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

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Approvals

The investigator agrees to conduct the trial as described in the protocol in accordance with all FDA regulations, and according to current ICH GCP.

By agreement to this protocol, the investigator agrees to allow direct access to all essential documents, including source documents to authorized individuals representing the sponsor (including monitors, auditors and other personnel), to institutional review boards (IRBs) and to regulatory authorities.

[redacted]

Principal Investigator:

_____ _____
Date

Name: _____

Protocol Synopsis

Title	Randomized, Placebo-Controlled, Phase 3 Trial of RHB-102 (Ondansetron 24 mg Bimodal Release Tablets) for Presumed Acute Gastroenteritis or Gastritis
Study location	US multicenter
Study drug	RHB-102 (Ondansetron 24 mg Bimodal Release Tablets)
Comparator	Placebo
Rationale	Ondansetron was the first 5-HT_3 antagonist approved as an antiemetic. It has been approved for use for prevention and treatment of nausea and vomiting due to cytotoxic chemotherapy and radiotherapy, as well as for prevention of postoperative nausea and vomiting. Despite several clinical trials and much anecdotal evidence of efficacy against acute gastroenteritis, no formulation of ondansetron or any other 5-HT_3 antagonist has ever been approved by the FDA for this indication. RHB-102 is a modified release oral tablet formulation of ondansetron. It contains 6 mg ondansetron for immediate release and 18 mg in an extended release core. It provides early ondansetron levels similar to a single 8 mg immediate release tablet and sustained release over a 24-hour period. This should enable once daily dosing, so that a single dose of RHB-102 should be sufficient to control nausea and vomiting from acute gastroenteritis for most patients. A variety of agents are used for symptomatic treatment of acute gastritis and gastroenteritis. The most commonly used non-5- HT_3 antiemetics, prochlorperazine and promethazine, while reasonably effective may cause significant adverse events much more commonly than ondansetron. In recent published studies of patients with acute gastroenteritis, 50% or more who receive placebo do not vomit during the study observation period. Thus, patients may be exposed to potential toxicity without therapeutic benefit. Therefore, use of a placebo with rescue is justified in this situation. Ondansetron causes side effects in few patients, but gastroenteritis patients administered intravenous or immediate release oral ondansetron frequently require multiple doses to control their symptoms. Thus, use of a modified release formulation may be of considerable benefit by providing rapid relief of symptoms and maintaining relief without need for redosing over the course of the illness, which is usually approximately one day.
Objectives	
Primary:	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 $\geq$30 minutes after the first dose of study medication through 24 hours after the first dose of study medication.

Secondary:	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, Appendix I): 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
Population	Adults and children ≥age 12 with vomiting from presumed acute gastroenteritis or gastritis of ≤36 hours duration Inclusion criteria: • Patients must have vomited at least twice in the 4 hours preceding signing informed consent A vomiting episode is defined as an episode of forceful expulsion of stomach contents. Retching if a patient has already emptied his or her gastric contents is also considered a vomiting episode. A distinct episode is characterized by a clear break in vomiting activity of at least 5 minutes • Emesis must have been nonbloody (streaks of blood presumed due to force of retching are allowed) • All patients (or a parent or guardian for patients <age 18) must sign informed consent. Patients <age 18 must also sign assent. Exclusion criteria: • Severe dehydration For purposes of this study, severe dehydration is defined as two or more of the following criteria in the presence of decreased intake and increased output due to vomiting or diarrhea: ○ Absent or severely decreased urine output, ○ Weak pulse and/or low blood pressure, ○ Parched mucous membranes, ○ Lethargy, confusion, delirium or loss of consciousness. • Signs and symptoms severe enough to require immediate parenteral hydration and/or parenteral antiemetic medication • Temperature>39.0°C • Likely etiologies for acute vomiting and diarrhea other than acute infectious or toxic gastroenteritis or gastritis ○ This includes signs of an acute abdomen, which may require surgical intervention

	• Chemically-induced gastroenteritis, e.g., from alcohol, other drugs of abuse or other irritant chemicals
	• Use within 24 hours of study entry of specific medication for treatment of nausea and/or vomiting, e.g., 5-HT3 antagonists or phenothiazines, or receipt of any IV fluid for any reason. Nonspecific gastrointestinal remedies, such as antacids, proton pump inhibitors and homeopathic remedies, are permitted.
	• Congestive heart failure, bradyarrhythmia (baseline pulse<55/min), known long QT syndrome
	• Patient who have known QTc prolongation>450 msec, noted on prior or screening ECG, or who are taking medication known to cause QT prolongation
	  ○ Note: For current list of medications known to cause QT prolongation see: https://www.crediblemeds.org/healthcare-providers/drug-list/ Use list showing drugs with known risk of TdP.
	• Known underlying disease which could affect assessment of hydration or modify outcome of treatment, e.g., renal failure, diabetes mellitus, liver disease, alcoholism
	  ○ Patients with type 2 diabetes mellitus controlled by diet or oral medications and whose baseline blood glucose is <200 may be entered into the study
	• Abdominal surgery within the past 3 months
	• History of bariatric surgery or bowel obstruction at any time
	• Hypersensitivity or other known intolerance to ondansetron or other 5-HT_3 antagonists
	• Patient has taken apomorphine within 24 hours of screening
	• Patient has previously participated in this study
	• Patient has participated in another interventional clinical trial, for any indication, in the past 30 days
	• For women of childbearing potential: documented or possible pregnancy. See body of protocol for detailed definition.

Design	Randomized, double-blind, placebo-controlled, parallel group study
Methodology	Patients presenting to the emergency department who fulfill entry criteria will be asked to participate. 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. Patients will receive one oral dose of study medication as soon as feasible. If a patient vomits within 15 minutes of the initial dose of study medication, he/she will receive a second dose. If a patient vomits again, regardless of how long after the second dose of study medication, no further study medication will be administered. Patients vomiting ≥30 minutes after the first dose of study medication may receive rescue antiemetics, either parenterally or orally. In addition, a) patients with severe nausea ≥30 minutes after dosing with study medication and who in the treating physician‘s opinion require treatment, may receive rescue medication. b) These patients may receive intravenous hydration in addition to or in place of parenteral antiemetics if they are unable to tolerate oral hydration. However, only severely symptomatic patients clearly unable to tolerate oral hydration may receive intravenous hydration.

	Any patient receiving rescue medication or parenteral hydration will be deemed a treatment failure. Metoclopramide 0.3 mg/kg, maximum dose 10 mg, administered intravenously will be the default rescue medication. Oral metoclopramide or other antiemetics administered either intravenously or orally may be used at the investigator's discretion. **However, patients are not to receive ondansetron or other 5-HT_3 antagonists by any route for at least 24 hours after administration of study medication.** The following 5-HT_3 antagonists are available in the US: alosetron (Lotronex), dolasetron (Anzemet), granisetron (Sancuso and others), ondansetron (Zofran, Zuplenz and others), palonsetron (Aloxi). Oral fluids will be administered as tolerated once a patient has not vomited for 30 minutes after dosing with study medication (second dose for those patients receiving 2 doses in the ED). Guidelines for administration of oral fluids are shown on page 20, section 4.4.1, of the protocol. Patients tolerating oral fluids will be discharged once deemed stable by the attending physician but not prior to 4 hours after dosing. On discharge, patients will be given 3 additional doses of study medication to take once daily if necessary. Patients who do not tolerate oral fluids may receive parenteral hydration. Data will be collected daily for up to 4 days following study initiation (until symptoms have resolved) to ascertain whether the patient had further vomiting, other sequelae of the acute gastroenteritis or required further medical care for the gastroenteritis. Data may be collected by entry by the patient or a caregiver into a web-based system or on paper, or by telephone contact daily from a study staff member. If during the follow-up period, symptoms progress or worsen or new symptoms develop, the patient may be asked to return for further evaluation. If by day 4 after discharge (i.e., the day after the last dose of study medication), the patient still notes gastroenteritis symptoms, he or she will be instructed to return for further evaluation.

Endpoints
Efficacy:
	Primary:
	Absence of vomiting without use of rescue medication or parenteral hydration from 30 minutes through 24 hours after the first dose of study medication.
	Secondary:
	• Treatment success, as defined above, through 4 days following first dose of study medication
	• Individual components of treatment failure through 4 days following first dose of study medication:
	  ○ Vomiting
	  ○ Requirement for rescue antiemetic
	  ○ Treatment with intravenous hydration
	• Severity of nausea
	• Diarrhea will be reported in two ways:
	  ○ Bristol Stool Scale (BSS): number and distribution by grade of grade ≥5 stools daily throughout the study
	  ○ Stool consistency, as recorded per prior versions of protocol, none/formed (normal)/soft/watery (diarrhea)
	• Incidence and severity of other symptoms of gastroenteritis, as recorded in CRF and patient diaries
	• 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) • Hospital admission • Return to emergency department for gastrointestinal symptoms •
Safety:	Incidence and severity of adverse events through time of last follow-up call
Statistics	Successful treatment is absence of further vomiting from 30 minutes through 24 hours after initial administration of study administration without use of rescue antiemetic or parenteral hydration. It is expected that 40% of the placebo group and 20% of the ondansetron group will fail therapy. To demonstrate a statistically significant difference with two-tailed p value=0.01 and power=90%, 320 patients will be entered into the study, 192 randomized to RHB-102 and 128 to placebo. Patients will be stratified by age (< or ≥age 18) at baseline. Patient demographics and disease characteristics will be summarized with descriptive statistics. Safety and efficacy analyses will be based on all patients who receive any study medication. A subgroup of patients, as defined in section 7.2 of the protocol, will also be evaluated for efficacy. The incidence of treatment failure (vomiting, use of rescue medication or parenteral hydration from 30 minutes through 24 hours after initial administration of study medication) will be compared by Mantel-Haenszel test. No interim analysis will be conducted.

Study Assessments

Day	1	1	1	2	3	4	5
Time, hours	-1 to 0	0	0-T	NA	NA	NA	NA
Baseline assessments[a]	X						
Study drug administration		X[e]		X[f]	X[f]	X[f]	
Observation[b]			X			X[c]	X[c]
Patient reported events[c]				X	X	X	X
Concomitant medications[d]	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X

Notes:

[a]History, physical including VS (pulse, respiratory rate, blood pressure, temperature and, at baseline only height and weight), informed consent. For all patients: CBC with platelet count, biochemical profile and ECG. Urinalysis is required for all patients ≥age 40 and with a history of diabetes; it is optional for other patients. Blood and urine specimens should be taken expeditiously at the beginning of assessment, but patient entry into the study and treatment need not wait for lab results (other than pregnancy test and fingerstick blood glucose when required) unless clinically indicated. After phlebotomy, a saline lock may be placed so that the patient will not require an additional needle stick should he/she require intravenous fluids subsequently. History of present illness should include questioning regarding precipitating/causative factors, as well as recording of number and character of emetic and diarrheal episodes.

Patients with diet-controlled type 2 diabetes mellitus are to have a finger stick blood glucose.

For women of childbearing potential, as defined in the exclusion criteria: urine or serum pregnancy test. Negative pregnancy test result must be obtained prior to treating a patient on study.

[b]Patients are to be observed in the emergency department for a minimum of 4 hours after initial dose of study medication, with VS at least once every hour and recording of intake (both oral and parenteral) and number of voidings. All episodes of vomiting and diarrhea are to be recorded, and severity of nausea at baseline and every hour while in the ED noted.

All patients are to have a repeat ECG 4±0.25 hours after initial dosing with study medication. At a minimum of 4 hours after initial administration of study medication, after repeat ECG, patients may be discharged when clinically appropriate. **Any patient who has an on-study ECG showing QTc>500 msec must have a follow-up ECG showing resolution of the QTc prolongation. Timing of follow-up ECG(s) at investigator discretion. If the QTc does not decrease below 500 msec during follow-up, the medical monitor must be contacted to discuss further follow-up**.

[c]Prior to discharge, patients will be given diary pages to record their course after discharge. Patients will be contacted each day following treatment to a maximum of 4 days to determine whether they had further nausea and vomiting after leaving the emergency department, the occurrence and quality of bowel movements, including assessment using the Bristol stool scale (Appendix I), and the nature, occurrence and severity of other symptoms, whether they required further care for the acute gastroenteritis, and details regarding the continuation, if any, of the illness. If symptoms persist for 3 or more days after study entry, the patient is to be instructed to return for further evaluation.

[d]To include all medications taken within 7 days prior to study entry, all treatments (including parenteral fluids) on the day of study entry, and all medication, including rescue medications, from the time of study entry through last follow-up.

[e]Patients are to receive the first dose of study medication within one hour of signing informed consent.

[f]Patients may take study medication daily for up to 3 days after study entry (maximum total of 4 doses, plus one additional if patient vomits within 15 minutes of first dose) if symptoms persist. Patients should stop taking study medication if symptoms have resolved, though they may resume study medication once daily if symptoms recur after discontinuation. Patients are not to take any remaining study medication after day 4. They will be given mailers to return any unused study medication.

List of Abbreviations

°C	degrees Celsius
β-HCG	beta-human chorionic gonadotropin
5-HT3	5-hydroxytryptamine$_3$
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CO_2	bicarbonate
CRF	case report form
ED	Emergency department (emergency room)
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HIPAA	Health Information Portability and Accountability Act
ICH	International Committee on Harmonisation
IRB	institutional review board
Kg	Kilogram
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram
NCI-CTCAE v 4	National Cancer Institute common terminology criteria for adverse events, version 4
SAE	serious adverse event
VS	vital signs
vs	versus
WBC	white blood count
WOCBP	women of childbearing potential

1. Background and Rationale

1.1 Acute Gastroenteritis

Acute gastroenteritis is inflammation of the stomach, small intestine or large intestine, leading to a combination of abdominal pain, cramping, nausea, vomiting and diarrhea (Graves, 2013). Acute gastritis is inflammation of the stomach; patients with acute gastritis may have vomiting without diarrhea. For purposes of this protocol, patients must present with at least vomiting, as described below, with or without other symptoms.

Acute gastroenteritis is a major health problem worldwide. While mortality is greatest in developing countries and in both the very young and old, morbidity of acute gastroenteritis is shared by all ages and economic strata. In the US, most cases of acute gastroenteritis are viral, most commonly rotavirus and norovirus (Chow et al, 2010; Graves, 2013). In the US, there are between 15-25 million episodes of viral gastroenteritis annually, leading to 3-5 million office visits and 200,000 hospitalizations. While mortality is low, among the 17,000 people dying from acute gastroenteritis in the US each year, 83% are over age 65 (CDC, 2012).

Most cases are self-limited, resolving in one to several days. Mild to moderate cases are generally treated symptomatically. In children, there are guidelines for oral rehydration therapy. More severe and prolonged cases may require diagnostic studies for etiologic organisms. Depending on the severity and etiology, treatment varies from dietary modifications, including oral rehydration therapy, to intravenous fluids and antibiotics. Antiemetics and antidiarrheals are often used. Prochlorperazine and perphenazine are both approved for treatment of nausea and vomiting in general, i.e., including for treatment of acute gastroenteritis. Several other products approved for treatment of nausea and vomiting in special situations, e.g., postoperatively or in association with cancer chemotherapy, are also used for this indication. Ondansetron is often used in both children and adults with acute gastroenteritis, but has never been approved for this indication in any country.

1.2 Ondansetron for Acute Gastroenteritis

Ondansetron has been studied in several studies in acute gastroenteritis, primarily in children (Chow et al, 2010. In seven studies, either intravenous (3 studies) or oral (4 studies) ondansetron was compared against placebo, and in two intravenous ondansetron was compared against active agents. Most of the studies against active agents demonstrated a significant decrease in the proportion of patients with vomiting subsequent to dosing. Overall, the proportion of patients with vomiting in the emergency department after ondansetron was about half that after placebo. Only one study, comparing ondansetron with prochlorperazine, was entirely in adults, and one additional study, with ondansetron compared to placebo, was in children and adults, though most participants were children. Thus, ondansetron has not been studied extensively in clinical trials in adults with acute gastroenteritis.

1.3 RHB-102

RHB-102 is a bimodal release oral formulation of ondansetron. It contains 24 mg of ondansetron, 6 mg immediate release and 18 mg in an extended release matrix. Pharmacokinetic studies in healthy volunteers have demonstrated rapid early release, with appearance of drug in the plasma within half an hour of dosing, similarly to immediate release Zofran®, but with sustained drug availability over 24 hours. Thus, RHB-102 should provide rapid relief from nausea and vomiting in patients not requiring immediate intravenous medication, yet require only once daily dosing for a sustained effect over the several days of illness. The safety profile of RHB-102 is similar to that of Zofran 8 mg, as demonstrated in volunteer studies.

1.4 Study Rationale

As noted above, ondansetron has been studied in acute gastroenteritis against placebo in seven clinical trials and against other agents in two studies. While often used clinically, its activity in adults and adolescents with acute gastroenteritis has not been demonstrated. Thus, a prospective randomized study of ondansetron in a major patient population will provide clear evidence of the efficacy of the drug, or lack thereof, in this population.

The study will of necessity enroll only those patients who are likely to tolerate oral medications. Patients with vomiting at a frequency which make it difficult for them to hold down a pill for half an hour are not appropriate for this study and will be excluded. However, for the large population of patients with moderate gastroenteritis, treatment of the disease without intravenous is clearly preferable. In addition to being easier and more comfortable even in an emergency department setting, it will allow treatment of patients outside the emergency room, providing both patient convenience and economic benefits as compared to parenteral treatments in an emergency department.

Use of a placebo control allows demonstration of activity with a reasonable sample size. Ondansetron has a very benign safety profile; one of the side effects of ondansetron, constipation, is actually a therapeutic benefit in the intended indication. In contrast, adverse events are more common with phenothiazines and metoclopramide, and they may be severe. These include dystonia and akasthesia. Therefore, use of a placebo control in patients with moderate gastroenteritis may spare some patients toxicity in a situation where not all patients require pharamacologic intervention. Those patients who do require medication will promptly receive an active rescue intervention.

2. Objectives

2.1 Primary

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.

2.2 Secondary

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. The Bristol Stool Scale is shown in Appendix I.
  - 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

3. Study Population

A total of 320 adults and children ≥age 12 with vomiting from presumed acute gastroenteritis or gastritis of ≤36 hours duration will be enrolled in this study.

3.1 Inclusion Criteria

1. Patients must have vomited at least twice in the 4 hours preceding signing informed consent.
2. A vomiting episode is defined as an episode of forceful expulsion of stomach contents. Retching if a patient has already emptied his or her gastric contents is also considered a vomiting episode. A distinct episode is characterized by a clear break in vomiting activity of at least 5 minutes. Emesis must have been nonbloody (streaks of blood presumed due to force of retching are allowed).
3. All patients (or a parent or guardian for patients <age 18) must sign informed consent. Patients <age 18 must also give assent to participate.

3.2 Exclusion Criteria

1. Severe dehydration

   There is no generally accepted definition of severe dehydration in adults. As a working definition for purposes of this study, severe dehydration is defined as two or more of the following criteria in the presence of decreased intake and increased output due to vomiting or diarrhea:

   - absent or severely decreased urine output,
   - weak pulse and/or low blood pressure,
   - parched mucus membranes,
   - lethargy, confusion, delirium or loss of consciousness.
2. Signs and symptoms severe enough to require immediate parenteral hydration and/or parenteral antiemetic medication
3. Temperature>39.0°C
4. Likely etiologies for acute vomiting and diarrhea other than acute infectious or toxic gastroenteritis or gastritis
   a. This includes signs of an acute abdomen, which may require surgical intervention
5. Chemically-induced gastroenteritis, e.g., from alcohol, other drugs of abuse or other irritant chemicals
6. Use within 24 hours of study entry of specific medication for treatment of nausea and/or vomiting, e.g., 5-HT3 antagonists or phenothiazines, or receipt of any IV fluid for any reason. Nonspecific gastrointestinal remedies, such as antacids, proton pump inhibitors and homeopathic remedies, are permitted
7. Congestive heart failure, bradyarrhythmia (baseline pulse<55/min), known long QT syndrome

8. Patients who have QTc prolongation>450 msec, noted on prior or screening ECG (per standard algorithm used by institution), or who are taking medication known to cause QT prolongation

   Note: For current list of medications known to cause QT prolongation see:

   https://www.crediblemeds.org/healthcare-providers/drug-list/

   There are several risk categories. Use the list showing those drugs known to cause torsade de pointes (TdP).
9. Known underlying disease which could affect assessment of hydration or modify outcome of treatment, e.g., renal failure, diabetes mellitus, liver disease, alcoholism

   Patients with type 2 diabetes mellitus controlled by diet or oral medications and whose baseline blood glucose is <200 may be entered into the study
10. Abdominal surgery within the past 3 months
11. History of bariatric surgery or bowel obstruction at any time
12. Hypersensitivity or other known intolerance to ondansetron or other 5-HT_3 antagonists
13. Patient has taken apomorphine within 24 hours of screening
14. Patient has previously participated in this study
15. Patient has participated in another interventional clinical trial, for any indication, in the past 30 days
16. For women of childbearing potential (WOCBP): documented or possible pregnancy. WOCBP include any female who has experienced menarche and who has not been surgically sterilized or is not postmenopausal (defined as amenorrhea ≥ 12 consecutive months). WOCBP are excluded if either a) they have a positive pregnancy test on screening, or b) they think they may be pregnant, even if screening pregnancy test is negative. Time since last menstrual period is not a criterion for determining pregnancy status.

4. Study Design

4.1 Overview

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. However, 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.

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. If a patient leaves the ED less than 4 hours after dosing, an ECG should be obtained if at all possible, even if the patient is leaving against protocol requirements.

On discharge, patients 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.

4.2 Study Drug Administration

After results of the pregnancy test and/or blood glucose (when required) are obtained and determined to be negative/within acceptable limits and the patient is randomized, the investigator or a designate will administer the first dose of study medication under observation. If the patient vomits within 15 minutes, regardless of whether pill fragments are seen, a second dose of study medication will be administered by the investigator or a designate. If a patient retches but does not actually vomit any gastric contents, no second dose will be administered. If a patient vomits again, regardless of how long after the second dose of study medication, no further study medication will be administered.

Patients vomiting ≥30 minutes after the first dose of study medication may receive rescue antiemetics, either parenterally or orally. In addition, patients with

severe nausea ≥30 minutes after dosing with study medication and which in the investigator's opinion requires treatment may receive rescue medication. Metoclopramide 0.3 mg/kg, maximum dose 10 mg, administered intravenously will be the default rescue medication. Oral metoclopramide or other antiemetics administered either intravenously or orally may be used at the investigator's discretion. **However, patients are not to receive ondansetron or other 5-HT_3 antagonists by any route for at least 24 hours after administration of study medication either in the ED or after discharge.** The following 5-HT_3 antagonists are available in the US: alosetron (Lotronex), dolasetron (Anzemet), granisetron (Sancuso and others), ondansetron (Zofran, Zuplenz and others), palonsetron (Aloxi).

Oral fluids will be administered as tolerated once a patient has not vomited for 30 minutes after dosing with study medication (second dose for those patients receiving 2 doses in the ED). Only patients who do not tolerate oral fluids after an adequate attempt at oral hydration may receive parenteral hydration. Patients are not to receive intravenous hydration until it is clear to the treating physician that the patient is clearly in need of parenteral hydration.

Patients tolerating oral fluids will be discharged once deemed stable by the attending physician but not prior to 4 hours after dosing and repeat ECG.

Patients who do not tolerate oral fluids will receive parenteral hydration.

Patients who are admitted but have not vomited or received antiemetics other than study medication may, at the investigator's discretion, continue treatment with study medication.

4.3 Randomization and Blinding

As noted above, patients will be stratified by age and randomized 60:40 to receive either RHB-102 or matching placebo. Medication will be provided in kits of 5 pills: one for initial administration, one if repeat dosing is required in the emergency department (and which will be retained by the investigator if not required), and three which the patient will take home.

4.4 Concomitant Therapy

If deemed necessary by the investigator, patients may take rescue antiemetics, either orally or intravenously, as described in section 4.2, above. Also, if deemed necessary by the investigator, patients may receive parenteral hydration. However, every effort should be made to avoid both rescue medications and parenteral hydration, and to proceed with oral hydration, unless it is clear that the patient will not be able to tolerate oral hydration.

From the time a patient takes any antiemetic other than study medication, whether while in or after leaving the emergency department, or receives parenteral hydration, he or she will be deemed a treatment failure, even in the absence of vomiting.

Patients may take antipyretic and antidiarrheal medication as needed prior to or after initial dosing with study medication. Patients may also take medications for gastrointestinal symptoms as long as they are not specifically antiemetics. For

example, they may use proton pump inhibitors or antacids. Once vomiting is controlled, patients should resume any medications they routinely take.

Patients for whom an intravenous medication (other than antiemetic) is indicated once on study may receive that medication in up to 100 mL fluid. This will not be considered parenteral *hydration*. For example, if a patient has a urinalysis suggesting infection and the investigator or other physician wish to give the patient an intravenous antibiotic dose, that will not be considered treatment failure as long as the drug is given in ≤100 mL fluid.

If once on study, a patient requires a medication which may prolong the QTc interval, he or she should not receive further study medication. However, evaluation of the patient should continue per protocol.

4.4.1 Oral hydration guidelines

The following are guidelines for oral rehydration. These are suggested but not required; investigators may follow institutional procedures and should use clinical judgment in determining when and how much oral fluid to administer.

1. After ingestion of the study drug along with small amount of fluids, nothing else by mouth for the first 30 minutes.
2. At approximately 30 minutes after study drug administration, gently encourage drinking of approximately 8 ounces (240 mL) of fluid over the next 30 minutes.
3. At approximately 60 minutes after study drug administration, further encourage oral hydration according to patient symptoms, as follows:
    a. The overall goal is for the patient to ingest approximately one liter over 1-2 hours after study drug administration. One liter is common, although as much as 2 liters may be taken, depending on the patient's volume status and symptom of nausea.
    b. Alternatively, a patient may ingest 600-700 mL, indicate feeling better and want to be discharged. If, based on improvement in symptoms, the investigator feels confident the patient will do well at home, the discharge takes place.

Please note the following:

- Too much fluid given too quickly may increase symptoms of nausea.
- Too little fluid: in the absence of at least some ED rehydration, it is difficult to be confident the patient will further tolerate reasonable amounts of fluid at home (or to determine if the patient is failing hydration in the ED).

From the time a patient takes any antiemetic other than study medication, whether while in or after leaving the emergency department, or receives any parenteral hydration, he or she will be deemed a treatment failure.

4.4.2 Serotonin syndrome

5-HT_3 antagonists, including ondansetron, have been associated with serotonin syndrome. When given as a single agent, ondansetron overdose has been associated with serotonin syndrome. However, most reports of serotonin syndrome have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be warned about and monitored for the emergence of serotonin syndrome, especially with concomitant use of other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue RHB-102 and initiate supportive treatment.

All medications taken in the 7 days prior to study entry and from the time the patient arrives in the emergency room until he or she completes the study will be recorded in the case report form (CRF).

4.5 Duration of Treatment

On discharge, patients who have not had further vomiting and have not required rescue medication in the emergency department will be given 3 additional doses of study medication to take once daily if necessary. Patients will be instructed to take additional study medication if they are nauseated (whether persistent or recurrent) or have any vomiting. However, patients are not to take study medication more than 3 days after study entry. Thus, if a patient receives an initial dose of study medication in the emergency department, feels well the next day and does not take study medication, but subsequently has a recurrence of symptoms, that patient may not take the remaining dose of study medication on day 5. Rather, the patient should return for reassessment during the follow-up period.

Patients or their caregivers are to complete a diary each day for 4 days, recording episodes of vomiting, diarrhea, presence and severity of nausea, presence/development of other signs or symptoms related to the gastroenteritis, and occurrence of adverse events. This diary may be completed either on paper or through a web-based system. Alternatively, patients or their caregivers will be contacted daily for up to 4 days following study initiation (until symptoms have resolved) to ascertain whether the patient had further vomiting, other sequelae of the acute gastroenteritis or required further medical care for the gastroenteritis. If symptoms persist for 3 days after study entry, the patient will be instructed to return for further evaluation on the third or fourth day.

For patients discharged prior to 8:00 pm, the ED day diary page is to be completed. The ED day diary page is to include only information regarding events after discharge from the ED; information on events during the patient's ED stay is not to be repeated in the diary. For those discharged 8:00 pm to midnight, or later, diary information is to be recorded only on the follow-up diaries. But vomiting episodes and adverse events occurring between 8:00 pm and midnight the preceding day should be included in the information captured.

4.6 Discontinuation of Treatment

Patients may take study medication daily for up to 4 days (day 1 medication is the one or two tablets administered in the emergency department).

- If a patient vomits or otherwise receives rescue medication in the emergency department, he or she is not to receive additional study medication, even if nausea and/or vomiting is controlled with rescue medication.
- If the QTc interval at 4 hours after initial dose of study medication is >500 msec, study medication is to be discontinued.
- Patients experiencing recurrent nausea or vomiting after discharge from the emergency department and initial discontinuation of study medication due to resolution of symptoms may opt to resume study medication.

If a patient experiences an adverse event, regardless of relationship to study medication, which, in the investigator's opinion endangers or makes it difficult to evaluate the patient, the investigator may elect to have the patient stop study medication.

If once on study, a patient requires a medication which may prolong the QTc interval, he or she should not receive further study medication. However, evaluation of the patient should continue per protocol.

Patients may elect to discontinue treatment at any time.

4.7 Replacement of Subjects

Patients who are randomized but do not receive study medication will be replaced. Patients who receive any study medication, even if they vomit immediately thereafter or cannot swallow the medication, will not be replaced.

5. Study Evaluations

5.1 Schedule of Evaluations

A flow chart of study evaluations is shown above, on page 10.

5.2 Description of Study Procedures

5.2.1 Baseline procedures

- History and physical, including vital signs. History should include detailed history of present illness, including questioning about similarity of this episode with prior episodes, exposures to similar illnesses, and questioning about etiologies if not obvious.
- Physical examination should include all pertinent body symptoms.
- Vital signs should include height, weight, temperature, pulse, blood pressure, respiratory rate. All units should be metric.
- Baseline laboratory studies:
    - Required of all patients: CBC, biochemical profile, ECG
        - CBC to include: total RBC, total WBC count, absolute values for individual white blood cell types and platelet count.
        - Biochemical profile to include: albumin, alkaline phosphatase, ALT, AST, (total) bilirubin, BUN, calcium, chloride, CO_2, creatinine, glucose, magnesium, potassium, sodium, total protein.
        - Standard 12-lead ECG
    - All patients ≥40 years of age and those with type 2 diabetes regardless of age: urinalysis, to include at a minimum: routine: dipstick tests for protein, glucose, ketones, blood, pH, specific gravity; microscopic: erythrocytes, leukocytes, bacteria, crystals, casts. Urinalysis is optional for patients <age 40.
    - For patients with diet-controlled type 2 diabetes mellitus: finger stick blood glucose
    - For women of childbearing potential, serum or urine pregnancy test (β-HCG)
- When drawing blood, a saline lock may be placed so that if the patient requires subsequent intravenous medications or hydration, he or she will not have to be stuck again.

Treatment can start once the urinary pregnancy test results are obtained and determined to be negative, and, for type 2 diabetics, finger stick results obtained and blood glucose is <200 mg/dL. Results of chemistries, CBC and urinalysis do not have to be available prior to start of study medication.

5.2.2 Observation while in emergency department

To start immediately after administration of study medication:

- Intake and output hourly:
    - all oral and parenteral intake

- urination: number of voidings
- vomiting: number of episodes
- stool output: number, consistency (per scale in original protocol and per Bristol Stool Scale, Appendix I)

- Vital signs at least hourly and just prior to discharge: temperature, blood pressure, pulse, respiratory rate
- Questioning regarding adverse events: hourly and just prior to discharge
- Assessments of nausea: on signing informed consent, just prior to first dose of study medication, hourly, just prior to discharge from emergency department. A 5-point Likert scale will be used:

  0 No nausea

  1 Mild nausea

  2 Moderate nausea

  3 Severe nausea

  4 Nausea as bad as can be

- 12-lead ECG 4±0.25 hours after initial dose of study medication (regardless of whether dose was repeated in ED). If patient leaves ED <4 hours after dosing, an ECG should still be obtained just prior to discharge.
- Brief physical examination of pertinent systems prior to discharge

If a patient vomits ≥30 minutes after taking the first dose of study medication, requires rescue antiemetic or parenteral hydration, he or she will be considered a treatment failure. The patient will be followed according to the schedule above for a total of 4 hours from the time of first administration of study medication or until discharged home, whichever comes first. After that, for patients still in the emergency department or hospital, the patient will be followed per standard protocol, according to the patient's condition.

5.2.3 Procedures after discharge from emergency department:

Any patient who has a post-dosing ECG showing QTc>500 msec must have a follow-up ECG within 72 hours of initial dosing showing resolution of the QTc prolongation. This may be performed on an inpatient or outpatient basis at the investigator's discretion. If the QTc does not decrease below 500 msec during initial follow-up, the medical monitor must be contacted to discuss further follow-up.

If a patient vomits from 30 minutes after taking the first dose of study medication until 24 hours after the first dose of study medication or requires rescue antiemetic or parenteral hydration during that period, even without vomiting, he or she will be considered a treatment failure. In that case, the only post-emergency department follow-up will be a call 72-96 hours after discharge from the emergency department to ascertain whether the patient's symptoms have

resolved, whether any adverse events occurred, and whether the patient required further medical follow-up, either in an emergency department or other medical facility.

Prior to discharge, patients who are treatment successes (i.e., no vomiting, no rescue medication and no parenteral hydration while in emergency department) will be given a diary card to record:

- all episodes of vomiting and bowel movements, with description of each bowel movement
- severity of nausea (on a 5-point Likert scale) three times a day: before breakfast or the time at which the patient usually eats breakfast, between 1:00-2:00 pm, and at bedtime
- any symptoms the patient may have related to gastroenteritis, such as chills, fever, abdominal pain
- adverse events
- medications taken, either for gastroenteritis (study medication and others) or other conditions

Patients will be contacted at least once daily for 4 days after discharge from the emergency department to question them about the presence of gastroenteritis symptoms and adverse events, to ask if and when they took study medication, and to ask whether they have returned to normal daily activities. The information recorded by the patient on his/her diary card will form the basis for data collected in the follow-up calls. If during the follow-up period, symptoms progress or worsen or new symptoms develop, the patient may be asked to return for further evaluation. If by day four after discharge (i.e., the day after the last dose of study medication), the patient still notes gastroenteritis symptoms, he or she will be instructed to return to see the investigator or his/her designate for further assessment. In addition, if the investigator is concerned that a patient may not be entering the data promptly and appropriately or as an added stimulus to data entry by the patient, the investigator may also contact the patient.

For patients returning due to persistent gastroenteritis 3 days after discharge from the ED, an interim history and physical examination will be performed. Laboratory studies may be performed if clinically indicated, and results of these studies will be entered into the CRF.

6. Safety Reporting

All subjects will be assessed regularly for potential adverse events (AEs) occurring at any time after the subject signs the informed consent, until discharge after the last dose of study medication. AEs ongoing at the time of last dose of study medication will be followed until resolution or until 30 days after the last dose of study medication, whichever comes first. Post-study follow-up will be by telephone or e-mail after subjects are discharged. All subjects dosed will be contacted per the schedule above and queried regarding the occurrence of AEs and serious adverse events (SAEs).

6.1 Terminology

An *Adverse Event (AE)* is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (may also be referred to as an adverse experience) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational or marketed) product, whether or not considered related to the medicinal (investigational or marketed) product and from any route of administration, formulation, or dose, including an overdose.

A *Serious Adverse Event (SAE)* is any untoward medical occurrence that at <u>any dose results in any of the following outcomes</u>:

death;

is a life-threatening adverse event (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe);

requires in-patient hospitalization or causes prolongation of existing hospitalization;

a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;

a congenital anomaly/birth defect;

is an important medical event. This is defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

If either the sponsor or investigator believes that the event is serious, the event must be considered serious and be evaluated by the Sponsor for expedited reporting.

Admission for gastroenteritis is not a serious adverse event, as the gastroenteritis is a preexisting condition, not an adverse event. Admission for gastroenteritis will be considered lack of efficacy, and is recorded as such as a secondary efficacy outcome.

If, however, a patient develops new symptoms in the ED, such as findings leading to a diagnosis of an acute abdomen, and is admitted, that would be considered a serious adverse event.

A *suspected adverse reaction* means any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed.

6.2 Assessment of Causal Relationship

The following categories and definitions for assessing the causal relationship of an event to the investigational product(s) are provided as a guide to be used for evaluating adverse events reported in this study to determine "suspected adverse reactions" that require expedited reported to regulatory agencies if they are unexpected. In addition to the assessment below, the aggregate number of occurrences will be considered to decide whether the event is a reportable event and requires an IND safety report.

Table 1. Relationship of Study Medication to Adverse Events

Unrelated	The study drug almost certainly (or certainly) did not cause the event. Guidelines: There is no reasonable temporal relationship of the event to the administration of drug; The pattern is inconsistent with that known for the drug; and/or There is another obvious etiology.
Probably not related	It is more likely that the event is due to another etiology than due to the study drug. Guidelines: There is no reasonable temporal relationship of the event to the administration of drug; The pattern is inconsistent with that known for the drug; and/or There is another more likely etiology.
Possibly related	It is approximately equally likely that the event is due to the study drug as it is due to another etiology. Guidelines: There is a reasonable temporal relationship of the event to the study drug; The drug seems as likely as other etiologies to have caused the effect
Probably related	It is more likely that the event is due to the study drug than due to another etiology. Guidelines: There is a reasonable temporal relationship of the event to the study drug; The event may be consistent with a known pattern of drug (or drug class) effects; The drug seems more likely than other etiologies to cause the effect; The adverse event diminished upon cessation of study drug exposure or reduction in dose; and/or The adverse event worsened or recurred upon unintentional re-exposure to the study drug (Intentional rechallenge for the purpose of assigning causality should not be performed.)

Definitely related	The evidence is compelling that the study drug caused the adverse event. Guidelines: There is a reasonable temporal relationship of the event to the study drug; The event is consistent with a known pattern of drug (or drug class) effects; The drug is far more likely than other etiologies to have caused the effect; The adverse event diminished upon cessation of study drug exposure or reduction in dose; The adverse event worsened or recurred upon unintentional re-exposure to the study drug (Intentional rechallenge for the purpose of assigning causality should not be performed.)
Unknown	The data are inadequate to assign any of the above causal relationship categories to the study drug.

6.3 Adverse Event Grading and Coding

Adverse events will be graded according to the NCI-CTCAE v 4. These criteria can be accessed at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

For AEs not included in the NCI-CTCAE v 4, the following criteria will apply:

Grade	Description
1	Mild
2	Moderate
3	Severe
4	Life-threatening or disabling
5	Fatal

AEs will be coded, grouped and tabulated by MedDRA preferred terms by body system organ class. MedDRA version 13.1 will be used for the entire study.

6.4 Handling of Serious Adverse Events

Adverse events classified as serious must be recorded on the AE page of the CRF and require expeditious handling and reporting to the sponsor, RedHill Biopharma, to comply with regulatory requirements. These SAEs will include deaths, regardless of their causal relationship to investigational product. All SAEs must be reported using the Serious Adverse Event Report form. To the extent possible, the descriptive terminologies and other SAE attributes entered on the SAE report form should approximate similar information in the CRF. The completed SAE report form with supporting documentation must be provided to the sponsor within 24 hours of the study site personnel's initial notification/awareness of the event. All telephone communication regarding SAE must be followed by a written report.

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information that becomes available as the SAE evolves, as well as supporting documentation (e.g. hospital discharge summaries, additional lab and test results, autopsy reports, etc.), should be collected subsequently, if not available at the time of the initial report, and immediately sent to sponsor using the same procedure as the initial SAE report. Information on the SAE must be in

sufficient detail to allow for a complete medical assessment of the case and independent determination of causality.

For ease of analysis, worldwide standardization, and regulatory reporting, the sponsor will code each reported adverse event or symptom to its corresponding preferred term and body system/organ class in the MedDRA dictionary version adopted for the study. The principal investigator will be responsible for assessing severity based on the intensity of the event as it presented using the criteria listed in section 6.3, above.

All SAE reports must be e-mailed or faxed directly to [redacted]

As required, all investigators will be notified of all AE reports that are determined to be serious, unexpected, and related (by the reporting investigator or sponsor) to the investigational product. The notification will be in the form of a Safety Update (Dear Doctor Letter).

The notification is considered an addendum to the current Investigator's Brochure; therefore, upon receiving such notices, the investigator must review and immediately submit a copy to the IRB according to local regulations. The notification must be retained within the Investigator's Brochure. The investigator and IRB will determine if the informed consent requires revision.

6.5 Laboratory Test Abnormalities

If any laboratory tests are performed on study, all new abnormal laboratory findings after initial administration of study medication 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] v4.0) are considered AEs. Laboratory AEs for which there is no clinical intervention will be recorded only on the laboratory data pages of the eCRF. Laboratory AEs not listed in the NCI CTCAE v4.0 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, described above.

6.6 Other Safety Considerations

Any clinically significant changes noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded on the AE page of the CRF.

7. Data Analysis and Statistical Considerations

7.1 Sample Size Considerations

The primary endpoint is a composite of the following three parameters from 30 minutes until 24 hours after the first dose of study medication:

- absence of vomiting
- no use of rescue medication, and
- 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.

It is expected that approximately 40% of the placebo group will fail treatment during the 24 hours after initial dosing and that RHB-102 will reduce the incidence of treatment failure by approximately 50%, i.e., to an incidence of 20% in the active treatment group. Patients will be stratified by age (<18, ≥18 years of age) and randomized 60:40 to active versus placebo. To demonstrate a statistically significant decrease in the incidence of vomiting with a 2-tailed p-value=0.01 and power=90%, 320 patients will be entered into the study, 192 randomized to RHB-102 and 128 to placebo.

7.2 Analysis Datasets

Safety and efficacy analyses will be based on all patients who receive any study medication, even if they vomit shortly after administration or are unable to swallow the medication.

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

7.3 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.

7.4 Efficacy Analyses

The primary endpoint is described above.

7.4.1 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 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).

7.4.2 Primary Analysis

The study 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.

In addition, subgroup analyses by each age group (<18, ≥18 years of age) will be conducted for the primary and selected secondary endpoints. For a given age group, unstratified CMH test will be performed.

An additional subgroup analysis will be performed which will exclude those patients determined during the course of their treatment and study follow-up to have a diagnosis other than acute gastroenteritis or gastritis.

7.4.3 Handing 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 will be imputed as failures/non-responders for the primary analysis. Sensitivity analyses using different imputations for missing values will be specified in the SAP.

7.4.4 Secondary Analyses

Additional analyses will be done comparing the following parameters between treatment groups:

- 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
- 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

7.5 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.

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

7.5.1 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 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.

7.5.2 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.

7.6 Interim Analysis

No interim analysis will be conducted.

8. Study Medications

Study medication, either RHB-102 or matching placebo, will be provided by the sponsor in kits of 5, labeled with a randomization code and required drug information.

Study medication is to be stored at 15-30°C.

Each RHB-102 tablet contains a total of 24 mg of ondansetron. Matching placebo containing no active drug will also be provided.

On randomization, the appropriate bottle of study medication will be provided by ED pharmacist. The investigator or a designate will administer the first dose of study medication under observation.

If the patient vomits within 15 minutes, regardless of whether pill fragments are seen, a second dose of study medication will be administered by the investigator or a designate. If the patient experiences no vomiting in the ED after administration of the first dose of study medication, the second tablet will be retained for audit purposes. Patients who have not failed therapy before ED discharge will take the bottle containing the remaining 3 tablets home on discharge.

After each patient completes the study, he or she will send any remaining study medication back to the investigator in a prepaid, addressed mailer to be provided.

9. Investigator Responsibilities

9.1 Compliance with Declaration of Helsinki and Good Clinical Practices

The study will be performed in accordance with the Declaration of Helsinki (1964) as revised, most recently in Fortaleza, Brazil (2013), US FDA regulations and the ICH Guideline for Good Clinical Practice, E6(R1). The investigator will ensure that all those concerned with conducting the study (such as pharmacists, research nurses and co-investigators) are provided with copies of the protocol and all safety information prior to the start of the study.

9.2 Institutional Review Board (IRB) Review and Approval

The investigator is responsible for obtaining IRB approval to conduct this study (including IRB approval of the Informed Consent form) and for ensuring continuing review as required by the IRB. Written confirmation of this approval and periodic review must be provided to the sponsor prior to the start of the study and at appropriate intervals.

9.3 Informed Consent

The investigator will inform subjects as to the nature, expected duration and purpose of the study, the administration of the study medication, and the hazards involved, as well as the potential benefits that may come from treatment with this investigational drug. Informed consent must be obtained in accordance with US Code of Federal Regulations (21 CFR Part 50).

The subject will be informed that his/her medical records will be subject to review by the sponsor and possibly by a representative of the Food and Drug Administration. Subjects will be informed that they are free to refuse participation in this clinical investigation, and if they should participate, it will be made clear to them that they may withdraw from this study at any time without prejudicing further care. Signed written informed consent must be obtained from every subject prior to study entry. The original will be kept by the investigator and will be subject to review by the sponsor; a copy will be given to the subject.

9.4 Confidentiality

All information provided to the investigator relevant to the study medication, as well as information obtained during the course of the study, will be regarded as confidential. The investigator and members of his/her research team agree not to disclose or publish such information in any way to any third-party without prior written permission from the sponsor, except as required by law.

9.5 Source Documentation

The investigator will allow inspections of the study site and documentation by clinical research and audit personnel from the sponsor, external auditors or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the case report forms. In order to do this direct access to the subjects' medical or clinic records is necessary. The investigator will ensure that certain information is contained in the medical or clinic records of the subject and that the entries are signed and dated, as follows:

- sufficient data to allow verification of the entry criteria in terms of past and present medical and medication histories;
- a note on the day the subject entered the study describing the study number, the drug being evaluated, the study number assigned to that subject and a statement that consent was obtained;
- a note of each subsequent study visit including any concerns about adverse events or abnormal laboratory data and their resolution;
- notes of all concomitant medication taken by the subject including start and stop dates;
- a note of when the subject terminated from the study, the reason for termination and the subject's general condition at termination;
- a copy of the signed informed consent form should be kept in the medical records of each subject during the clinical phase of the study (thereafter it will be archived with the study file).

9.6 Drug Accountability

The investigator agrees to supervise the maintenance of records of the receipt, dispensing and return of study material supplied by the sponsor. All unused study medication, both individual tablets and unused kits, must be returned to the sponsor's designated agent. The dispensing record must make it clear which subject received which material.

9.7 Data Monitoring and Collection

Suitably qualified and trained clinical research personnel of the sponsor will visit the study center at regular intervals during the study for monitoring purposes and to assist the research staff with any queries they may have.

9.8 Case Report Forms, Investigator's Study File and Record Retention

All case report forms and supporting source documentation must be available to the sponsor during monitoring visits.

Prior to review of the case report forms by the sponsor's representative, they should be reviewed for completeness and accuracy by the investigator or a member of the research team.

The investigator will maintain all records relating to the study (including copies of case report forms) for at least 2 years after written notification by the sponsor that the investigational drug program has been either completed or terminated, or that a New Drug Application (NDA) has been approved by the FDA. Should the investigator retire, relocate, or for other reasons withdraw from the responsibility of keeping the study records, custody must be transferred to a person who will accept that responsibility, and the sponsor must be notified in writing of the name and address of said person.

9.9 Non-Protocol Research

No investigational procedures other than those outlined in this protocol may be undertaken on the subjects in this study without the prior written permission of the subject, the sponsor and the IRB.

10. Sponsor Responsibilities

10.1 General

The sponsor agrees to adhere to US FDA Guidelines on Good Clinical (Research) Practices and with the ICH Guideline for Good Clinical Practice, E6(R1). The sponsor has a legal responsibility to report fully to regulatory authorities the results of this study. It is the sponsor's responsibility to obtain appropriate regulatory approval to perform the study.

10.2 Case Report Forms

Case report forms will be provided by the sponsor or, upon agreement with the sponsor, forms generated by the investigative site may be used. If an electronic data collection system is used, the system will be compliant with applicable aspects of 21 CRF Part 11, ICH guidelines, GCP and HIPAA.

10.3 Data Monitoring and Collection

Suitably qualified and trained clinical research personnel of the sponsor will visit the study center at regular intervals during the study for monitoring purposes and to assist the research staff with any queries they may have. Case report forms and source documentation will be available for review during monitoring visits to the center. The function of this monitoring is to ensure compliance with the protocol, adherence to regulatory and good clinical (research) practice obligations, proper maintenance of records including drug accountability records, correct administration of study medications including storage conditions and accurate reporting of adverse events.

10.4 Audit

The sponsor has an obligation to audit a proportion of studies; this is usually undertaken by a department other than the clinical research department. Therefore the sponsor, an independent auditor or a regulatory authority may wish to audit the study site and documentation and these audits may take place as the study is running or up to several years later.

10.5 Confidentiality

The sponsor will not keep any material on file bearing any subject's name, and the subject's confidentiality will be maintained at all times.

11. Protocol Modifications

If necessary during the course of the study, the protocol may be modified by the sponsor in consultation with the investigator. Except in the case of modifications to resolve an imminent safety issue, any protocol modification or revision must be reviewed and approved by the investigator's IRB prior to implementation.

12. Publication

Redhill has agreed to provide unblended data to a publications committee for publication of the results of this study once completed and all data have been cleaned and the blind broken. The publications committee will be constituted according to the guidelines set out in the letter to investigators dated September 17, 2015. If deemed necessary by the sponsor for protection of proprietary information prior to patent filing, the investigator agrees to delay for 60 days before any presentation or publication is submitted.

13. References

Chow CM, Leung AKC, Hon KL. Acute gastroenteritis: from guidelines to real life. Clin Exp Gastroenterol 2010;3:97-112.

Deaths from gastroenteritis double. CDC press release 14 March 2012. http://www.cdc.gov/media/releases/2012/p0314_gastroenteritis.html?s_cid=ccu032612_013 Downloaded 24 Feb 2014.

Graves NS. Acute gastroenteritis. Primary Care Clin Office Pract 2013;40:727-41.

Appendix I. Bristol Stool Scale