Enrolled	A screened patient who has received the study medication.
Randomization	The process of assigning trial patients to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screened	A patient who has signed informed consent and has performed the screening visit.
Serious Adverse Event	An adverse event is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: results in death, is life threatening, results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, results in congenital anomaly, or birth defect, requires inpatient hospitalization or leads to prolongation of hospitalization, or a medically important event.

3 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

The SAP is finalized and signed prior to any of the following: study unblinding, database hard lock. For operational efficiency an earlier time is usually targeted. If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled. If conflicts arise between the SAP and protocol, the SAP will supersede the protocol.

[redacted]

4 STUDY OBJECTIVES

4.1 Primary Objective

Proportion of patients in each treatment group with response in stool consistency on study as compared to baseline. The primary endpoint is based on overall stool response, as defined in section 7.2.1.1. In addition, the proportion of patients in each treatment group who are weekly responders will be summarized over time.

4.2 Secondary Objectives

4.2.1 Efficacy

Changes in the following assessed for each treatment group:

- Decrease in worst abdominal pain
- Decrease in discomfort
- Decrease in frequency of defecation
- Decrease in interference by irritable bowel syndrome (IBS) with activities of daily living

Results of each of the secondary efficacy endpoints will be compared between the active treatment group and the placebo group. In addition, a composite efficacy endpoint of stool consistency and worst abdominal pain, per FDA guidance, will be calculated for each patient. An abdominal pain response per FDA guidance will be calculated separately. A patient is a composite responder (FDA endpoint) during a given week if he or she meets criteria for the primary endpoint, above, and meets the criteria for abdominal pain response, a decrease in the weekly average of worst abdominal pain in the past 24 hours of ≥30% compared with baseline.

4.2.2 Safety

Incidence and severity of adverse events by treatment group

4.2.3 Exploratory

- Decrease in urgency
- Use of rescue medication

This will be evaluated similarly to other secondary endpoints, above.

5 STUDY DESIGN

5.1 Description of the Disease

Irritable bowel syndrome (IBS) is a functional bowel disorder in which abdominal pain or discomfort is associated with disordered defecation (Longstreth et al, 2006). Unlike inflammatory bowel diseases, no anatomic or biochemical abnormalities have been correlated with IBS. The disease may cause substantial discomfort and morbidity, and often results in considerable reduction in quality of life (Canavan et al, 2014).

Over 10% of adults worldwide have symptoms of IBS (Canavan et al, 2014). In most studies, prevalence is much greater in females than males, with ratios of 1.5-3.0 to 1 reported in various studies.

IBS-D (IBS with diarrhea) is IBS with at least 25% of stools loose or watery and not more than 25% of stools hard or lumpy.

5.2 Study Design Overview and Drug Administration

This is a randomized, double-blind, 2-arm parallel group study conducted in USA.

After qualifying for the study, patients will undergo a two-week observation period during which stool consistency and frequency data and symptom data (refer section 12) will be collected. Patients will then be randomized 60:40 to once daily treatment with either RHB-102 12 mg (Group A) or placebo (Group B). Patients will continue on treatment for 8 weeks. All medications will be given orally.

After randomization, patients will be given a four week supply of drug and instructed to take it once daily, before breakfast with approximately 240 mL (8 oz) of water. If a patient forgets to take the medication before breakfast, he or she can take it later in the day; the time of administration should be recorded.

Patients will also be instructed to complete a diary, including information about stool consistency (Bristol chart), worst abdominal pain, discomfort, interference with daily activities, concomitant medications (including rescue medications) and adverse events.

5.3 Flow Chart

A flow chart of study evaluations or procedures is shown below in Table 1.

Table 1 Study procedures

Procedure \ Week	-4 to -2	-2 and -1[a]	1	2[b]	3	5	7	9	13
Screening assessments[c]	X								
Physical examination inc VS[d]	X		X		X	X	X	X	X
Pregnancy test[e]	X		X						
Stool, pain and discomfort assessments[f]		X	X	X	X	X	X	X	X
CBC, biochemical profile[g]	X		X			X		X	X
Urinalysis	X					X		X	X
Electrolytes[h]					X				
Pharmacokinetic sampling[i]			X		X	X			
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
Study medication dispensing			X			X			
Review of study medication use				X	X	X	X	X	

a. During weeks -2 and -1, patients will collect baseline data, including the daily assessments, use of concomitant medications including those for symptoms of IBS, and occurrence of adverse events. These data will be provided to and reviewed by the investigator and/or staff prior to the week 1 visit, at which time the patient will be randomized and start treatment.
b. Week 2 visit may be a phone contact
c. Informed consent, history, serum TSH and free T_4, urinalysis, INR, C-reactive protein, colonoscopy if not performed within 24 months of start of screening, fecal calprotectin if colonoscopy >3 months prior to consent, serology for celiac disease, stool for ova, parasites and C diff, respectively, if positive history for any of these, ECG.
d. Physical examination including vital signs: full physical examination at baseline; interim examinations of pertinent systems with attention to areas of change based on symptoms at subsequent examinations. At each visit: temperature, blood pressure, pulse, respiratory rate, weight. Height to be recorded at initial screening visit only.
e. For women of childbearing potential.
f. Stool and symptom assessments: daily Bristol chart; diaries for urgency, worst abdominal pain and worst abdominal discomfort during each day, using 11-point Likert scale (0-10) for each, with 0= no pain or no discomfort and 10= as bad as can be; daily assessment of interference by IBS with activities of daily living on a 5-point Likert scale; daily count of number of bowel movements; adverse events also to be recorded in diary. Diary may be given to patient at initial screening visit or any time thereafter.
g. Safety labs: CBC, platelet count, biochemical profile to include at a minimum albumin, alkaline phosphatase, ALT, AST, bicarbonate, total bilirubin, BUN, calcium, chloride, creatinine, glucose, magnesium, potassium, total protein, sodium.
h. Serum Ca, Cl, HCO_3, K, Mg, Na. Need not be fasting or predose.
i. Pharmacokinetic sampling will be performed on all patients on day 1 prior to initial dosing and on day 1 of weeks 3 and 5. See Table 2 for details of pharmacokinetic sampling procedure.

Table 2 Pharmacokinetic sampling

	Time, relative to dose	
Week/day	**Group A**	**Group B**
1/1	Predose	Predose
3/1	Predose, 1 h postdose	6 h postdose
5/1	6 h postdose	Predose, 1 h postdose

5.4 Randomization and Blinding

Patients will be stratified by gender (male/female) and randomized 60:40 to treatment with one of two matching products:

- RHB-102 12 mg tablets
- Placebo

At least 25% and not more than 65% of patients entered are to be males. If the planned enrollment for either gender is reached before the end of the study, no more patients of that gender will be enrolled in the study.

5.5 Duration of Treatment

Patients will be treated daily for 8 weeks.

5.6 Dose Modification

Patients who develop constipation are to reduce dosing to once every other day. When constipation resolves, if symptoms recur or worsen, the patient may, in consultation with the investigator, increase the dose back to once daily. If constipation recurs, the patient is to again decrease the dose to once every other day.

If constipation persists despite decrease in dose to once every other day, study medication is to be discontinued.

Constipation is defined as no bowel movement for 48 hours or more.

5.7 Discontinuation of Treatment

Patients must discontinue therapy if they require any medication prohibited in this study. Additional reasons for discontinuation, at the investigator's discretion:

- Clinically significant adverse event, regardless of relation to study medication
- Lack of efficacy: worsening symptoms persisting for at least two weeks during the study

In addition, patients may elect to discontinue study therapy at any time.

The investigator shall attempt to obtain follow-up assessments per protocol regardless of when the patient discontinues therapy. The procedures and tests required for the week 9 visit per Table 1 should be performed at the time of early discontinuation of therapy. The follow-up visit (week 13 in Table 1) should be conducted 4 weeks after the early termination visit.

5.8 Replacement of Patients

Patients who are randomized but receive no study medication shall be replaced.

Patients who receive any study medication shall not be replaced.

5.9 Sample Size Justification

Sample size is calculated based on expected results for achievement of the FDA-specified endpoint for stool consistency:

> A stool consistency weekly responder is defined as a patient who experiences ≥50% reduction in the number of days per week with at least one stool that has a consistency of type 6 or 7 compared with baseline.
>
> A patient will be characterized as an overall responder if the patient was a weekly responder for ≥50% of the planned weeks of treatment.

In addition, to be considered a responder for the week, the patient cannot have an increase in average abdominal pain >10% over baseline during that week. Based on Garsed et al, 2013, it is expected that approximately 80% of patients in the active treatment group and 40% of patients in the placebo group will be responder. Using a continuity-corrected Chi-Square test, to achieve a statistically significant difference between the active group and the placebo group with 80% power and significance level of $\alpha = 0.05$ using 1:1 randomization, 28 patients per group must be treated. To allow for a smaller difference, i.e., 70% response rate in the active group and 40% in placebo group, and for a 3:2 randomization ratio, a total of 104 patients would be necessary to achieve this power. In order to allow for some further decrease in the actual difference in response rates between active and placebo, e.g., unexpectedly high early drop-out rate or variability in study data, a total of 120 patients will be randomized, 72 to RHB-102 and 48 to placebo. If no substantial violations impact the results of the study, this sample size will achieve a power of 87.5%.

6 ANALYSIS SETS/POPULATIONS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

Detailed criteria for analysis sets will be laid out in Classification Specifications (CS) and the allocation of patients to analysis sets will be determined prior to database hard lock.

6.1 Modified Intent-to-Treat (mITT) population

The mITT population will include all patients who took at least 1 dose of double-blinded study drug after randomization.

In the mITT population, patients will be analyzed by the treatment they were randomized to. The population will be used for the summary of all baseline characteristics, including demographics, disease state data, prior medications, prior medical history and a statistical analysis of efficacy endpoints.

6.2 Per-Protocol (PP) Population

The PP population will include all patients from the mITT population who do not have a major protocol deviation (PD) that would affect treatment evaluation. Patients who discontinue the study due to documented lack of treatment effect will be included in the PP.

Major PD include but are not limited to:

- Lack of compliance defined as having administered <75% of the planned study medication until discontinuation.
- Fewer than 12 days (of planned 14 days) of baseline data.
- Fewer than 7 days of data if not discontinued before due to lack of efficacy.
- Use of forbidden IBS medications*.
- Failure to fulfill inclusion/exclusion criteria defining IBS-D.

  *includes the specific medications (e.g. eluxadoline) or non-specific medications (e.g. usage of loperamide more than 4 mg per day).

All efficacy analyses will be conducted in the mITT and PP populations.

6.3 Safety Population (SAF)

The SAF will include all patients who received at least 1 dose of study drug (even if the patient vomits immediately after drug administration).

In the SAF, patients will be analyzed by the actual treatment they received.

The SAF will be used for summarizing demographic and safety data.

6.4 Pharmacokinetic Population (PKP)

The PKP will include all patients treated with RHB-102 with quantifiable concentrations of ondansetron in plasma and sufficient and reliable dosing and sampling information to permit estimation of elapsed time since the prior dose.

All Pharmacokinetic (PK) analyses will be conducted in the PKP.

7 ENDPOINTS & ANALYSIS VARIABLES

7.1 Efficacy Endpoints

7.1.1 Primary Efficacy Endpoint

- Stool consistency each stool, per Bristol Stool Form scale

7.1.2 Secondary Efficacy Endpoints

- Worst abdominal pain intensity per 24-hour period, on an 11-point Likert scale
- Combined endpoint of stool consistency and worst abdominal pain (FDA endpoint)
- Frequency of bowel movements
- Worst discomfort per 24-hour period, on an 11-point Likert scale
- Interference of IBS with general functioning, on a 5-point Likert scale

7.1.3 Exploratory Efficacy Endpoints

- Urgency, on a 11-point Likert scale
- Use of rescue medication

7.2 Efficacy Variables

7.2.1 Primary Efficacy Variable

7.2.1.1 Stool Consistency

A weekly stool consistency responder is defined in the FDA guidance on IBS-D as a patient who experiences during a week a ≥50% reduction in the number of days with at least one stool that has a consistency of Type 6 or 7 on the Bristol stool scale (refer Appendix 1) compared with baseline. In addition, to be considered a responder for the week, the patient cannot have an increase in average abdominal pain >10% over baseline during that week. A patient will be characterized as an overall stool consistency responder if the patient was a weekly responder for at least 50% of the planned weeks of treatment.

In case a patient took rescue medication on a day this day will be counted as "failed day", i.e. it will be treated as if the patient had at least one stool that has a consistency of Type 6 or 7 on the Bristol stool scale on this day.

7.2.2 Secondary Efficacy Variables

7.2.2.1 Pain Response

A weekly pain responder is defined as a patient who experiences a decrease in the weekly average of worst abdominal pain in the past 24 hours score ≥30% compared with baseline and no increase in the number of days per week with stools with consistency of Type 6 or 7.

An overall pain responder is defined as patient who was a weekly pain responder for at least 50% of the planned weeks of treatment.

7.2.2.2 Overall Response

A patient is characterized as a weekly responder if the patient meets both the stool consistency and pain response definitions for a given week.

A patient is characterized as an overall study responder if the patient meets the criteria for both weekly stool consistency and pain response for at least 50% of the planned weeks of treatment.

7.2.2.3 Abdominal Pain

Abdominal pain is measured as the worst abdominal pain during a 24-hour period, on an 11-point Likert scale ranging from 0 (no pain) to 10 (as bad as can be imagined).

7.2.2.4 Discomfort

Discomfort is measured on an 11-point Likert scale ranging from 0 (no discomfort) to 10 (as bad as can be imagined).

7.2.2.5 Interference by IBS with Activities of Daily Living

Interference with daily activities is measured on a 5-point Likert scale ranging from 0 (no interference) to 4 (unable to carry out activities of daily living).

Refer Appendix 2 for sample diary card for abdominal pain, discomfort and IBS interference with daily activities.

7.2.3 Exploratory Efficacy Variables

7.2.3.1 Urgency

Urgency is the feeling of a need to defecate and inability to control or incomplete control over defecation. Urgency over the course of the day, is measured on an 11-point Likert scale ranging from 0 (no urgency) to 10 (as bad as can be imagined).

7.2.3.2 Use of Rescue Medication

Use of rescue medication is the use of any IBS-D related medication after start of randomized treatment, including allowed rescue medication loperamide.

7.3 Safety Endpoints

- Occurrence of adverse events, both clinical and laboratory.

Adverse events will be tabulated by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) version 13.1. Adverse events will be graded 1-5 according to NCI-CTCAE v4 criteria.

7.4 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug).

- Vital signs
- Physical Examination
- 12-lead electrocardiogram (ECG)
- Clinical laboratory variables (CBC, serum chemistry including liver function tests, and urinalysis)

7.5 Other Variables

7.5.1 Duration of Exposure

For each patient the duration of exposure on double-blind treatment will be calculated in days using the following formula:

(Date of last dose of study drug – Date of first dose of study drug) + 1

where the dates of the first and last known double-blind treatment are recorded on the study drug dosing eCRF pages. If they are missing, then no imputed dates will be used. Any gaps in dosing will be included in the total number of days on double-blind treatment.

7.5.2 Percent Compliance

Percent compliance for the study medication (either RHB102 12 mg or matching placebo) during treatment period is defined for each patient as the number of tablets taken, divided by the number of tablets that should have been taken times 100.

The number of tablets that should have been taken is calculated as 1 + (date of last intake of study medication – date of first intake of study medication) times the prescribed daily dose (i.e. 1 tablet per day). In case a patient has to reduce the dose due to constipation to once every other day, the number of days that should have been without dosing will be subtracted from the calculated number. The number of tablets taken is the total number of tablets recorded as taken based on the CRF, summed over the days counted when calculating the number of tablets that should have been taken, including the day of the last study treatment dose.

7.5.3 Prior, Concomitant, and Follow-up Medication

7.5.3.1 Prior Medication

Prior medication is defined as medication that stopped before the date of the first dose of treatment (i.e. last medication intake is prior to first dose of treatment date (exclusive)). All prior medications (includes IBS-D related or non- IBS-D related), regardless of when they were taken, will be collected on the eCRF.

7.5.3.2 Concomitant Medication

Concomitant medication (includes IBS-D related or non-IBS-D related) is defined as a medication with either

- a recorded medication start date falling within the treatment period, or

- a recorded medication start date prior to the first day of study medication during the randomized treatment period without any recorded medication stop date prior to the start of the randomized treatment period.

This means that concomitant medications will be any medication taken from start of the randomized treatment period up to the end of the randomized treatment period. Medications with incomplete start or stop dates will be considered concomitant medications if it is possible that they could have been concomitant medications.

7.5.3.3 Follow-up Medication

Follow-up medication (includes IBS-D related or non-IBS-D related) is defined as any medication starting after the week 9 visit date.

7.5.4 Demographics

The patient's year of birth, sex, race, ethnicity, height, and weight will be recorded at Screening Visit.

8 STATISTICAL METHODOLOGY

8.1 General Considerations

All data processing, summarization, and analyses will be performed using SAS® Version 9.3 or higher. Specifications for table, figures, and data listing formats can be found in the TLF specifications for this study.

Continuous variables will be summarized using the standard descriptive statistics which includes number of patients (n), arithmetic mean, standard deviation (SD), minimum, median, and maximum. When needed, the use of other percentiles (e.g. 10%, 25%, 75% and 90%) will be mentioned in the relevant section. Categorical variables will be described using absolute and relative frequencies (n & %'s). Percentages by categories will be based on the number of patients with no missing data, i.e. will add up to 100%. Shift tables will be provided, where appropriate. Confidence Intervals (CI) will be two-sided 95% Cis if not otherwise specified. If not specified otherwise, statistical tests will be two-sided with a significance level of $\alpha = 0.05$.

In general, baseline is defined as the last measurement before the first dose of double-blind study drug. In this study, if baseline values for (semi-) continuous variables are derived from the daily assessments during the two-week observation period preceding randomization, these will be defined as the average of the respective measurements over this two-week period.

All analyses and summary tables will be displayed by treatment group. Primary and few key secondary endpoints will be analyzed by subgroups. For the definition of subgroups of interest please refer to section 8.8.

8.1.1 Model Structure or SAS Codes

8.1.1.1 Chi-Square Test with Continuity Correction

The following SAS statements will be used for the primary and secondary endpoint analyses:

```
PROC FREQ data=<dataset name>;
      TABLES response variable*grouping variable/CHISQ OUT=< output dataset name>
       OUTPUT OUT=stats;
RUN;
```

Note: In case the assumption of Chi-square test is not met (e.g. expected cell frequencies < 5), a Fisher's exact test will also be carried out as supportive analysis for the primary and binary secondary endpoints. The SAS code is similar but with "FISHER" option in the "TABLES" statement above.

8.1.1.2 Logistic Regression

For the primary secondary and secondary endpoint analyses, a logistic regression model for the response rate (*RR)* will be modeled with the logit link as follows:

$$logit(E(RR_{ij})) = \beta_0 + Trt_i + Gender_j$$

where $(E(RR_{ij}))$ is the probability that a patient *s* from treatment group *i*, and gender *j* demonstrates a response.

The odds ratio (OR) as well as its two-sided Wald 95% CIs and p-value for Treatment vs placebo will be derived.

The SAS code used to implement this test will be similar to that shown below:

```
PROC GENMOD DATA =<dataset name> order=data;
CLASS Trt Gender;
      MODEL Responder(event='1') = Trt Gender/ DIST=bin LINK=logit
      LRCI type3 wald;
      ESTIMATE 'Treatment versus placebo' Trt 1 -1 / EXP;
      LSMEANS Trt / DIFF CL CORR PDIFF;
RUN;
```

8.1.1.3 Analysis of Covariance

Changes from baseline to a post-baseline visit (in every treatment week for worst abdominal pain discomfort, Interference by IBS, frequency of defecation, and urgency) will be analyzed using the following Analysis of Covariance (ANCOVA) model:

$$Ch_{ijks} = \beta_0 + \beta_1 Base_{ijks} + Trt_i + Site_j + Gender_k + \in_{ijks}$$

where Ch_{ijks} is the change from baseline for patient s from treatment group i, study site j, and gender k. β_0 and β_1 are the intercept and the slope of Ch_{ijks} as a function of the baseline value and $\in_{ijks}$ is the residual for each patient.

The ANCOVA model results will be presented with least squares (LS) means and two-sided 95% confidence intervals (CIs) for mean changes from baseline within each treatment group. Differences in LS means between treatment vs placebo will be derived together with two-sided 95% CIs and p-values.

The SAS code used to implement this test will be similar to that shown below:

```
PROC MIXED DATA=dataset COVTEST NOCLPRINT;
        CLASS Trt Site Gender;
        MODEL Ch=Base Trt Site Gender / SOLUTION CL;
        LSMEANS Trt / CL OM AT MEANS PDIFF;
        ESTIMATE 'Treatment versus placebo' Trt 1 -1 /EST CL;
RUN;
```

8.1.1.4 Mixed Model Repeated Measures (MMRM)

To assess the impact of time, weekly changes from baseline to each post-baseline visit "t" (e.g. in mean values in worst abdominal pain, discomfort, interference by IBS with activities of daily life, and frequency of defecation etc.,) will be analyzed using the following MMRM model:

$$Ch_{ijkst} = \beta_0 + \beta_1 Base_{ijks} + Trt_i + Site_j + Gender_k + Week_t + Trt*Week_{it} + \in_{ijkst}$$

where Ch_{ijkst} is the change from baseline (i.e. time = 0 week) for patient s from treatment group i, Study site group j, Gender k and for given week t ($t= 1,...,8$). β_0 and β_1 are the intercept and the slope of Ch_{ijks} as a function of the baseline value and $\in_{ijkst}$ is the residual for each patient. $Trt*Week_{it}$ is the time-by-treatment interaction effect. The unstructured co-variance matrix will be used to adjust for the within-patient error variance co-variance.

The MMRM model results will be presented with LS means, standard errors and two-sided 95% CIs for mean change from baseline overall and at all time points (weeks 1 to 8) within each treatment group. The denominator degrees of freedom will be calculated according to the Kenward-Roger method.

The SAS code used to implement this test will be similar to that shown below:

```
PROC MIXED DATA=dataset COVTEST NOCLPRINT METHOD=REML;
     CLASS ID Trt Time Site Gender;
     MODEL ch=Base Trt Site Gender Time Time*Trt /
     SOLUTION CL DDFM=KenwardRoger;
     REPEATED Time /SUBJECT = ID TYPE = UN R RCORR;
     LSMEANS Trt / CL PDIFF;
```

```
      ESTIMATE 'Ondansetron versus placebo' Trt 1 -1 /EST
CL;
RUN;
```

In case of non-convergence of the above model, the same model but with AutoRegressive-1 (AR(1) covariance matrix) will be preferred. If the problem is still not resolved, the model could be fitted by removing study site from the list of covariates.

8.2 Study Population

8.2.1 Disposition of Patients

The following patient data will be presented:

- Number of patients with informed consent, discontinued before randomization, randomized (overall only);
- Number and percentage of patients randomized in each analysis set/population, by treatment group and overall;
- Number and percentage of patients completed and discontinued treatment, by primary reason for treatment discontinuation for randomized patients, by treatment group;
- Number and percentage of patients completed and discontinued the study (as defined by investigator's assessment per End of Study page of the CRF), by primary reason for study discontinuation for randomized patients and by treatment group;
- Number and percentage of patients who completed the study according to the following objective definition: A patient is defined as a completer if the following conditions are fulfilled: (i) completion of at least 7.6 calendar weeks of treatment (with or without treatment gaps), (ii) attendance of an end-of-study visit 28 ± 11 days after the last date of study medication intake.
- Number and percentage of patients excluded from PP population by reason for exclusion defined in section 6.2, by treatment group for mITT.

8.2.2 Protocol Deviations

Major protocol deviations as defined in the study protocol (Section 7.2.2 Protocol Deviations) will be assessed for all randomized patients. The number and percentage of patients meeting any criteria will be summarized for each criterion and overall, by treatment group and total as well as by study site. Patients deviating from a major criterion more than once will be counted once for the corresponding criterion. Any patients who have more than one major protocol deviation will be counted once in the overall summary. A data listing will be provided by site and patient for all the major and minor protocol deviations.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

Protocol Deviation (PD)1 - Lack of compliance defined as having administered <75% of the planned study medication until discontinuation,

PD2 - Fewer than 12 days (of planned 14 days) of baseline data,

PD3 - Fewer than 7 days of data if not discontinued before due to lack of efficacy,

PD4 - Use of forbidden IBS medications*,

PD5 – Failure to fulfill inclusion/exclusion criteria defining IBS-D,

PD6 – Presence of excluded conditions at baseline.

*includes specific medications (e.g. eluxadoline) or non-specific medications (e.g. loperamide over allowed amount).

Note: Failure to fulfill the other entry criteria such as laboratory parameters outside the limits will be considered as minor protocol deviations.

8.2.3 Demographic and Other Baseline Characteristics

Demographic and pre-treatment patient characteristics, including disease parameters and comorbidities, will be summarized with descriptive statistics by treatment group.

Descriptive statistics for age (in years), baseline weight (in kg), body mass index (BMI), body surface area (BSA) and height (in cm) at study entry will be presented. Frequency tabulations for sex, ethnicity, age group (< 65, ≥ 65 years), race, Irritable Bowel Syndrome Symptomatology as collected in the eCRF will be presented. This will be done for the SAF, mITT and PP Populations by treatment group.

BMI is calculated as BMI (kg/m^2) = weight (kg) / height^2 (m).

BSA is calculated as BSA (m^2) = weight$^{0.5}$ (kg) x height$^{0.5}$ (m) / 6 (Mosteller formula).

Medical history is coded in MedDRA v 13.1, and will be summarized by System Organ Class (SOC) and Preferred Term (PT), by treatment group for the SAF.

8.2.4 Prior and Concomitant Medications

Prior medications (IBS-D related or non-IBS-D related) are coded with World Health Organization – Drug Dictionary (WHO-DD) March 2015 Enhanced, and will be summarized by therapeutic subgroup (Anatomical Therapeutic Chemical (ATC) 2nd level) and chemical subgroup (ATC 4th level) and preferred World Health Organization (WHO) name by treatment group for the SAF.

As with prior medications, concomitant medications (includes IBS-D related or non- IBS-D related) will be summarized for each treatment group by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the SAF. Patients taking the same medication multiple times will be counted once per medication and investigational period.

Please refer section 7.5.3 for case definitions.

8.3 Study Drugs

8.3.1 Exposure

The following information on drug exposure will be presented for each treatment group for the SAF:

- Descriptive statistics for number of days treatment was received will be presented by treatment group
- Descriptive statistics will be presented for the duration of exposure by treatment group.

8.3.2 Treatment Compliance

Overall compliance will be examined for patients in the SAF whose total study drug count and first and last days of treatment are known.

Percent overall compliance will be summarized in two ways for the SAF:

- Descriptive statistics will be presented by treatment group.
- Percent compliance will be categorized according to the following categories by treatment group:
    - less than 50%
    - at least 50%, less than 75%
    - at least 75%, less than 90%
    - at least 90%, less than 110%
    - greater than 110%
    - unknown.

8.4 Analysis of Efficacy

All efficacy analyses will be conducted in the mITT and PP populations.

8.4.1 Analysis of Primary Endpoint

8.4.1.1 Primary Analysis

The primary endpoint in the study is stool consistency response in the absence of increase in pain ≥10%.

Hypotheses:

Let p_O denote the response rate under RHB-102 and p_P denote the response rate under placebo then the primary two-sided hypothesis to be tested is

H_0: $p_O - p_P = 0$

vs the alternative

H_1: $p_O - p_P \neq 0$.

A Chi-Square test with continuity correction at the significance level $\alpha = 0.05$ will be employed for the primary (confirmatory) analysis of the primary endpoint.

In case the assumptions of Chi-square test is not met (e.g. expected cell frequencies < 5), a Fisher's exact test in addition to Chi-square test with continuity correction will be carried out as supportive analysis. This analysis holds also for the other binary endpoints.

8.4.1.2 Secondary Analysis

The weekly response rates will also be compared for each week between the treatment groups with a Chi-Square test with continuity correction.

For each treatment week the change in average daily stool consistency (as measured on the Bristol Stool Form scale) from baseline will be compared between the treatment groups with an ANCOVA model including treatment group, study site and gender as independent variables and baseline daily stool consistency (see section 8.1) as covariate. If on a day no stool was confirmed, a value of 0 will be assigned for this day.

To assess the impact of time a Repeated Measurement Model will be applied with the weekly changes from baseline as dependent variable, treatment group, study site, gender, week and treatment x week interaction as independent variables and baseline daily stool consistency as covariate. Study site could be removed from the covariates in case of convergence issues.

To assess the effect of gender on the primary endpoint, a logistic regression model with treatment group and gender as covariates will be modeled.

8.4.2 Analysis of Secondary Endpoints

Secondary efficacy endpoints include the following:

- Proportion of patients in each treatment group who are pain responders, per FDA guidance definition
- Proportion of patients in each treatment group who are overall responders, per FDA guidance definition
- Differences between treatment groups in
    - Abdominal pain
    - Discomfort
    - Frequency of defecation
    - Interference by IBS with activities of daily living

All secondary analyses are considered as exploratory, no adjustments for multiplicity will be made.

8.4.2.1 Pain Response

Refer section 7.2.2.1 to understand the derived pain response variable.

A Chi-Square test with continuity correction at the significance level $\alpha = 0.05$ will be employed for the comparison of the treatment groups regarding overall and weekly pain response.

To assess the effect of gender on the overall pain response, a logistic regression model with treatment group and gender as covariates will be applied.

8.4.2.2 Overall Response

Refer section 7.2.2.2 to understand the derived overall response variable.

A Chi-Square test with continuity correction at the significance level $\alpha = 0.05$ will be employed for the comparison of the treatment groups regarding overall and weekly study response.

To assess the effect of gender on the overall study response, a logistic regression model with treatment group and gender as covariates will be applied.

8.4.2.3 Abdominal Pain

Refer section 7.2.2.3 to understand the abdominal pain variable.

For each treatment week the change in the weekly average of worst abdominal pain from baseline will be compared between the treatment groups with an ANCOVA model including treatment group, study site and gender as independent variables and baseline worst abdominal pain (see section 8.1) as covariate.

To assess the impact of time, a Repeated Measurement Model will be applied with the weekly changes from baseline as dependent variables, treatment group, study site, gender, week and treatment x week interaction as independent variables and baseline worst abdominal pain as covariate. Study site could be removed from the covariates in case of convergence issues.

8.4.2.4 Discomfort

Refer section 7.2.2.4 to understand the discomfort variable.

For each treatment week the change in the weekly average of discomfort from baseline will be compared between the treatment groups with an ANCOVA model including treatment group, study site and gender as independent variables and baseline discomfort (see section 8.1) as covariate.

To assess the impact of time, a Repeated Measurement Model will be applied with the weekly changes from baseline as dependent variables, treatment group, study site, gender, week and treatment x week interaction as independent variables and baseline discomfort as covariate. Study site could be removed from the covariates in case of convergence issues.

8.4.2.5 Interference by IBS with Activities of Daily Living

Refer section 7.2.2.5 to understand the interference by IBS with activities of daily living variable.

For each treatment week the change in the weekly average of interference from baseline will be compared between the treatment groups with an ANCOVA model including treatment group, study site and gender as independent variables and baseline interference score (see section 8.1) as covariate.

To assess the impact of time, a Repeated Measurement Model will be applied with the weekly changes from baseline as dependent variables, treatment group, study site, gender, week and treatment x week interaction as independent variables and baseline interference score as covariate. Study site could be removed from the covariates in case of convergence issues.

8.4.2.6 Frequency of Defecation

For each treatment week the change in average daily frequency of defecation from baseline will be compared between the treatment groups with an ANCOVA model including treatment group, study site and gender as independent variables and baseline daily frequency of defecation (see section 8.1) as covariate.

To assess the impact of time a Repeated Measurement Model will be applied with the weekly changes from baseline as dependent variable, treatment group, study site, gender, week and treatment x week interaction as independent variables and baseline daily frequency of defecation as covariate. Study site could be removed from the covariates in case of convergence issues.

8.4.3 Analysis of Exploratory Endpoints

8.4.3.1 Urgency

For each treatment week the change in the weekly average of urgency from baseline will be compared between the treatment groups with an ANCOVA model including treatment group, study site and gender as independent variables and baseline urgency (see section 8.1) as covariate. To assess the impact of time, a Repeated Measurement Model will be applied with the weekly changes from baseline as dependent variables, treatment group, study site, gender, week and treatment x week interaction as independent variables and baseline urgency as covariate.

8.4.3.2 Use of Rescue Medication

Use of rescue medication will be analyzed qualitatively and quantitatively. The number of patients using any rescue medication (any dosage) during the complete treatment phase will be compared between the treatment groups using a continuity corrected Chi-Square test.

The only rescue medication allowed as per protocol is loperamide, which may not be taken more often than package insert instructions, i.e., maximum daily dose two 2 mg pills (total of 4 mg) or equivalent in other dosage forms. The number of patients using loperamide (any dosage) during the complete treatment phase will be compared between the treatment groups using a continuity corrected Chi-Square test. The average weekly dosage (mg/week) of loperamide for each treatment week and overall will be summarized by descriptive statistics and compared between the treatment groups using a two-sided t-test.

8.4.4 Sub-group Analyses

The primary endpoint, improvement in stool consistency, and the secondary endpoints pain response and overall response will be analyzed for all patients and by gender, CRP value at baseline (≤ or > median CRP, the median value in the mITT population will be used for defining the subgroups) and use of rescue medication after start of randomized treatment, i.e. Chi-square test with continuity correction will be repeated by gender, CRP value at baseline and use of rescue medication as described under the sections 8.4.1.1, 8.4.2.1 and 8.4.2.2.

To evaluate the differences in effect by gender, additional efficacy endpoints may be analyzed by gender if trends towards differences (p-value from logistic regression ≤ 0.1) are seen in the endpoints initially analyzed by gender.

Further sub-group analyses may be performed as ad-hoc analyses after the protocol-defined analyses if this is suggested by the data.

8.5 Analysis of Safety

The safety and tolerability of RHB-102 will be determined by reported AEs, physical examinations, vital signs, and laboratory tests. All analyses of safety will be performed in the Safety population.

No inferential comparison between treatment groups will be performed for the safety analysis in this study.

8.5.1 Adverse Events

The incidence of treatment-emergent AEs will be summarized for each treatment group by MedDRA v 13.1 SOC and PT. An AE is defined as treatment-emergent if its onset date/time is on or after the date/time of the first intake of study drug or if a pre-existing condition becomes worse after the date/time of first intake of study drug. An AE is defined as pre-treatment if its onset date/time is before the date/time of the first intake of study drug. If it is not possible to determine whether an AE is treatment–emergent, due to a missing or incomplete start date, the AE will be regarded as treatment–emergent unless the stop date definitely indicates that the event was prior to first dose of study drug.

All new abnormal laboratory findings and those abnormal at baseline which change significantly (i.e., by at least one toxicity grade as defined in the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03) are considered AEs. Laboratory AEs for which there is no clinical intervention will be extracted from the laboratory data programmatically. Laboratory AEs not listed in the NCI CTCAE v4.03 will be considered as grade 1 (mild) if there is no clinical effect or intervention. Laboratory values outside the normal range for certain parameters will not be considered AEs if they are generally not considered as indicating an abnormality; this includes such parameters as liver enzymes which are below the normal range. If there is a clinical sequela or intervention, the laboratory abnormality is to be graded according to the criteria used for clinical AEs.

The NCI CTCAE v4.03 can be downloaded in pdf, Excel or OWL format at:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

AEs will be summarized according to the following:

- An overview of the absolute and relative frequencies of patients with at least one AE will be given for the categories pre-treatment and treatment-emergent by seriousness, severity, and causality.
- Further tables will present the absolute and relative frequencies of patients with at least one treatment-emergent AE classified by SOC and PT and, in addition, by severity and causality.
- The absolute and relative frequencies of patients with at least one SAE will be summarized by SOC and PT.
- Individual patient data listings will be provided for all discontinuation of study medication due to AEs.

Regarding the summaries by severity and causality, the following rule will be applied:

If a patient experiences more than one AE within the same SOC or with the same PT, the AE with the highest severity or closest relationship to study drug will be used for the analysis.

8.5.2 Clinical Safety Laboratory Tests

Key laboratory data (biochemistry, hematology, and urinalysis) will be subjected to both a quantitative analysis (descriptive summary statistics such as mean, standard deviation, minimum, maximum, and median) and qualitative analysis where frequencies of normal, abnormal low, and abnormal high values will be computed.

The following parameter will be analyzed:

Complete blood count (CBC) including:

- hemoglobin,
- total white blood cells (WBC) count,
- absolute values for individual white blood cell types (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
- platelet count.

Biochemical profile including:

- albumin,
- alkaline phosphatase,
- alanine transaminase (ALT),
- aspartate transaminase (AST),
- (total) bilirubin,
- blood urea nitrogen (BUN),

- calcium,
- chloride,
- CO_2,
- creatinine,
- glucose,
- magnesium,
- potassium,
- sodium,
- total protein.

Urinalysis including:

- routine: dipstick tests for protein, glucose, ketones, blood, pH, specific gravity;
- microscopic: erythrocytes, leukocytes, bacteria, crystals, casts.

At screening only also the following parameters will be evaluated: INR (at baseline only), serum TSH and free T_4, INR, and C-reactive protein.

The following analyses will be performed for CBC and biochemical profile, results for urinalysis will be listed only:

- Standard descriptive summary statistics will be calculated at each scheduled measuring time point and the last individual measuring time point.
- Standard descriptive summary statistics will be calculated for the absolute change from baseline to each scheduled measuring time point after baseline and the last individual measuring time point.
- Shift tables displaying changes with respect to the normal range between baseline and the worst value measured after baseline will be provided. Shift tables will show changes by grade for analytes graded in the NCI CTCAE v 4.03 criteria.
- A listing of all patients with abnormal values at any time point will be given.

For the summary tables laboratory parameter will be reported using US conventional units. No inferential testing will be performed to compare the differences between the treatment groups; a paired-sample t-test may be provided for each group for change from baseline if data warrant.

8.5.3 Other Parameters

The results from physical examination, including vital signs, will be presented in the patient data listings. Findings on physical examination, including vital signs, which constitute clinically significant changes will be listed as adverse events.

8.5.3.1 Electrocardiograms (ECGs)

ECG variables (heart rate, PR interval, RR interval, QRS interval, QT interval, and QTcF interval) will be summarized using descriptive statistics or frequencies and percentages for each treatment group at baseline.

Number and percent of patients with normal, not clinically significant abnormal, and clinically significant abnormal results as assessed by local investigator for the 12 lead ECG will be tabulated by treatment group at baseline.

8.5.3.2 Pregnancy Test Results

By-patients listing of pregnancy test results will be provided using Safety population.

8.6 Analysis of Pharmacokinetics (PK)

Ondansetron concentrations will be listed and summarized by visit and PK randomization group. In the listing, the date and time will be recorded for the dose of RHB-102 (or placebo) taken prior to blood sampling to determine ondansetron concentration in plasma. This is the dose of the prior day for pre-dose PK samples.

Nonlinear mixed-effects methods will be used to develop a population-based pharmacokinetic (PopPK) model of ondansetron concentrations in plasma after administration of RHB-102. Individual post hoc Bayesian estimates of pharmacokinetic (PK) model parameters will be used to estimate the steady-state peak (Cmax) and trough (Cτ) concentrations and the area under the curve of concentration versus time over the dosing interval (AUCτ). PopPK modeling will be described in a separate modeling and simulation analysis plan.

8.7 Analysis of Pharmacodynamics (PD)

Cmax, Cτ, and AUCτ will serve as exposure metrics in exploratory plots of exposure versus relevant efficacy and safety endpoints. Exposure-response (ER) models may be developed to describe emerging trends.

ER modeling will be described in a separate modeling and simulation analysis plan.

8.8 Subgroups of Interest

Primary efficacy endpoint and few secondary endpoints will be summarized by treatment group for the subgroups defined on the basis of the categorized variables listed below:

Grouping variable	Subgroups
Gender	Male
	Female
Use of rescue medication after start of randomized treatment	Yes
	No
CRP value at baseline	≤ median CRP
	> median CRP

8.9 Other Analyses

Not applicable

8.10 Handling of Missing Data, Outliers, Visit Windows, and Other Information

8.10.1 Missing Data

If a patient fails to provide any assessments after baseline (e.g. if the diary is missing completely) he/she will be counted as a non-responder in any of the overall responder analyses (overall stool consistency response, overall pain response, overall study response). To be included in one of the weekly analyses for the primary or any of the secondary endpoints a patient has to provide data for this endpoint at least on 4 days of the respective week, otherwise the patient will be considered a non-responder for that week for the weekly response analyses or will be excluded from the analysis for the quantitative analyses. If a patient fails to be included in more than two of the weekly responder analyses, he/she will also be counted as non-responder in any of the overall responder analyses. Otherwise missing values will not be imputed. For the treatment of missing/incomplete start and stop dates of adverse events and medications refer to the corresponding sections.

8.10.2 Outliers

No outlier detection will be performed.

8.10.3 Visit Windows

Day 1 for the randomized study treatment period is the start date of study medication. The following visit windows will apply for the measurements (vital signs and laboratory data) collected in the eCRF .

Analysis visit	Protocol defined visit window	Actual assessment window (Study Days)
Screening	-4 to -2 weeks	
Baseline	-2 to -1 week	
Week 1	Within 6 weeks of consent	
Week 2	Week 2 ± 2 days	5 - 9
Week 3	Week 3 ± 2 days	12 - 16
Week 5	Week 5 ± 2 days	26 - 30
Week 7	Week 7 ± 2 days	40 - 44
Week 9/End of Treatment	Week 9 ± 2 days	54 - 58
Week 13/Follow-up	Week 13 ± 4 days	80 - 88

NOTE: visit windows/study days will be calculated based on the Week 1 date.

Values falling outside of the visit windows will be listed only but will not contribute to any summary statistics except for the laboratory shift tables to worst value after baseline.

For laboratory and non-laboratory parameters, if a patient has more than one measurement included within a window, the assessment closest to the target day will be used. In case of ties between observations located on different sides of the target day, the earlier assessment will be used.

9 INTERIM ANALYSIS

No interim analyses or safety data monitoring reports are planned for this study.

10 CHANGES TO PLANNED ANALYSES

The following analyses have been added/clarified in the SAP.

- An objective definition of study completion has been added in section 8.2.1.
- Fisher's exact test in case the expected cell frequency is < 5 for Chi-square test with continuity correction.
- For MMRM, proposal to remove study site as one of the covariates in case of issues with convergence.
- Subgroup analyses with subgroups defined by the use of rescue medication and the baseline CRP value (≤ or > median) have been added.
- An analysis of weekly mean daily stool consistency was added.
- The analysis of rescue medication use was clarified. The following summaries will be presented
    - Overall Use of Rescue Medication
    - Overall Use of loperamide
    - Overall Mean Weekly Dosage (mg/week) of loperamide
    - Mean Weekly Dosage (mg/week) of loperamide

Use of rescue medication was now defined as an exploratory endpoint in this study.

- No summaries of SAEs by severity and causality and no patient listing for cases of death will be generated.

11 REFERENCES

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Garsed K, Chernova J, Hastings M, Lam C, Marciani L, Singh G, Henry A, Hall I, Whorwell P, Spiller R. A randomised trial of ondansetron for the treatment of irritable bowel syndrome with diarrhea. Gut 2014;63:1617-25.

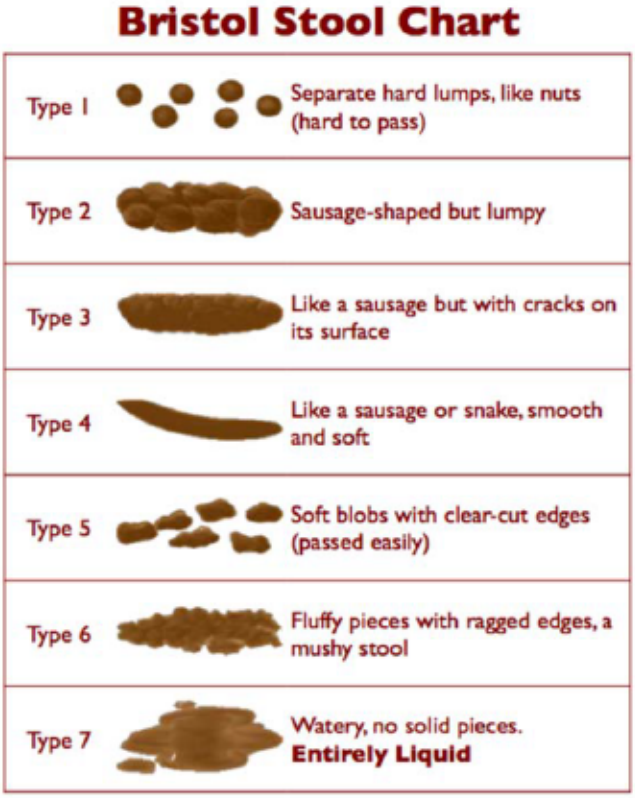
ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics)

Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterol 2006;130;1480-91.

12 APPENDICES

Appendix 1: Bristol Stool Form Scale



Appendix 2: Diary card for abdominal pain, discomfort and IBS interfere with daily activities

Instructions:
- Please complete this diary card at the end of the day

How bad was your worst abdominal pain over the past 24 hours? Please select one number:

0 — No pain
1 — Barely felt pain
2
3 — Mild
4
5 — Moderate
6
7 — Severe
8
9 — Excruciating
10 — As bad as can be imagined

How much discomfort did you have over the past 24 hours? Please select one number:

0 — No discomfort
1 — Barely felt discomfort
2
3 — Mild
4
5 — Moderate
6
7 — Severe
8
9 — Excruciating
10 — As bad as can be imagined

How much did your IBS interfere with your daily activities over the past 24 hours? Please select one number:

0 — No interference
1 — Mild interference
2 — Moderate interference
3 — Severe interference
4 — Unable to carry out activities of daily living

STATISTICAL ANALYSIS PLAN

Addendum 1.0 dated 28th November 2017

Randomized, Double-blind, Placebo-controlled, Phase 2 Trial of RHB-102 (Ondansetron 12 mg Bimodal Release Tablets) for Diarrhea Predominant Irritable Bowel Syndrome (IBS-D)

Protocol number: RHB-102-02
Protocol Date: Amendment 4 dated 16th February 2017
SAP Date: Version 1.0 dated 28th June 2017

Sponsor:
RedHill Biopharma Ltd.
21 Ha'arba'a St.
Tel-Aviv 64739, Israel

Signatures

1 REVISION HISTORY

Date	Version	Description	Author
28th June 2017	Final 1.0	Final Version	[redacted]
28th November 2017	Addendum 1.0	Addendum to the Final Version	

Table of Contents

2 INTRODUCTION

This Addendum to the Statistical Analysis Plan (SAP), Final 1.0, June 28th 2017, contains a description of the additional analyses requested to support the final TFLs. These analyses are ad-hoc analyses which were requested after the study was unblinded. The analyses described in this document do not replace the analyses conducted according to the final version of the SAP.

3 GENERAL CONSIDERATIONS

3.1 Study Populations

As the mITT and Safety population are identical in this study, the tables for the latter population will be not generated for the final report when the same table is also to be generated for the mITT population. A footnote will be added to the table in the mITT population indicating the reason for omitting the table in the safety population.

To assess the impact of the results of the PK analysis on the study outcomes two further study populations will be defined in addition to those defined in the study protocol and SAP:

Per Protocol Pharmacokinetic Population (PPPK population)

The PPPK population will include all patients from the PK population whose PK results are appropriate to the treatment that they have received.

For patients treated with RHB-102:

- Positive values not below the level of quantification (BLQ) and not greater than 100 ng/mL for ondensatron concentrations measured 1 hour or 6 hours after dosing at the week 3 and the week 5 visits.
- Pre-dose values of ondensatron concentrations BLQ at the week 1 visit.
- Pre-dose values of ondensatron concentrations at the week 3 and week 5 visit may be positive, but not greater than 100 ng/mL, or BLQ.

For patients treated with placebo all measured concentrations of ondensatron must be BLQ for inclusion in the PPPK population.

Non-Per Protocol Pharmacokinetic Population (Non-PPPK population)

All patients in the PK population that do not fulfill the conditions to be included in the PPPK population will be included in the Non-PPPK population.

These two new analysis populations are introduced to show that the efficacy results in these populations are similar to the results in the mITT populations and to each other.

3.2 Use of Rescue Medication

For classifications regarding the use of rescue medication the analyses so far utilized the information from the patient diary and the eCRF page for IBS-D related medications. For the final analysis the information from the diary will not be used anymore (except in the special

case outlined below). Especially for the calculation of the primary and two key secondary efficacy endpoints - stool consistency response, pain response and study response as defined in section 7.2 of the SAP - "failed days" due to the intake of rescue medication will not be defined by the corresponding entries in the diary but according to the recoded medication use in the eCRF.

- If the dose of an IBS-D related medication is not denoted as per need (PRN) a day will be counted as "failed day" regarding the consistency if it is in the interval between start date and end date (both dates inclusive) of the recorded medication. If the medication is ongoing then all days on or after the start date will be counted as "failed days".
- If the dose of an IBS-D related medication is denoted as per need (PRN), then and only then also the entries in the patient diary will be taken into account. A day will be counted as "failed day" if it lies between the start and the end date (both dates inclusive) of the pertaining medication and if the use of rescue medication for this day is answered with yes in the diary. If for a day between start and the end date of the pertaining medication use of rescue medication is not supported in the diary this day will be categorized according to the recorded values of the Bristol Stool Scale. If the medication is ongoing then this rule will be applied to all days after the medication start date.

For the subgroup analyses by use of rescue medication the two groups (use of rescue mediation/ no use of rescue medication) will solely be defined by the records from the eCRF.

4 ADDITIONAL ANALYSES

4.1 Patient Disposition

In Table 14.1.1.1 the reasons for discontinuation of study medication will be added. Further three additional categories will be displayed:

(1) Patients in the PPPK population

(2) Patients in the Non-PPPK population

(3) Patients who completed treatment with study medication but discontinued the study

A listing will be generated that includes patients with different outcomes recorded on the end of treatment and end of study page from the eCRF.

4.2 Reasons for Screening Failures

An analysis will be added that summarizes the reason for screening failures (violated inclusion and met exclusion criteria). Patients who failed screening without documented violation of an entry criterion will be summarized under "Unknown reason".

4.3 Baseline Characteristics

In addition to the Irritable Bowel Syndrome Symptomatology as collected in the eCRF, the number and frequency of patients will be presented who have:

(1) at least one symptom rated as moderate or severe.

(2) at least one symptom rated as severe.

This will be done for the mITT and PP Populations by treatment group.

4.4 Efficacy Analyses

4.4.1 Analyses in the PPPK and Non-PPPK Populations

The primary efficacy variable (overall stool response) and the two key secondary efficacy variables (overall pain response and overall study response) will also be analyzed in the PPPK population and Non-PPPK population as defined in Section 3.1 of this Addendum.

4.4.2 Previous Use of IBS-D Related Medications as Covariate

The summary of previous use of IBS-D related medications showed an imbalance between subjects later randomized to RHB-102 12 mg and placebo (32% in RHB-102 vs. 22% in placebo group). To investigate a possible effect, a logistic regression model will be applied to the primary efficacy variable (overall stool response) and the two key secondary efficacy variables (overall pain response and overall study response). This logistic regression model will include treatment group and previous use of IBS-D related medications (yes/no) as covariates. The same modelling will be used as has been applied in the SAP defined analysis for gender (see section 8.1.1.2 of the SAP). The analyses will be performed for the mITT population.

4.4.3 Sensitivity Analysis Regarding Use of Rescue Medication

According to the SAP (Section 7.2.1.1) in case a patient took rescue medication on a day this day will be counted as "failed day", i.e. it will be treated as if the patient had at least one stool that has a consistency of Type 6 or 7 on the Bristol stool scale on this day. To assess the impact of this imputation rule on the primary and key secondary efficacy parameters a sensitivity analysis will be performed where the values of the Bristol stool scale as recorded in the diary, and not the imputed values, will be used.

This analysis will be performed in the mITT population for weekly and overall stool consistency response and for weekly and overall study response.

4.4.4 Figures for Weekly and Overall Response Variables

In addition to the bar charts for weekly and overall stool consistency response, bar charts for weekly and overall pain response and weekly and overall study response will be generated for the mITT population. The p-values for the weekly and overall comparisons between RHB-102 and placebo will be added to the graphical presentations.

4.4.5 Figures for Baseline CRP versus Efficacy Parameter

The subgroup analysis by baseline CRP showed quite different results for the subgroup with baseline CRP $\leq$ median and baseline CRP > median. For the first subgroup there were no significant differences between RHB-102 and placebo whereas for the second subgroup RHB-102 was superior to placebo for overall stool consistency response and overall study

response and nearly so for overall pain response. To visualize the effect of baseline CRP different plots will be generated for the primary efficacy variable overall stool consistency response and the two key secondary efficacy variables overall pain and overall study response:

(1) Scatterplots of baseline CRP against the response (horizontal lines intersecting the y-axis for response and non-response, respectively, and baseline CRP on the x-axis).

(2) "ROC-curves" with use of a different cut-off value for definition of the subgroups (cut-off value plotted against the response probabilities in the RHB-102 and placebo groups for patients with baseline CRP exceeding the cut-off value and not exceeding the cut-off value).

4.5 PK analyses

Table 14.2.19 – Summary of Ondansetron Plasma Concentrations (ng/mL) - will also be generated for the PPPK Population.

4.6 Safety Analyses

4.6.1 Adverse Events

The following summaries of Adverse Events (AEs) will be generated in addition to those contained in the SAP defined analysis:

(1) Treatment emergent AEs by System Organ Class (SOC) and Preferred Term by gender. Restricted to SOCs Gastrointestinal Disorders, Investigations and Nervous System Disorders.

(2) Treatment emergent AEs by System Organ Class (SOC), Preferred Term and Intensity by gender. Restricted to AEs of moderate and severe intensity in the SOC Gastrointestinal Disorders and AEs with Preferred Term Constipation (all intensities)

(3) Treatment emergent AEs by System Organ Class (SOC) and Preferred Term by onset of AE (onset during treatment with RHB-102/placebo vs. onset during follow-up).

(4) Summary of patients with AE of either increase in ALT or increase in AST.

Further a listing of laboratory adverse events with a CTCAE grade of 3 or higher will be generated including the following parameter: ALT, AST, glucose and potassium.

4.6.2 Laboratory Parameter

As there is a discrepancy between laboratory adverse events concerning creatinine and the laboratory shift table with respect to CTCAE grades the CTCAE criteria for creatinine will be modified to include grading only for values above the normal limit but not for values that increased compared to the baseline value.