STATISTICAL ANALYSIS PLAN

Protocol Number RHB-102-01

Randomized, Placebo-Controlled, Phase 3 Trial of RHB-102 (Ondansetron 24 mg Bimodal Release Tablets) for Presumed Acute Gastroenteritis or Gastritis

SAP Version: 4.0

SAP Date: May 29, 2017

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1. REVIEW AND APPROVAL

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2. REVISION HISTORY

SAP Version	SAP Version Date	Which version of Protocol or Protocol Amendment is the SAP based on? Rationales for Changes if applicable
Version 1.0	April 16, 2015	First SAP based on Protocol Amendment 2 dated April 9, 2015.
Version 2.0	September 22, 2016	Amended based on Protocol Amendment 5 dated June 9, 2016. Major changes included: • Extended primary endpoint timeframe to 24 hours • Updated the secondary endpoint list per Protocol Amendment 3 • Added sensitivity analyses for the primary endpoint, per FDA's request • Added analysis of Bristol Stool Scale (BSS) and concordance assessment between BSS and Stool Consistency, as recorded per original protocol • Additional subgroup analyses • 12-lead ECG analyses
Version 3.0	May 18, 2017	Three changes: • Added adjudication process in primary endpoint section 7.1 • Added diary date imputation in handing of missing values section 8. • Updated project manager's name in SAP review and approval section
Version 4.0	May 29, 2017	Four changes or updates: • Added a subgroup definition in subgroup analysis set section 6.2. • Updated adjudication process in primary endpoint section 7.1 • Clarified missing imputation when the primary endpoint is unknown in handing of missing values section 8. • Clarified sensitivity analyses when the primary endpoint is unknown and added a subgroup analysis in analysis of primary endpoint section 9.2

3. INTRODUCTION

This document describes the planned data summaries and statistical analyses for Protocol RHB-102-01, entitled "Randomized, Placebo-Controlled, Phase 3 Trial of RHB-102 (Ondansetron 24 mg Bimodal Release Tablets) for Presumed Acute Gastroenteritis or Gastritis". It is meant to supplement the study protocol which should be referred to for details regarding the objectives and design of the study. Any deviation to this analysis plan will be described in the Clinical Study Report.

Based on feedback from telephone conferences with the FDA on [redacted] preteleconference memos and posteleconference minutes, and on subsequent discussions with investigators, this SAP has been revised. No unblinding took place prior to this revision.

3.1. Study Design

Patients presenting to the emergency department who fulfill entry criteria will be asked to participate. A screening log will be kept listing all patients considered with reasons for patients not entering the study. Any patient whose information is reviewed in consideration for the study, even if not actually approached, is to be included in the screening log. The screening log will differentiate between those who are prescreened, i.e., who are reviewed but never progress to request for consent, from those who are screened, i.e., who are approached for consent, whether or not they actually sign consent or eventually participate in the study. Qualifying patients, once they have signed consent, will be stratified by age (≥ vs <age 18) and randomized 60:40 to RHB-102 or matching placebo. All patients will undergo laboratory testing and ECG, as specified below, once they have signed consent. Of the blood and urine tests, only results of the pregnancy test (for women of childbearing potential) and a finger stick blood glucose (for patients with type 2 diabetes mellitus controlled by diet or oral medications) are required prior to treatment. The pretreatment ECG results are available immediately and are to be used to qualify patients.

Patients will be started on oral fluids ≥30 minutes after taking study medication (second dose for patients who receive 2 doses in ED) if they have not vomited during that period. Intravenous hydration should not be administered unless the patient has vomited or is clearly unable, after a reasonable period of time has elapsed since administration of study medication, to tolerate oral fluids.

At 4±0.25 hours after initial dosing, all patients are to have a repeat 12-lead ECG. Once stable, but not less than 4 hours after initial dosing, patients may be discharged from the emergency department. On discharge, patients who are not treatment failures will be given an additional 3 doses of study medication to take at 24-hour intervals if nausea persists. Patients will be contacted daily for 4 days after discharge to determine their condition. Those patients who have persistent, worsening or recurrent nausea and/or vomiting during the follow-up period may be asked to come in for follow-up assessment by study personnel.

3.2. Study Objectives

1.2.1 Primary Objective

Comparison of the proportion of patients who are treatment successes, i.e., fulfill all three of the following criteria:

a) without further vomiting,
b) without rescue medication, and
c) who were not given intravenous hydration from 30 minutes after the first dose of study medication through 24 hours after the first dose of study medication.

1.2.2 Secondary Objectives

Comparison between ondansetron and placebo groups of

- Treatment success, as defined above, through 4 days following first dose of study medication
- Proportion of patients who experience each of the components of treatment failure:
  - Vomiting
  - Rescue antiemetic therapy
  - Intravenous hydration
- Severity of nausea
- Diarrhea as reported by
  - Bristol Stool Scale (BSS): number and distribution by grade of grade ≥5 stools daily throughout the study
  - Stool consistency, as recorded per original protocol, none/formed (normal)/soft/watery (diarrhea)
- Incidence and severity of other symptoms of gastroenteritis
- Time from first dose of study medication to discharge from ED, extended observation unit or hospital, whichever comes last
- Time to resumption of normal activities (work/school/household)
- Proportion of patients requiring hospitalization
- Proportion of patients returning to emergency department for gastrointestinal symptoms within 4 days of initial discharge
- Adverse events

4. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No interim analysis will be conducted.

5. HYPOTHESES AND DECISION RULES

5.1. Statistical Hypotheses

The primary objective for the study is to test for superiority of RHB-102 vs placebo for the proportion of the primary endpoint.

The null hypothesis is that the odds ratio between the two treatment groups is one, i.e. there is no treatment difference in the proportions of the primary endpoint. Cochran Mantel Haenszel (CMH) test stratified by age will be used to test the null hypothesis. The hypothesis will be tested at an overall level of 0.05 (2-sided).

5.2. Statistical Decision Rules

If the observed 2-sided pvalue is less than 0.05, then statistical significance will be declared. If the proportions are in favor of RHB-102 treatment arm, then "proportion of patients with success with RHB-102 is statistically significant better than proportion of patients with success with placebo" will be declared.

6. ANALYSIS SETS

6.1. Full Analysis Set

The intent-to-treat population (ITT) will consist of all patients who receive any study medication, even if they vomit shortly after administration or are unable to swallow the medication. The primary efficacy analysis will be conducted using ITT population.

6.2. Subgroup Analysis Sets

6.2.1. Subgroup Population 1

Primary and selected secondary efficacy analyses will also be performed on a predefined subgroup of patients defined as follows:

1. Meet all inclusion/exclusion criteria

2. If they vomit within 15 minutes of receiving the first dose of study medication, receive a second dose

3. Do not have a primary diagnosis on discharge from the ED (or, if admitted, on discharge from the hospital) other than acute gastroenteritis or gastritis

6.2.2. Subgroup Population 2

Another subgroup analysis set will include subjects from sites who enroll 5 or more patients. Analyses of the primary and the first secondary endpoint (treatment success through 4 days) will be performed. Nine of the 21 sites which enrolled patients enrolled fewer than 5 each; this group comprised 7% of total patients treated on study. Patients from these sites had a disproportionately high incidence of major protocol deviations, 42% versus 6% for patients from

sites which enrolled at least 5 patients. Several of these sites appeared to have significant difficulty not only enrolling but also in following protocol procedures. Accordingly, analyzing results excluding these sites is another sensitivity analysis, akin to a per protocol analysis.

6.3. Safety Analysis Set

The safety analysis set will include all patients who receive any study medication, even if they vomit shortly after administration or are unable to swallow the medication.

6.4. Treatment Misallocations

If a subject is randomized but took incorrect treatment, then they will be reported under their randomized treatment group for all efficacy analyses, but will reported under the treatment they actually received for all safety analyses.

6.5. Protocol Deviations

Significant protocol deviations may include, but not limited to:

- Failure to meet significant inclusion/exclusion criteria
- No evidence of adequate compliance to study medication
- Receiving excluded concomitant medication, including additional doses of study medication not administered per protocol
- Failure to obtain required efficacy data:
    - While in ER: patients who sign out AMA or who are otherwise uncooperative in providing protocol-specified efficacy or safety data, including failure to stay in ED for 4 hours following dosing for a follow-up ECG
    - After discharge: patients who fail to provide protocol-specified follow-up data, including data on drug compliance and efficacy assessments

7. ENDPOINTS AND COVARIATES

7.1. Efficacy Endpoint(s)

1) Primary Efficacy Endpoint: the proportion of patients who fulfill all the following 3 criteria from 30 minutes after first administration of study medication until 24 hours after the first dose of study medication:

    a. absence of vomiting

    b. no use of rescue medication, and

    c. no intravenous hydration

If all of the above three criteria are fulfilled, the patient is considered a treatment success for the primary analysis. If one or more of the above three criteria are not fulfilled, i.e., the patient either experiences vomiting, receives rescue medication or receives intravenous hydration from 30 minutes through 24 hours after the first dose of study medication, the patient is considered a treatment failure.

Based on the 2nd blinded dry run conducted on [redacted], there were 28 subjects who did not have all the information needed to determine per the algorithm used if they met the primary endpoint successfully. For 17 patients, all treated under amendment 1 or 2, in which the primary endpoint was treatment success on emergency department discharge, the reason for not having complete information was the lack of an ER day diary. For these patients, based on all follow up data available, no treatment failure events occurred. Therefore, these patients are considered treatment successes. Among the other eleven, data were reviewed and several queries issued. Based on this review, patients were assessed by the medical monitor to be treatment successes (n=4), failures (n=1) or unknown (n=6). The adjudicated primary endpoint outcomes will be used for the primary analyses.

2) Secondary and Tertiary Efficacy Endpoints:

- Treatment success, as defined above, through 4 days following first dose of study medication
- Proportion of patients who experience or require each of the components of treatment failure:
  - Vomiting
  - Rescue antiemetic therapy
  - Intravenous hydration
- Severity of nausea
- Incidence and severity of diarrhea
- Incidence and severity of other symptoms of gastroenteritis
- Time from first dose of study medication to discharge from ED, extended observation unit or hospital, whichever comes last
- Days to resumption of normal activities (work/school/household)
- Proportion of patients requiring hospitalization
- Proportion of patients returning to emergency department for gastrointestinal symptoms within 4 days of initial discharge

7.2. Safety Endpoints

- Adverse Events (AE) graded by NCI-CTCAE v4.0 system
- Serious AE (SAE)
- Death, if any
- Vital signs
- Laboratory tests
- Physical examination
- 12-lead ECG

7.3. Covariates

The analyses of the primary and secondary endpoints will be performed using the following randomization stratification factor as covariate:

- Age (<18, ≥18 years of age)

Analyses of a given continue endpoint will also include its corresponding baseline as a covariate.

8. HANDLING OF MISSING VALUES

Every effort will be made to collect all vomiting-related information. In the ED, patients will be under observation, complete efficacy data is expected. Rare cases may occur in which a patient leaves the ED before any observations can be made. In addition, some patients may not report events between the time they leave the ED and 24 hours after first dose of study medication. It is expected that >90% of patients will provide data until at least 24 hours after initial dosing. Patients who drop out of the study and patients who have unknown primary endpoint will be imputed as failures/non-responders for the primary analysis.

Diary dates will be imputed based on nominal date. For example, a subject's first dose in ED is 18May2017, his/her ER day diary date will be 18May2017 and his/her Day 1 diary date will be 19May2017.

9. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

9.1. Study Population and Demographics

Demographic and pretreatment patient characteristics, including disease parameters and comorbidities, will be summarized with descriptive statistics. The descriptive statistics will include sample size, mean, standard deviation, median, minimum, and maximum for continuous variables and number and percentages for discrete variables.

Baseline chemistry, CBC and urinalyses were performed on selected patients prior to amendment 4. Beginning with amendment 4, instituted in March, 2016, all patients were required to have chemistry and CBC performed; urinalysis remained optional. In addition beginning with amendment 4, pre- and 4 hr post-treatment ECGs were required of all patients.

Data for chemistry, CBC and urinalysis parameters are analyzed by treatment group, as described above. ECGs, which are performed pre- and post-treatment, are analyzed in greater detail, as described below.

9.2. Analyses of Primary Endpoint

Primary efficacy analysis will be based on the ITT population. The primary endpoint will be tested by Cochran Mantel Haenszel (CMH) test stratified by age. Common odds ratio and its 95% confidence interval will be provided. If the observed 2-sided p-value from the CMH test is

less than 0.05, statistical significance will be declared. Point estimates of the proportions for each treatment arm will be provided along with the corresponding 2-sided 95% confidence intervals. The point estimate of the difference of the proportions between treatment arms will also be provided along with corresponding 2-sided 95% confidence intervals.

For the above primary analysis, Patients who drop out of the study and patients who have unknown primary endpoint will be imputed as failures/non-responders, as stated in the handing of missing value section above.

As a sensitivity analysis, patients who drop out of the study and patients who have unknown primary endpoint will be imputed as responders. The primary analysis of CHM by age will be repeated.

One additional sensitivity analysis, the most conservative approach, will have following imputations:

- patients who drop out of the study and patients who have unknown primary endpoint in active arm will be imputed as failures/non-responders
- patients who drop out of the study and patients who have unknown primary endpoint in placebo arm will be imputed as responders

In addition, subgroup analyses by each age group (<18, ≥18 years of age) will be conducted. For a given age group, unstratified CMH test will be performed. Furthermore, subgroup analyses by baseline nausea severity will also be conducted. None and mild severity will be combined as one group. For a given severity group, unstratified CMH test will be performed.

Primary analysis will also be performed on Subgroup Population 1 and Subgroup Population 2.

9.3. Efficacy Analyses for Secondary and Tertiary Endpoints

ITT population will be used for the analyses of all secondary and tertiary endpoints.

1) Analyses of Binary/Proportion Endpoint

Same statistical test as for the analyses of the primary endpoint, as stated in Section 9.2, will be used for analyzing other proportion endpoints.

2) Analyses of Time-to-Event Endpoints

Time to event endpoints will be compared between the treatment arms using stratified log-rank test adjusting the age stratification factor. The endpoints will also be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% confidence interval for each median will be provided.

3) Analyses of Continuous Endpoints

Descriptive statistics, including the mean, standard deviation, median, minimum, and maximum values, will be provided for continuous endpoints.

4) Analyses of Ordinal Categorical Endpoints

The number and percentage of patients in each category will be provided for categorical endpoints. Bristol Stool Scale (BSS), added in the Protocol Amendment 3, is an 8 point ordinal categorical variable. Wilcoxon rank sum test will be used to compare the two treatment groups.

5) Concordance Assessment of Bristol Stool Scale and Stool consistency

Stool consistency, as recorded per original protocol, none/formed (normal)/soft/watery (diarrhea), is a 4 point ordinal categorical variable. Cross-tabulation of stool consistency and BSS among all the patients who have both assessments at a given time point will be created to evaluate the concordance of the two scales. Cohen's Weighted Kappa Coefficient and 95% confidence interval will be provided.

9.4. Safety Analyses

The safety and tolerability of RHB-102 will be determined by reported AEs, physical examinations, vital signs, and, if performed on study, laboratory tests. Subjects who receive any RHB-102 (even if they vomit shortly after administration) are considered evaluable for safety. Physical exam findings will not be analyzed separately. Rather, new and worsening abnormalities will be considered AEs and analyzed with those data.

1) Adverse Events

The NCI-CTCAE v4.0 system will be used to grade new or worsening laboratory abnormalities. New laboratory abnormalities for which there are no CTCAE v4.0 criteria will be assigned grade 1 if there were no clinical effects or interventions, and according to the criteria in protocol section 6.3 if there were clinical effects and/or interventions. AEs will be grouped and tabulated by MedDRA preferred terms by system organ class.

The Medical Dictionary for Regulated Activities (MedDRA) version 13.1 will be used to classify all AEs with respect to system organ class and preferred term.

Summary tables of AEs and SAEs will be prepared by system organ class, preferred term and severity for each treatment group. AEs that lead to premature discontinuation from the study or to death will be listed separately via data listings.

2) Other Parameters

Findings on physical examination, including vital signs, which constitute clinically significant changes, will be listed as adverse events. The incidence of hospitalization will be compared between treatment groups as an efficacy parameter. The causes for hospitalization, other than for gastroenteritis, will be listed as SAEs.

ECGs of patients who undergo paired ECGs on the study will be analyzed for shifts in QTcF and QTcB.

10. REFERENCES

None.

SUPPLEMENTAL STATISTICAL ANALYSIS PLAN

Protocol Number RHB-102-01

Randomized, Placebo-Controlled, Phase 3 Trial of RHB-102 (Ondansetron 24 mg Bimodal Release Tablets) for Presumed Acute Gastroenteritis or Gastritis

Supplemental SAP Version: 1.0

SAP Date: June 23, 2017

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1. REVIEW AND APPROVAL

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Date

2. REVISION HISTORY

SAP Version	SAP Version Date	Which version of Protocol or Protocol Amendment is the SAP based on? Rationales for Changes if applicable
Version 1.0	June 23, 2017,	Supplemental SAP to final SAP Version 4.0 dated on May 29, 2017 and signed on June 1, 2017

3. INTRODUCTION

This is a Supplemental SAP to final SAP Version 4.0 dated on May 29, 2017 and signed on June 1, 2017. Study was unblinded on June 3, 2017. This document describes supplemental analyses beyond the original planned analyses. For detail of study design, please refer to Protocol RHB-102-01, entitled "Randomized, Placebo-Controlled, Phase 3 Trial of RHB-102 (Ondansetron 24 mg Bimodal Release Tablets) for Presumed Acute Gastroenteritis or Gastritis". For details of main study analyses, please refer to the final SAP Version 4.0.

4. COVARIATES

The final SAP defined randomization stratification factor as covariate:

- Age (<18, ≥18 years of age)

In this supplemental SAP, two additional covariates will be defined. Subjects who are ≥18 years of age will be grouped by age terciles. Actual cut-point will be derived based on the distribution of age. Covariate variable Age will be coded as below:

Age	<18	1st 1/3 group of ≥18 years of age	2nd 1/3 group of ≥18 years of age	3rd 1/3 group of ≥18 years of age
Coding	1	2	3	4

Another covariate is Baseline Nausea Severity. Baseline nausea severity will be coded as below:

Baseline nausea severity	No Nausea	Mild Nausea	Moderate Nausea	Severe Nausea	Nausea as bad as can be
Coding	1	2	3	4	5

5. SENSITIVITY ANALYSIS (SAFETY POPULATION)

Subject 23-001 was randomized to Placebo treatment but received RHB-102 treatment. This subject is classified as Placebo subject in ITT Population but RHB-102 subject in Safety Population.

A sensitivity analysis of primary endpoint will be performed based on actual treatment received (Safety Population).

6. PRIMARY ENDPOINT UNTIL DISCHARGE FROM THE ED

Primary endpoint 2 will be defined as the same as primary endpoint in main SAP except the timeframe will be from 30 minutes of first study dose administration to discharge from ED.

Based on both ITT and Subgroup Population 1, primary endpoint 2 will be analyzed as the same as the primary endpoint, as described in the final SAP.

7. PRIMARY ENDPOINT ANALYSIS (SUBGROUP POPULATION 1) BY AGE

Based on Subgroup Population 1, perform Primary Analysis Table 14.2.1.3 by Age (<18, ≥18 years of age).

8. PRIMARY ENDPOINT ANALYSIS BY AGE TERCILE GROUPS

Based on both ITT and Subgroup Population 1, perform Primary Analysis Table 14.2.1.3 by 3 age tercile groups (as defined in covariate section).

9. LOGISTIC REGRESSIONS

Per final SAP, the primary endpoint was analyzed and tested by using Cochran Mantel Haenszel (CMH) test stratified by age. In order to adjust for covariates, logistic regressions will be used in this supplemental SAP.

In this section, all logistical regression analyses will be performed for both ITT population and Subgroup Population 1.

9.1. Primary endpoint analysis by logistic regression

Primary endpoint will be analyzed using logistic regression with treatment as a factor and age (<18, ≥18 years of age) as a covariate. Pvalues and odds ratios of treatment and age from the logistic regression will be presented. This analysis is to mimic the CMH analysis performed in the final SAP.

9.2. Primary endpoint analysis by logistic regression adjusted by age as continuous variable

Primary endpoint will be analyzed using logistic regression with treatment as a factor and age as a continuous covariate. Pvalues and odds ratios of treatment and age from the logistic regression will be presented.

9.3. Primary endpoint analysis by logistic regression adjusted by baseline nausea severity

Primary endpoint will be analyzed using logistic regression with treatment as a factor and baseline nausea severity as a continuous covariates (as defined in covariate section). Pvalues and odds ratios of treatment and baseline nausea severity from the logistic regression will be presented.

9.4. Primary endpoint analysis by logistic regression adjusted by age and baseline nausea severity

Primary endpoint will be analyzed using logistic regression with treatment as a factor and age as a continuous covariate and baseline nausea severity as a continuous covariate (as defined in covariate section). Pvalues and odds ratios of treatment, age and baseline nausea severity from the logistic regression will be presented.

10. SUCCESS AND FAILURE BY INVESTIGATIVE SITE

A table summarizing success/failure/early dropout or inevaluable by treatment and by site will be provided. Sites accrued at least 20 patients will have its own entry and the remaining low recruitment sites will be pulled together. This will be based on ITT population and Subgroup Population 1.

11. HIERARCHICAL ANALYSIS OF REASON FOR TREATMENT FAILURE

Based on ITT population and Subgroup Population 1, a hierarchical analysis of reason for treatment failure will be provided. The failure hierarchical order with code for analysis will be:

1. (code=2) Treatment failure by vomiting, regardless of receipt of IV fluid or rescue medication
2. (code=3) Treatment failure by receipt of IV fluid or rescue med in patients who did not vomit
3. (code=4) Early dropout
4. (code=5) Patients who don't have sufficient information to be evaluated for the primary endpoint

Treatment success will be assigned a code = 1. Distribution of treatment success and failure reasons will be tabulated. Wilcoxon rank sum test will be used to test between RHB-102 arm and Placebo arm.

12. ANALYSIS OF VOMITTING

Based on ITT population and Subgroup population 1, subjects who didn't vomit from 30 minutes after first administration of study medication until 24 hours post first dose will be analyzed by CMH stratified by age. Subjects who have missing vomiting status will be treated as "yes."

13. ANALYSIS OF NAUSEA

Based on ITT population and Subgroup Population 1, time to No Nausea will be displayed using Kaplan-Meier method with pvalues.

Hourly observation data in ED will be used to derive time to the first "No Nausea" as an event or censor. Time to first rescue medication and time to first IV fluid (volume >100 mL) will also be derived for censor. Time to No Nausea will be evaluated based on the following three time duration.

- Time to first No Nausea (for event or censor)
- Time to first rescue (for censor)
- Time to first IV fluid (volume > 100 mL) (for censor)

The earliest event or censor will be used for Time to No Nausea. e.g if the earliest is Time to first No Nausea event, then it will be used as an event. If the earliest is rescue or IV fluid, then the time to first rescue or first IV fluid will be used for censor.

14. CORRELATION BETWEEN AGE AND BASELINE SEVERITY NAUSEA

Based on the ITT population, Spearman correlation statistics will be presented between age as continuous variable and baseline nausea severity (as defined in covariate section).

15. LISTING OF REDOSED SUBJECTS DUE TO VOMITTING

Based on ITT population, a listing of patients who were redosed because they vomited within 15 minutes after the first dose will be provided. Following variables will be included:

- Subject ID
- Treatment received,

- Success/failure/LTF/unknown,
- Reason for failure (further vomiting regardless of subsequent IV fluid/rescue med, received IV fluid only, received rescue meds only, received both IV fluid and rescue med),
- Time of failure relative to FIRST dose of study med, hr:min

16. LISTING OF SUBJECTS EXCLUDED FROM SUBGROUP POPULATION 1

There were 22 subjects excluded from Subgroup Population 1. A listing of reasons being excluded from subgroup population 1 will be generated. The listing should contain Subject ID, Treatment Received, and Reason being excluded from Subgroup Population 1.