# CLINICAL STUDY PROTOCOL

## Cover Page

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| **Protocol No.:** | RACE3002 | **Protocol Date:** | 09 OCT 2017 |
| | | **Amendment 1** | 07 NOV 2018 |
| | | **Amendment 2** | 22 NOV 2019 |
| **Study Title:** | **Efficacy and Safety of Racecadotril in the treatment of Taiwanese children aged 3 to 60 months suffering from acute diarrhea: A prospective, open-label, multicenter, single-arm study** | | |
| **IND No.:** | N/A | | |
| **EudractCT No:** | N/A | | |
| **Phase of Development:** | III | | |
| **Sponsor:** | Abbott Laboratories Services Corp Taiwan Branch | | |
| **Global Clinical Director** | [redacted] | | |
| **Protocol Author (s)** | [redacted] | | |

## SYNOPSIS

| **Name of Sponsor:** Abbott Taiwan | **Name of Finished Product:** Hidrasec Infants Granules for Oral Suspension 10 mg Hidrasec Children Granules for Oral Suspension 30 mg | **Name of Active Ingredient(s):** Racecadotril |
|---|---|---|
| **Title of Study:** Efficacy and Safety of Racecadotril in the treatment of Taiwanese children aged 3 to 60 months suffering from acute diarrhea: A *prospective*, open-label, multicenter, single arm study | | |
| [redacted] | | |
| **Study Duration:** approximately 2 years (from First Subject First Visit until Last Subject Last Visit) End of Study is defined as Last Subject Last Visit. | | Phase of Development: III (post approval commitment) |

**Objectives:**

**Primary objective:**
The primary objective is to evaluate the efficacy of Racecadotril in addition to standard treatment oral rehydration solution (ORS) in infants and children (3 months until *60 months*) with acute diarrhea measured as duration of diarrhea (hours) between the start of treatment until final diarrheal/watery stool or end of study treatment (treatment duration maximal 5 days).
Duration of diarrhea is defined as date and time of the evacuation of the final watery/diarrheal stool derived from the daily diary.

**Secondary objective(s):**

- Time until recovery, defined as date and time of the evacuation of the first of two consecutive normal stools or no stool within 12 hours *after the first normal stool*.
- Number of recovered subjects in total and until each individual treatment day. Mean and median time until recovery.
- Global Physician Assessment (GPA) at the end of treatment (at the discretion of the investigator):
  - 1 = Complete relief of acute diarrhea,
  - 2 = marked improvement of acute diarrhea,
  - 3 = moderate improvement of acute diarrhea,

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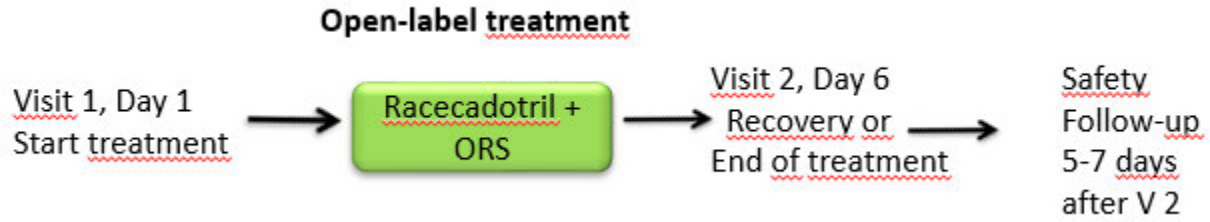
- 4 = slight improvement of acute diarrhea,
- 5 = no change in acute diarrhea,
- 6 = worsening of acute diarrhea.

(Treatment success = GPA score of 1 or 2).

- For toilet trained children only: number of stools per day as well as number of watery stools per day from start of treatment and until end of study treatment.

**Safety and tolerability:** To evaluate the safety and tolerability of Racecadotril in addition to ORS in infants and children with acute diarrhea by adverse events, physical examination and vital signs.

**Methodology:**
This is a prospective, open-label, multicenter, single-arm study evaluating the efficacy and safety of Racecadotril in infants and children with acute diarrhea.




**Screening and Enrolment (Day 1, Visit 1)**
Subjects presenting with acute diarrhea will be evaluated for eligibility. They will undergo a physical examination including vital signs, a review of their medical history including vaccination history and concomitant medication. If the subjects are eligible, demographics, number of stools during the last 12 hours will be assessed as baseline values. On Day 1, the subject will start with study treatment. The starting dose will either be the noon or evening dose.

**Treatment period (until recovery, maximally five days)**
Subjects will be treated with Racecadotril three times daily according to the body weight dose requirement on an out-patient basis for maximum 5 days in addition to ORS. ORS will be prescribed by the investigator. The parent(s)/caregiver(s)/legal representative(s) will be instructed to stop treatment when the patient recovered. Recovery is defined by the evacuation of the first of two consecutive normal stools or no stool within 12 hours. In the evening of each day, the parent(s)/caregiver(s)/legal representative(s) will fill in their diaries, documenting date and time of each individual stool, the stool consistency of each stool, ORS amount and the study drug intake. AEs are to be reported on an ongoing basis. Treatment will stop at recovery ***(last dose***

| **Name of Sponsor:** Abbott Taiwan | **Name of Finished Product:** Hidrasec Infants Granules for Oral Suspension 10 mg Hidrasec Children Granules for Oral Suspension 30 mg | **Name of Active Ingredient(s):** Racecadotril |
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will be taken in the morning after recovery, ORS can be continued until Visit 2) or after the morning dose of day 6, if not recovered.

**End of treatment (at recovery or Day 6, Visit 2)**
The last dose of study drug intake will be the morning dose of day 6, if not recovered earlier. The parent(s)/caregiver(s)/legal representative(s) will visit the site for the end of study visit of the child. Data on vital signs, AEs, physical examination and concomitant medication will be collected. The parent(s)/caregiver(s)/legal representative(s) will return the diaries and unused medication.

**Safety follow-up *call (Day 11-13)***
A phone call contact will be performed 5-7 days after the end of the treatment period or recovery for the safety follow-up.

**Table 1. Flow Chart of Study Assessments**

| **Period** | **Screening** | **End of Treatment period** | **Safety follow-up (phone call,-7 days after Visit 2)** |
|---|---|---|---|
| **Visit** | **1** | **2** | **3** |
| **Day** | **1** | **6[2]** | **11-13** |
| Informed consent | X | | |
| Inclusion/exclusion criteria | X | | |
| | | | |
| Demographic data | X | | |
| Medical history including vaccination history | X | | |
| Physical examination | X | X | |
| Vitals signs | X | X | |
| Dispense study drug | X | | |
| Concomitant medication | X | X | X |
| Compliance check | | X | |
| Global physician assessment | | X | |
| Adverse events | X | X | X |

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| | | | |
|---|---|---|---|
| Collect study drug | | X | |
| Dispense diary | X[1] | | |
| Collect diary | | X | |

[1] Subjects' parent(s)/caregiver(s)/legal representative(s) have to fill in their daily diaries continuously.
[2] or within 24 hours (in exceptional justified cases within 48 hours) after recovery if this occurs before day 6

**Number of Subjects (Planned):**
A **maximum** number of 48 subjects will be enrolled***. ~~with a minimum number of 20 subjects in each age group (< 24 months of age and ≥ 24 months of age).~~*** **Recruitment will be stopped once 40 subjects completed the study.**

Approximately 50 subjects should be screened**.**

**Diagnosis and Main Criteria for Inclusion:**

(1) Signed informed consent from one of the parent(s)/legal representative(s).
(2) Subjects, both genders, aged 3 to 60 months.
(3) Subjects with acute diarrhea (defined as the passage of three or more unformed or liquid stools within the last 24 hours and lasting for less than 3 days).

**Exclusion Criteria:**

(1) Known allergy to Racecadotril or any of its ingredients.
(2) Subjects suffering from renal or hepatic impairment.
(3) Subjects with fever > 39 degrees Celsius
(4) Subjects with bloody and/or purulent stools.
(5) Subjects suffering from antibiotic (e.g. amoxicillin)-associated diarrhea, chronic diarrhea or iatrogenic diarrhea.
(6) Subjects with alternating bouts of diarrhea and constipation.
(7) Diarrhea due to exacerbation of chronic gastrointestinal diseases such as irritable bowel syndrome, irritable bowel disease or pancreatic exocrine insufficiency.
(8) Cystic fibrosis or coeliac disease.
(9) Subjects suffering from prolonged or uncontrolled vomiting.
(10) Subjects with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption syndrome or sucrase isomaltase insufficiency.
(11) Subjects having received antibiotic treatment within 2 weeks prior to the current diarrhea event.
(12) Subjects having received antidiarrheal drugs (except pre-or probiotics see section 7.7) 48 hours prior to Day 1.
(13) Subjects with severe dehydration requiring intravenous fluid, electrolyte replacement or hospitalization treatment
(14) Subject with a history of angioedema or who had reported angioedema with angiotensin converting enzyme inhibitors (such as captopril, enalapril, lisinopril, perindopril,

| **Name of Sponsor:** | **Name of Finished Product:** | **Name of Active Ingredient(s):** |
|---|---|---|
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ramipril)

(15) Subjects with combined diseases or medical situations that would prevent to be enrolled into the study, depending on the judgment of the investigator
(16) Intake of experimental drug within 30 days prior to study start.
(17) Subjects with contraindications to ORS or susceptible to the warnings of ORS.

**Test Product, Dose and Mode of Administration:**

Racecadotril Infants Granules for Oral Suspension10 mg
Racecadotril Children Granules for Oral Suspension 30 mg

1.5 mg/kg of Racecadotril will be administered, 3 times daily, via the oral route.

In infants less than 9 kg: one 10 mg sachet 3 times daily.
In infants from 9 kg to < 13 kg: two 10 mg sachets 3 times daily.
In children from 13 kg to 27 kg: one 30 mg sachet 3 times daily.
In children of more than 27 kg: two 30 mg sachets 3 times daily.

Racecadotril will be given three times daily in addition to standard treatment ORS. For concomitant medication (please see section 7.7).

Standard treatment is oral rehydration solution (ORS) according to the registered local label and the instruction of the investigator. At the start of the trial, alignment will be reached on the understanding of treatment of standard ORS with the principal investigator with the aim to use the same brand of ORS and the same age-appropriate standardized treatment pattern for the subjects throughout the trial.

**Duration of Treatment:**

The first dose of Racecadotril will be taken on day 1, either noon, or evening dose. The treatment duration lasts until recovery (last dose in the morning after recovery), maximally 5 days, until the morning dose of day 6.

**Criteria for Evaluation:**

Efficacy:

Primary Efficacy Variable:
Duration of diarrhea (hours) between the start of treatment until last diarrheal/watery stool before recovery or end of study treatment (treatment duration maximal 5 days). Duration of diarrhea is defined as date and time of the evacuation of the final watery/diarrheal stool before recovery

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derived from the daily diary.

Secondary Efficacy Variables:

- Time until recovery, defined as date and time of the evacuation of the first of two consecutive normal stools or no stool within 12 hours after the first normal stool.
- Number of recovered subjects in total and until each individual treatment day. Mean and median time until recovery.
- Global Physician Assessment (GPA) at the end of treatment (at the discretion of the investigator):
  - 1 = Complete relief of acute diarrhea,
  - 2 = marked improvement of acute diarrhea,
  - 3 = moderate improvement of acute diarrhea,
  - 4 = slight improvement of acute diarrhea,
  - 5 = no change in acute diarrhea,
  - 6 = worsening of acute diarrhea.

  (Treatment success = GPA score of 1 or 2).
- For toilet trained children only: number of stools per day as well as number of watery stools per day from start of treatment and until end of study treatment.

Safety:

Adverse events, vital signs, physical examination.

**Statistical Methods:**

Efficacy:

In order to compare the primary efficacy parameter, duration of diarrhea between the treatment groups a Kaplan Meier analysis will be performed. The primary efficacy parameter, duration of diarrhea, will be analyzed using descriptive statistics. In addition, a Kaplan-Meier plot will be generated for which summary statistics will be presented as well. Secondary efficacy parameters will be analyzed similarly. All parameters will be summarized using descriptive statistics.

Safety:

The safety sample will be used for the analysis of the safety and tolerability data.

Treatment emergent AEs are summarized. Severity and drug-event relationship of treatment emergent AEs are summarized separately. Vitals signs, including changes from baseline will be

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summarized. A frequency table will be presented for markedly abnormal values.

Sample size

In total, 40 subjects will be allocated to receive Racecadotril treatment, ~~**20 subjects in each age group (< 24 months of age and ≥ 24 months of age).**~~ Results of a recently finalized study in Russian children showed that all children under Racecadotril treatment recovered within 3 days of drug treatment. A sample size of 40 subjects is sufficient to estimate a two-sided 95% confidence interval with the precision of 3.1 percentage points for a recovery of at least 99% of the subjects after 3 days of Racecadotril treatment. In order to account for drop-outs, **maximum** 48 subjects will be recruited. **Recruitment will be stopped once 40 subjects have completed the study.**

# TABLE OF CONTENTS

**LIST OF IN-TEXT TABLES**

**Es konnten keine Einträge für ein Abbildungsverzeichnis gefunden werden.**

## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| ACE | Angiotensin converting enzyme |
| ADR | adverse drug reaction |
| AE | adverse event |
| ATC | Anatomical Therapeutic Chemical |
| CFR | Code of Federal Regulations |
| CRF | case report form (paper or other media) |
| CRO | Contract Research Organization |
| DBP | diastolic blood pressure |
| ECG | electrocardiogram |
| EU | European Union |
| FA | full analysis |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| GPA | Global physician assessment |
| HLGT | high level group term |
| HLT | high level term |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| LLT | lowest level term |
| Max | Maximum |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Min | Minimum |
| ORS | oral rehydration solution |
| N/A | not applicable |
| PP | per-protocol |
| PT | preferred term |
| SADR | serious adverse drug reaction |

| | |
|---|---|
| SAE | serious adverse event |
| SBP | systolic blood pressure |
| SD | standard deviation |
| SmPC | Summary of Product Characteristics |
| SOC | system organ class |
| SUSAR | suspected unexpected serious adverse drug reaction |
| TEAE | treatment emergent adverse event |
| TFDA | Taiwan Food and Drug Administration |
| WHO | World Health Organization |

# 1 ETHICS

## 1.1 Independent Ethics Committee or Institutional Review Board

The Sponsor (or an authorized representative) or the Investigator (according to national provisions) is responsible for obtaining written approval for the clinical study protocol (including all substantial protocol amendments), the written subject informed consent form (including written assent, when applicable), informed consent updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects from an Independent Ethics Committee (IEC) / Institutional Review Board (IRB) that complies with the local regulatory requirements.

Written approval of the study must be obtained from the IEC/IRB prior to the study being implemented (i.e., shipment of clinical supplies to the Investigator or screening of subjects). Copies of the approval documentation will be maintained by both the Investigator and the Sponsor (or an authorized representative) in the designated study documentation files.

The Sponsor (or an authorized representative) or the Investigator (according to national provisions) will submit written reports of the clinical study status to the IEC/IRB annually, or more frequently if requested by the IEC/IRB. A final study notification should be forwarded to the IEC/IRB within 90 days after the study has completed, or in the event of premature termination of the study, within 15 days with the rationale for study termination clearly explained. Copies of all clinical study status reports (including termination) will be maintained by both the Investigator and the Sponsor (or an authorized representative) in the study documentation files.

In accordance with national provisions and the rules of the EU Clinical Trial Directive, the Sponsor (or an authorized representative) will inform all participating IECs/IRBs and national authorities of all SAEs/SADRs/SUSARs or other safety-related information, which occur during the clinical study.

## 1.2 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. The study will be conducted in compliance with GCP and the applicable national regulations to assure that the rights, safety, and wellbeing of the participating study subjects are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

## 1.3 Subject Information and Consent

Voluntary written informed consent will be obtained from one parent/legal representative of each subject prior to performing any study-related procedures. Each parent/legal representative will be given both verbal and written information describing the nature and duration of the clinical

study. The informed consent process will take place under conditions where the parent/legal representative has adequate time to consider the risks and benefits associated with the child's participation in the study. Subjects will not be screened or treated until the parent/legal representative has signed an approved informed consent written in a language that is understandable to the subject's parent/legal representative.

The IEC/IRB approved informed consent form will be signed and personally dated by the parent/legal representative and the person who conducted the informed consent discussion. Each parent/legal representative is to receive a copy of the signed and dated written informed consent form and any other written subject information.

The signature of an impartial witness is to be obtained in the event the subject or the subject's legally acceptable representative is unable to read. Additional signatures on the informed consent form may be required in accordance with IEC/IRB requirements or those of the Sponsor (or an authorized representative).

The Investigator is responsible for assuring the appropriate content of the informed consent form and that informed consent is obtained from each parent/legal representative in accordance with the applicable regulations and guidelines. The original signed informed consent is to be retained in the study documentation files.

The Investigator shall maintain a log of all parent(s)/legal representative(s) who sign the informed consent form and indicate if the subject received study drug or, if not, the reason why. The subject's medical records should also document that the informed consent form was signed and dated prior to any study-related procedures being performed.

# 2 INTRODUCTION

Racecadotril (acetorphan), an enkephalinase inhibitor, represents a promising approach to the treatment of diarrhea. Water and electrolyte transport in the intestinal mucosa is regulated by local messengers (neuropeptides, amines, and eicosanoids). Most of them act via the mediation of cyclic adenosine monophosphate (cAMP), activating or inhibiting its production from adenosine triphosphate. An increase in cAMP is induced by endogenous (e.g. VIP, PGE2) or exogenous agents (e.g. V. cholerae, E. coli toxins) and leads to net hypersecretion of water and electrolytes. Opiate neuropeptides are localized in the intestine myenteric and submucosal plexuses, where they modulate motility (mu receptors) and secretion (delta receptors). Activation of mu receptors prolongs intestinal transit while activation of delta receptors reduces intestinal secretion of water and electrolytes. Enkephalins activate delta receptors and inhibit adenylcyclase, thus facilitating a decrease in cAMP levels with a consequent reduction in water and electrolyte secretion. This anti-secretory action, however, is brief because enkephalins are rapidly degraded by the membrane peptidase enkephalinase (EC 3.4.24.11). Racecadotril is a prodrug that is rapidly hydrolysed in man into the active metabolite thiorphan, which is a powerful and selective enkephalinase inhibitor. Thus, the anti-secretory action of enkephalins is prolonged in the presence of thiorphan. Furthermore, unlike opiates and loperamide, Racecadotril does not act on mu receptors and therefore it does not prolong intestinal transit, nor does it favour bacterial growth in the small intestine. Racecadotril is devoid of any central or peripheral nervous side effect, at the opposite of opiates, such as respiratory depression or inhibition of intestinal transit.

Diarrhea is defined as the passage of unusually loose or watery stools, with a frequency of at least three times in a 24-hour period. The objective for treatment of acute diarrhea associated symptoms is to prevent and treat dehydration at first, to prevent nutritional damage and to reduce the duration and severity of diarrhea. Antidiarrheal drugs have been developed to prevent dehydration and to resolve diarrhea on top of with oral rehydration solution (ORS). Ideally antidiarrheal has a positive safety profile and have limited or no effects on motility and basal intestinal secretion.

[redacted]

# 3 STUDY OBJECTIVES

## 3.1 Primary Objective(s)

The primary objective is to evaluate the efficacy of Racecadotril in addition to standard treatment oral rehydration solution (ORS) in infants and children (3 months until 60 months) with acute diarrhea measured as duration of diarrhea (hours) between the start of treatment until final watery/diarrheal stool before recovery or end of study treatment (treatment duration maximal 5 days).

Duration of diarrhea is defined as date and time of the evacuation of the final watery/diarrheal stool before recovery derived from the daily diary.

## 3.2 Secondary Objective(s)

- Time until recovery, defined as date and time of the evacuation of the first of two consecutive normal stools or no stool within 12 hours after the first normal stool.
- Number of recovered subjects in total and until each individual treatment day.
- Global Physician Assessment (GPA) at the end of treatment (at the discretion of the investigator):
  - 1 = Complete relief of acute diarrhea,
  - 2 = marked improvement of acute diarrhea,
  - 3 = moderate improvement of acute diarrhea,
  - 4 = slight improvement of acute diarrhea,
  - 5 = no change in acute diarrhea,
  - 6 = worsening of acute diarrhea.

  (Treatment success = GPA score of 1 or 2).
- For toilet trained children only: number of stools per day as well as number of watery stools per day from start of treatment and until end of study treatment.

## 3.3 Safety Objective(s)

To evaluate the safety and tolerability of Racecadotril together with oral rehydration solution (ORS) in infants and children (3 months until 60 months) with acute diarrhea by adverse events, physical examination and vital signs.

# 4 STUDY DESIGN

## 4.1 Overall Study Design and Plan-Description

This is a prospective, open-label, multicenter, single-arm study evaluating the efficacy and safety of Racecadotril in infants and children with acute diarrhea in out-patients. The number of subjects to be screened is 50 in order to achieve 40 subjects treated with standard treatment (oral rehydration solution, ORS) plus Racecadotril.

1.5 mg/kg of Racecadotril will be administered, 3 times daily, via the oral route. Study drug intake will start either with the noon or evening dose on day 1.

In infants less than 9 kg: one 10 mg sachet 3 times daily.
In infants from 9 kg to <13 kg: two 10 mg sachets 3 times daily.
In children from 13 kg to 27 kg: one 30 mg sachet 3 times daily.
In children of more than 27 kg: two 30 mg sachets 3 times daily.

Standard treatment is oral rehydration solution (ORS) according to the registered local label and the instruction of the investigator. At the start of the trial, alignment will be reached on the understanding of treatment of standard ORS with the principal investigator with the aim to use the same brand of ORS for the subjects throughout the trial. ORS treatment will be documented in the CRF.

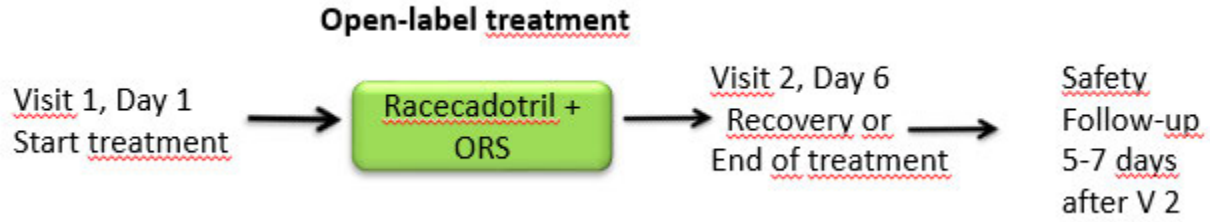
**Screening and Enrolment (Day 1, Visit 1)**
Subjects presenting with acute diarrhea will be evaluated for eligibility. They will undergo a physical examination including vital signs, a review of their medical history including vaccination history and concomitant medication. If the subjects are eligible, demographics, number of stools during the last 12 hours will be assessed as baseline values. On Day 1, the subject will start with study treatment. The starting dose will either be the noon, or evening dose depending on the timing of Visit 1.

**Treatment period (until recovery, maximally 5 days)**
Subjects will be treated with Racecadotril three times daily according to the body weight dose requirement on an out-patient basis for maximum 5 days. The subjects will be treated with ORS (according to the registered local label and the instruction of the investigator) in addition to Racecadotril. ORS will be prescribed by the investigator and will be taken according to the product label and the instruction of the investigator. The parent(s)/caregiver(s)/legal representative(s) will be instructed to stop study drug treatment when the patient recovered. On each day, the parent(s)/caregiver(s)/legal representative(s) will fill in their diaries, documenting the date and time of each individual stool, the stool consistency of each stool (diarrheal/watery or normal), the amount of ORS, and the study drug intake. After the occurrence of two consecutive normal stools or no stool within 12 hours, the parent(s)/caregiver(s)/legal representative(s) can stop recording of the diary and return to the study site for the end of treatment visit. The date of recovery is the day when the first of two consecutive normal stools were excreted or the day

when no stool within 12 hours after the first normal stool was observed. AEs are to be reported on an ongoing basis.

**End of treatment (Day 6 or early recovery, Visit 2)**
The last dose of study drug will be the morning dose of day 6, if not recovered earlier (last dose will be the morning dose after recovery, ORS can be continued until Visit 2). On the same day, or within 24 hours after recovery (in exceptional cases within 48 hours), the parent(s)/caregiver(s)/legal representative(s) will visit the site for the end of treatment visit of the child. Data on vital signs, AEs, physical examination and concomitant medication will be collected. Subjects will return their diaries and unused medication.

**Safety follow-up**
A phone call will be performed 5-7 days after the end of the treatment period for the safety follow-up.




## 4.2 Discussion of Study Design, Including the Choice of Control Groups

[redacted]

# 5 SELECTION OF STUDY POPULATION

## 5.1 Inclusion Criteria

(1) Signed informed consent from one of the parent(s)/legal representative(s).
(2) Subjects, both genders, aged 3 to 60 months.
(3) Subjects with acute diarrhea (defined as the passage of three or more unformed or liquid stools within the last 24 hours and lasting for less than 3 days).

## 5.2 Exclusion Criteria

(1) Known allergy to Racecadotril or any of its ingredients.
(2) Subjects suffering from renal or hepatic impairment.
(3) Subjects with fever > 39 degrees Celsius
(4) Subjects with bloody and/or purulent stools.
(5) Subjects suffering from antibiotic (e.g. amoxicillin)-associated diarrhea, chronic diarrhea or iatrogenic diarrhea.
(6) Subjects with alternating bouts of diarrhea and constipation.
(7) Diarrhea due to exacerbation of chronic gastrointestinal diseases such as irritable bowel syndrome, irritable bowel disease or pancreatic exocrine insufficiency.
(8) Cystic fibrosis or coeliac disease.
(9) Subjects suffering from prolonged or uncontrolled vomiting.
(10) Subjects with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption syndrome or sucrase isomaltase insufficiency.
(11) Subjects having received antibiotic treatment within 2 weeks prior to start of the current diarrhea episode.
(12) Subjects having received antidiarrheal drugs (except pre- or probiotics see section 7.7.) 48 hours prior to Day 1.
(13) Subjects with severe dehydration requiring intravenous fluid or electrolyte replacement or hospitalization treatment.
(14) Subject with a history of angioedema or who had reported angioedema with angiotensin converting enzyme inhibitors (such as captopril, enalapril, lisinopril, perindopril, ramipril)
(15) Subjects with combined diseases or medical situations that would prevent to be enrolled into the study, depending on the judgment of the investigator
(16) Intake of experimental drug within 30 days prior to study start.
(17) Subjects with contraindications to ORS or susceptible to the warnings of ORS.

# 6 REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified, and without penalty or loss of benefits to which the subject is otherwise entitled.

The Study Termination form must be completed for all subjects who did not fail screening, those who completed and those who prematurely terminated the study and an end of treatment visit should be performed.

In case of premature termination of the subject from the study, the primary reason for this premature termination is to be indicated according to the following definitions:

- Adverse event: discontinuation due to any adverse event (AE) with a corresponding entry reflected on the Adverse Events form in the CRF
- Lack of efficacy: subject fails to respond to the study drug at an acceptable level where the subject or the Investigator feels it is in the best interests of the subject to seek another treatment.
- Lost to follow-up: the subject's parent(s)/caregiver(s)/legal representative(s) fails to return to the study site for scheduled visits and does not respond to telephone or written attempts to contact.
- Withdrew consent: subject's parent(s)/legal representative(s) decides to stop subject's participation in the study for any reason other than an AE, or is unable to complete the study as described in the clinical study protocol (e.g., subject is relocating to another location).
- Administrative: the Sponsor decides to discontinue the study (either at the study site or the entire study), e.g., general safety problems leading the Sponsor to entirely stop the study.
- Protocol violation – anything which is in direct violation of the clinical study protocol (e.g., inclusion/exclusion violation).

Subjects will terminate the study at the discretion of the investigator and will undergo further diagnosis and alternative treatment under the following conditions.

***1.*** If the subject needs alternative treatments or rescue medication which are prohibited concomitant therapies in this study
   Any comedication which may interfere with the evaluation of the efficacy parameters of this study should be avoided (see section 7.7).
   Subjects who cannot complete the study duration of five days without continuous intake of concomitant medication or who need rescue medication should be withdrawn. The investigator should consult with the CRO/sponsor prior to withdrawal of the subject.
2. If the subject develops fever > 39 degrees Celsius (> 39 degrees Celsius in two repeated measurements within one hour)
3. If the subject develops bloody and purulent stools
4. If the subject has watery stool more than 10 times per day showing signs of apathy

5. If the subject's disease state worsens, e.g. dehydration or increased vomiting
6. If the subject needs hospitalization

# 7 TREATMENTS

Study drug (Racecadotril) will only be shipped to Investigators who have provided the Sponsor (or an authorized representative) with all required study documents, including IEC/IRB approval, and have signed a final study agreement.

## 7.1 Treatments to Be Administered

Racecadotril Infants Granules for Oral Suspension 10 mg
Racecadotril Children Granules for Oral Suspension 30 mg

1.5 mg/kg of Racecadotril will be administered, 3 times daily (morning, noon, evening), via the oral route.

In infants less than 9 kg: one 10 mg sachet 3 times daily.
In infants from 9 kg to <13 kg: two 10 mg sachets 3 times daily.
In children from 13 kg to 27 kg: one 30 mg sachet 3 times daily.
In children of more than 27 kg: two 30 mg sachets 3 times daily.

Standard treatment for pediatric subjects with diarrhea is oral rehydration solution (ORS). ORS will be given according to the registered local label of the brand and the instruction of the investigator. At the start of the trial, alignment will be reached on the understanding of treatment of standard ORS with the principal investigator with the aim to use the same brand of ORS and the same age-appropriate standardized treatment pattern for the subjects throughout the trial. ORS treatment will be documented in the CRF. Reporting obligations for ORS by the investigator will follow local regulations for marketed products. Racecadotril will be given in addition to ORS.

## 7.2 Packaging and Labeling

[redacted]

## 7.3 Storage and Dispensing of Study Drug

All clinical drug supplies are to be stored in a secure, monitored, limited-access area in accordance with labeled storage conditions. The Investigator will maintain accurate records of the disposition of all clinical drug supplies received during the study. These records shall include the amounts of drug supplies and the dates on which drug supplies were received from the Sponsor (or an authorized representative), dispensed to the subject, returned by the subject and returned to the Sponsor (or an authorized representative). If errors or damages in the clinical drug supply shipments occur, the Investigator must contact the Sponsor (or an authorized representative) immediately.

## 7.4 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned a 5-digit enrollment number . The medication will be identified using 6-digit kit numbers.

The subject numbers will be provided by Clinical Supply Management (Product Development) of Abbott Healthcare Products BV.

## 7.5 Selection of Doses and Timing in the Study

1.5 mg/kg of Racecadotril will be administered, 3 times daily (morning, noon and evening), via the oral route.

In infants less than 9 kg: one 10 mg sachet 3 times daily.
In infants from 9 kg to <13 kg: two 10 mg sachets 3 times daily.
In children from 13 kg to 27 kg: one 30 mg sachet 3 times daily.
In children of more than 27 kg: two 30 mg sachets 3 times daily.

This dosing regimen is registered by TFDA and described in the SmPC.

Standard treatment for pediatric patients with diarrhea is oral rehydration solution (ORS). ORS will be given according to the registered local label of the brand and the instruction of the investigator. It is recommended that all subjects will be prescribed the same brand of ORS. Racecadotril will be given in addition to ORS.

## 7.6 Blinding and Treatment Code Information

This is an open-label study; blinding will not be applied.

## 7.7 Prior and Concomitant Therapy

During the study, subjects are not allowed to be treated with the following treatments:

- Anti-peristaltic drugs, e.g. loperamide
- Antibiotics
- Antipyretics (suppositories)
  Oral antipyretics (acetaminophen or ibuprofen) are allowed to be used concomitantly as needed when ear temperature is above 38.3 degrees Celsius, but not longer than two consecutive days during the study. If the fever increases above 39 degrees Celsius with two repeated measurements within one hours, the subject will be withdrawn.
- Intestinal antiseptics, e.g. 8-hydroxyquinoline
- Respiratory decongestants, e.g. phenylephrine
- Antitussive medication, e.g. noscapine
  Any antitussive drugs, if indicated for pediatric patients, may be given for temporary relief of symptoms as PRN (administration on as needed basis) except those containing opium alkaloids and derivatives (e.g noscapine).
- Pre- or Probiotics, e.g. fructooligosaccharides, lactobacilli
  Subjects on continuous probiotic treatment at study start (e.g. Lactobacillus, Bifidobacterium, yeast) or probiotic-containing supplements/formula of the same product/brand prior to study start can be included. The initiation of pre- or probiotic treatment during the study is forbidden as well as the adaptation of the brand/product or dose.
- Absorbents, e. g. diosmectite, charcoal, pectin, psyllium
- Zinc-containing medication (**other than diaper rash ointments). Diaper rash ointments of any kind are allowed.**
- Homemade ORS
  ORS will be provided during the study as judged appropriate by the Investigator. Additional intake of self-purchase or self-made ORS is not allowed during the study duration
- ACE Inhibitors
- Antispasmodics
  Antispasmodics, indicated for pediatric patients, may be given for temporary relief of symptoms as PRN (administration on an as needed basis) in exceptional cases. If antispasmodics are needed as daily treatment during the study treatment, the subjects should be discontinued.
- Drugs for symptomatic treatment of diarrhea, e.g. pancreatic enzymes, anticholinergic drugs, opiates, diphenoxylate
- Intravenous fluid or electrolyte replacement.

The presence of bloody or purulent stool and fever above 39 degrees Celsius may indicate either the presence of invasive bacteria as a reason for diarrhea or the presence of another severe disease. In addition, Racecadotril has not been investigated in patients with antibiotic-associated diarrhea. Therefore, Racecadotril should not be administered under these conditions.

Subjects who need treatment with the above listed medication should be withdrawn from the study (see section 6).

Dietary modifications for thickening of the stools or yogurt are allowed. If needed, dietary consultation with dietitian or qualified healthcare worker is recommended in order to adapt the diet for thickening of stools or intake of yogurt.

Any intake of other medication is allowed as judged appropriate by the Investigator except those on the list of prohibited medications above.

All medication taken by the subject during the study (from signing the informed consent form through post-study follow-up) is to be recorded on the Concomitant Medication form, except for study drug.

## 7.8 Treatment Compliance

Drug Accountability

The Investigator is accountable for all clinical drug supplies shipped to his/her study site for the duration of the study. A final accounting of the clinical drug supplies will be required at the completion/termination of the study. The Investigator is required to provide written explanation for any discrepancies.

All used and unused clinical drug supplies will be inventoried and returned to the Sponsor (or an authorized representative) by a designated monitor.

Compliance

Each intake of study drug (Racecadotril) will be recorded in a patient diary and evaluated.

# 8 STUDY ASSESSMENTS AND FLOW CHART

## 8.1 Efficacy Measurements

Primary Efficacy Variable:
Duration of diarrhea (hours) between the start of treatment until the last watery/diarrheal stool before recovery or the end of study treatment (treatment duration maximal 5 days). Treatment will stop at recovery or after the morning dose of day 6, if not recovered.

Duration of diarrhea is defined as date and time of the evacuation of the final watery/diarrheal stool before recovery derived from the daily diary.

Secondary Efficacy Variables:

- Time until recovery, defined as date and time of the evacuation of the first of two consecutive normal stools or no stool within 12 hours after the first normal stool.

- Number of recovered subjects in total and until each individual treatment day.
- Global Physician Assessment (GPA) at the end of treatment, at the discretion of the investigator:
    - 1 = Complete relief of acute diarrhea,
    - 2 = marked improvement of acute diarrhea,
    - 3 = moderate improvement of acute diarrhea,
    - 4 = slight improvement of acute diarrhea,
    - 5 = no change in acute diarrhea,
    - 6 = worsening of acute diarrhea.

  (Treatment success = GPA score of 1 or 2).

- For toilet trained children only: number of stools per day as well as number of watery stools per day from start of treatment and until end of study treatment.

## 8.2 Safety Measurements

Adverse Events

Requirements for collecting, recording and reporting of AEs are described in Section 9. Each subject is to be evaluated at the termination visit. Should any AE be identified at this visit, the Investigator will continue to follow the subject as described in Section 9.1.2.

Vital Signs

Height and weight must be recorded.

Body temperature will be measured in the morning and in the evening with at least 12 hours interval. If the value is >39 degrees Celsius, the measurement has to be repeated within one hour to confirm the value.

Systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate are to be measured in pediatric appropriate setting.

Physical Examination

A physical examination should be performed and any relevant findings are to be recorded on the Medical History form in the CRF (for findings from the past that occurred prior to allocation to treatment), or on the Adverse Event form in the CRF for findings presently occurring.

## 8.3 Other Assessments

Informed Consent

Voluntary written informed consent must be obtained from one parent/legal representative prior to performing any study-related procedures (see Section 1.3).

Demographic Data

Demographic data (gender, age, year and month of birth, race) will be collected for all subjects.

Medical History

Any clinical event, including diagnosis, condition, or surgery, that occurred prior to allocation to treatment, is to be recorded on the Medical History form. In case a clinical event concerns a chronic disorder, which means it started in the past and it is still present at the screening visit, it should also be recorded on the Medical History Form. Examples of these events are diabetes, migraine, and hay fever.

Concomitant Medication

All medication taken by the subject during the study (from signing the informed consent form through post-study follow-up) is to be recorded on the Concomitant Medication form, except for study drug.

Subject Diary

The parent(s)/caregiver(s)/legal representative(s) have to document date and time of each individual stool of the subject and the stool consistency (watery, normal) of each evacuation continuously. The subject individual stool consistency before start of the diarrhea is defined as normal (e.g. taking into account the age and diet, e.g. breast feeding, of the individual subject).

Recording can be stopped after the excretion of two consecutive normal stools or no stool within 12 hours.

The date, time and dose of study drug intake as well as the amount ORS consumed has to be recorded.

Fever will be measured twice daily, once in the morning and once in the evening with at least 12-hour interval using the same device and method (preferably ear temperature), by the parent(s)/caregiver(s)/legal representative(s) and documented in the diary including method, time and value.

## 8.4 Appropriateness of Measurements

All measurements will be performed using standard methods which are generally recognized as being reliable, accurate, and relevant.

## 8.5 Primary Efficacy/ Variable(s)

The duration of diarrhea is an appropriate primary efficacy variable. Duration of diarrhea is defined as date and time of the evacuation of the final watery/diarrheal stool before recovery derived from the daily diary.

## 8.6 Flow Chart of Study Assessments

All study assessments will be conducted as indicated in Table 2, which displays the frequency and timing of all measurements.

**Table 2: Flow Chart of Study Assessments**

| Period | Screening | End of Treatment period | Safety follow-up (phone call 7 days after Visit 2) |
|---|---|---|---|
| **Visit** | **1** | **2** | **3** |
| **Day** | **1** | **6[2]** | **11-13** |
| Informed consent | X | | |
| Inclusion/exclusion criteria | X | | |
| | | | |
| Demographic data | X | | |
| Medical history including vaccination history | X | | |
| Physical examination | X | X | |
| Vitals signs | X | X | |
| Dispense study drug | X | | |
| Concomitant medication | X | X | X |
| Compliance check | | X | |
| Global physician assessment | | X | |
| Adverse events | X | X | X |
| Collect study drug | | X | |
| Dispense diary | X[1] | | |
| Collect diary | | X | |

[1] Subjects' parent(s)/caregiver(s)/legal representative(s) have to fill in their daily diaries continuously.
[2] or within 24 hours (in exceptional justified cases within 48 hours) after recovery if this occurs before day 6

# 9 ADVERSE EVENTS

[redacted]

## 9.1 Adverse Events

Definition of Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom (including an AE occurring from drug abuse, an AE occurring from drug withdrawal and any failure of expected pharmacological action), or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

### 9.1.1 Recording of Adverse Events

Any AE should be recorded on the Adverse Events form in the CRF and source documents. In order to avoid vague, ambiguous or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words. Whenever possible, the Investigator should group together into a single term signs and symptoms which constitute a single diagnosis.

The existence of or change in an AE may be concluded due to the necessity to administer a concomitant medication, from a spontaneous report of the subject, from the physical examination or from special tests like ECG, EEGs, laboratory assessments or other study specified tests (source of AE).

For each subject that has signed the informed consent and prior to study drug allocation at any dose, any change to medical status should be recorded in patient's medical file in accordance to local requirements and the medical history CRF only.

Any change to medical status, which occurs after study drug allocation at any dose in the specified study AE collection period will be handled as an (S)AE.

For each subject that has signed the informed consent but does not qualify for allocation to treatment, i.e. Screen Failure, any change to medical status (from the time of ICF signature until determination of non-qualification for the study) should be recorded in patient's medical file according to local requirements. The related medical status change information will not be reviewed by Abbott or delegated staff, and will not qualify as a study (S)AE.

Each AE, of the treatment arm, is to be evaluated for duration, severity, seriousness and causal relationship to the investigational drug. The action taken with study drug, the concomitant treatment/therapy introduced and the outcome as well as whether the event led to study termination will also be recorded.

The post-study AE collection period is defined as 30 days after the subject's safety follow-up call (collection of (S)AEs should be passive in this period unless otherwise specified).

Severity

The severity of the AE should be characterized as "mild, moderate or severe" according to the following definitions:

- Mild events are usually transient and do not interfere with the subject's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities.
- Severe events interrupt the subject's usual daily activity.

Drug-Event Relationship

The causal relationship between the study drug and the AE should be characterized according to the following:

- Unrelated – there is not a reasonable possibility that the study drug caused the AE.
- Unlikely – suggests that only a remote connection exists between the study drug and the event. Other conditions, including concurrent illness, progression or expression of the disease state or reaction to concomitant medication, appear to explain the AE.
- Possible – suggests that the association of the AE with the study drug is unknown, however the event is not reasonably supported by other conditions.
- Probable – suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of the disease state, or concomitant medication reactions) do not appear to explain the AE.
- Certain – suggests that an AE, including laboratory test abnormality, occurs in a plausible time relationship to drug administration, which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge)

should be clinically plausible. The AE must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.

Outcome

The outcome of the adverse event should be classified according to the following definitions:

- Recovered / resolved: the event has resolved (no further symptoms are present and no treatment is being received by the subject).
- Recovered / resolved with sequelae: the event has resolved but there may be lingering effects present (e.g., a scar following a cut or abrasion).
- Fatal: the subject died as a result of the event. This code should only be used for the event that caused the death, not any event that was present at the time of the subject's death. Fatal events require immediately reporting to the Sponsor (or an authorized representative).
- Unknown: may only be used in the event that the subject is lost to follow-up and no reliable data can be obtained.

All efforts should be made to classify the AE according to the above categories.

Note: when the AE is ongoing, the outcome will remain blank on the Adverse Events form in the CRF.

### 9.1.2 Follow-up of Adverse Events

All AEs occurring during the study are to be followed up in accordance with good medical practice until resolved or judged no longer clinically significant, or if a chronic condition, until fully characterized. All follow-up results are to be reported to the Sponsor (or an authorized representative).

## 9.2 Serious Adverse Events (SAEs)

Definitions of Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or prolongation of an existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,

- is any suspected transmission via a medicinal product of an infectious agent,
- is considered an important medical event (an event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasia, or convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse as well as spontaneous or elective abortions, stillbirths and ectopic pregnancies).

### 9.2.1 Reporting Serious Adverse Events

[redacted]

## 9.3 Pregnancy

Not applicable due to the age of the subjects.

# 10 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Data handling will be the responsibility of the CRO. The data will be inspected for inconsistencies by performing validation checks. Any inconsistencies found will be resolved by the monitor after contacting the Investigator. When the data in the database are considered clean and the subjects allocated to subject samples in a blind data review, the database will be locked to prevent unauthorized access. Next, the database will be made available as SAS® files for statistical analysis.

All details regarding the statistical analysis and the preparation of tables, listings and figures will be described in the Statistical Analysis Plan prepared by the CRO and approved by Abbott before database lock.

The statistical analysis will be performed by the CRO.

## 10.1 General Definitions and Conventions

Time-Related Definitions

All assessment dates will be related to the first day of study drug administration. This first day of drug administration is referred to as Day 1. Day –1 is the day that is preceding Day 1 and a Day 0 will not be defined.

The baseline period will be defined as the period from informed consent to the first study drug administration. The baseline value for a variable is defined as the last non-missing value collected before the first study drug administration.

The endpoint value for efficacy variables is defined as the last non-missing value assigned to treatment for the subject.

All variables planned to be measured at one or more time points and supposed to be time-related will be windowed.

Coding Systems

AEs and medical history terms will be assigned to a lowest level term (LLT) and a preferred term (PT) and will be classified by high level term (HLT), high level group term (HLGT) and primary system organ class (SOC) according to the MedDRA thesaurus.

Concomitant medications will be classified according to active drug substance using the WHO drug dictionary. The generic name, the preferred name and the WHO name will be assigned.

In addition, the Anatomical Therapeutic Chemical (ATC) classes will be assigned to the drug ID. ATC codes are defined to the 4th level. For each medication, the primary ATC class will be assigned manually based on the generic name and the reason for use.

Default Summary Statistics

The default summary statistics for quantitative and ordinal variables will be the number of observations (n), mean, standard deviation (SD), median, minimum (Min) and maximum (Max) for subjects with data. Any other summary statistics will be described on an individual basis.

Default Frequency Tabulations

For qualitative variables, per category the numbers and frequencies of subjects with non-missing data (n, %) will be the default summary presentation, and if appropriate and present, the number of missing values.

For AEs, medical history and concomitant medications, however, the denominator for the percentage calculation will be the number of subjects at risk ~~for the particular treatment arm~~. A subject will be considered at risk if the subject is in the safety sample and entered the respective study period.

Subject Listings

Individual subject listings will be produced for all raw data and a selection of the derived data.

## 10.2 Subject Samples

The main subject samples of interest are defined as follows.

The all subjects consented sample will consist of all subjects who:

- Gave their informed consent.

The all subjects <allocated to treatment> sample will consist of all subjects who:

- Were in the all subjects consented sample; and
- Were <allocated to treatment>.

The safety sample will consist of all subjects who:

- Were in the all subjects allocated to treatment sample; and
- Had at least one dose of study medication administered.

The full analysis (FA) sample will consist of all subjects who:

- Were included in the safety sample; and
- Had data for at least one post-baseline assessment of any efficacy measurement.

The per-protocol (PP) sample will be defined through blind data review and will consist of all subjects who:

- Were included in the FA sample; and
- Did not present any major protocol violation.

## 10.3 Efficacy

The primary efficacy variable is the duration (hours) of diarrhea (treatment duration max 5 days). Duration of diarrhea is defined as date of the evacuation of the last watery/diarrheal stool before recovery or end of treatment.

The primary parameter, duration of diarrhea, will be analyzed using descriptive statistics. In addition, a Kaplan-Meier plot will be generated for which summary statistics will be presented as well.

The secondary efficacy variables are

- Time until recovery, defined as date and time of the evacuation of the first of two consecutive normal stools or no stool within 12 hours after the first normal stool.
- Number of subjects recovered~~,~~ in total and until each individual treatment day
- Mean and median time until recovery
- Assessment of treatment success by the physician:
  The assessment of treatment success by the physician will be done using the Global Physician Assessment.
  GPA score:
  1 = Complete relief of acute diarrhea,
  2 = marked improvement of acute diarrhea,
  3 = moderate improvement of acute diarrhea,
  4 = slight improvement of acute diarrhea,
  5 = no change in acute diarrhea,
  6 = worsening of acute diarrhea.
  Treatment will be rated as success when the GPA score equals 1 or 2.

- Number of stools at baseline and per treatment day for toilet-trained subjects, only.
- Number of watery stools per day for toilet-trained subjects, only.

Secondary efficacy parameters will be analyzed similarly to the primary analysis. All parameters will also be summarized using descriptive statistics.

## 10.4 Safety

The safety sample will be used for the analysis of the safety and tolerability data.

AEs are considered treatment emergent (TE) if they start or worsen at or after the first administration of study drug and before or on the day of last administration of study drug plus a gap period of 1 day.

AEs will be reported on a per-subject basis, i.e. counting subjects rather than events. This means that if a subject suffers the same AEs repeatedly during the applicable study period, the event will be counted only once for that period. Repeated events per subject will be summarized according to the following rule: if a subject suffered the same AE more than once, the event will be assigned the worst severity, the closest relationship to the study drug and the earliest starting date. Only treatment emergent AEs will be reported. In the listings, however, all occurrences of the AEs will be presented.

Treatment emergent AEs will be summarized per primary SOC, per HLT by primary SOC and per PT by HLT and primary SOC. Severity and drug-event relationship of treatment emergent AEs are summarized separately. Non-TEAEs will be listed.

Vitals signs, including changes from baseline will be summarized. A frequency table will be presented for markedly abnormal values.

## 10.5 Other Assessments

The assignment of subjects to subject samples, the disposition of subjects with respect to premature termination, reason for premature termination, drug exposure and treatment compliance will be summarized for the treatment group.

Demographics and other baseline characteristics will be summarized for the treatment group.

Medical history, including coding data will be summarized per primary SOC, per HLT by primary SOC and per PT by HLT and primary SOC.

Major protocol deviations will be listed.

Concomitant medication, including coding data will be summarized per assigned treatment period for incidence per subject, for primary therapeutic subgroup (the 3rd level ATC code) and for generic name by therapeutic subgroup.

### 10.6 Subgroup Analysis

Key efficacy and safety results will be summarized across subgroups defined by age group (< 24 months old and ≥ 24 months old).

### 10.7 Interim Analysis

Not applicable

### 10.8 Determination of Sample Size

In total, 40 subjects will be allocated to receive Racecadotril treatment, ~~**20 subjects in each age group (< 24 months of age and ≥ 24 months of age)**~~. Results of a recently finalized study in Russian children showed that all children under Racecadotril treatment recovered within 3 days of drug treatment. A sample size of 40 subjects is sufficient to estimate a two-sided 95% confidence interval with the precision of 3.1 percentage points for a recovery of at least 99% of the subjects after 3 days of Racecadotril treatment. In order to account for drop-outs maximum 48 subjects will be recruited**. Recruitment will be stopped once 40 subjects have completed the study.**

# 11 INVESTIGATOR OBLIGATIONS

The Investigator agrees to conduct the clinical study in compliance with this protocol which was approved by the IEC/IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

## 11.1 Essential Study Documents

The Investigator is responsible for providing and maintaining essential study documents. Essential study documents are those documents that individually and collectively permit the evaluation of the conduct of the study and the quality of the data produced. These documents serve to demonstrate the compliance of the Investigator and the Sponsor (or an authorized representative) with the standards of GCPs and with all applicable national regulatory requirements.

Essential study documents will include regulatory documents as well as source documents which are original documents, data and records of clinical findings, observations and other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source documents will include hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratories and at medical/technical departments involved in the clinical study.

The Investigator agrees to allow direct access to all essential clinical study documents for the purpose of monitoring and/or auditing by the Sponsor (or an authorized representative) and inspection by the appropriate national and foreign regulatory authorities.

## 11.2 Case Report Form (CRF) Completion

Data reflecting the subject's participation with the study drug under investigation will be reported to the Sponsor (or an authorized representative). The data will be recorded on the designated (e)CRFs provided or approved by the Sponsor.

The (e)CRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, patient files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a

completed (e)CRF for each subject who did not fail screening. All supportive documentation submitted with the (e)CRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

All data must be entered in English. The (e)CRFs should always reflect the latest observations on the subjects participating in the trial. Therefore, the (e)CRFs are to be completed as soon as possible after the subject's eligibility has been confirmed and thereafter during or after the subject's visit. To avoid inter observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the (e)CRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the (e)CRF. The Investigator will be required to (electronically) sign off on the clinical data.

The monitor will review the (e)CRFs and evaluate them for completeness and consistency. The (e)CRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee. The monitor is not allowed to enter data in the (e)CRFs.

If additional corrections are needed, the responsible monitor or Data Manager will raise a query. The appropriate investigational staff will answer queries sent to the Investigator.

In case screen failure data is entered in the (e)CRF, these data should be clearly indicated in the raw datasets and removed from the analysis datasets.

## 11.3 Essential Records Retention

The Investigator should maintain the essential clinical study documents (including CRFs, source documents, clinical drug disposition records, signed subject informed consent forms, AE reports and other regulatory documents) as required by the applicable national regulatory requirements. The Investigator is to take adequate measures to prevent accidental or premature destruction of these documents. In the event of accidental destruction, the Investigator should notify the Sponsor (or an authorized representative) immediately.

Essential clinical study documents will be retained at least two (2) years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region OR at least two (2) years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents shall be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor (or an authorized representative).

The Investigator is required to notify the Sponsor (or an authorized representative) prior to changing the location or status of any essential clinical study documents. The Sponsor (or an authorized representative) will be responsible for informing the Investigator as to when these documents no longer need to be retained.

## 11.4 Investigator Agreement

The Investigator is responsible for assuring the proper implementation and conduct of the clinical study including those study-related duties delegated to other appropriately qualified individuals. The Investigator and his/her staff will cooperate with the Sponsor (or an authorized representative) during monitoring and auditing visits to assist with the review of the study data and resolve any discrepancies.

The Investigator will demonstrate due diligence in recruitment and screening of potential study subjects. The enrollment rate should be sufficient to complete the study as agreed with the Sponsor (or an authorized representative). The Sponsor (or an authorized representative) is to be notified of any projected delays, which may impact the completion of the study.

The Sponsor retains the right to terminate the clinical study at any time for any reason. In such an event, instructions on the requirements for the discontinuation of subjects will be provided by the Sponsor (or an authorized representative).

# 12 SPONSOR OBLIGATIONS

## 12.1 Protocol Amendments

Only the Sponsor (or an authorized representative) will make modifications to the clinical study protocol, which will be documented in a written amendment that describes all changes that will be implemented. Protocol amendments will be categorized as either substantial or non-substantial.

Protocol amendments will be considered substantial when the changes have significant impact on:

- The safety of physical or mental integrity of the subjects
- The scientific value of the study
- The conduct or management of the study
- The quality or safety of any investigational medicinal product or control used in the study

Protocol amendments will be considered non-substantial when the changes affect only administrative issues with the conduct of the study, i.e., changes in telephone numbers or addresses.

The Sponsor (or an authorized representative) will be responsible for notifying the appropriate national regulatory authorities in writing of any amendments to the protocol prior to the changes being implemented except in those cases where the changes are necessary to eliminate an immediate hazard to the clinical study subjects.

Substantial amendments will require written approval by the IEC/IRB prior to being implemented by the Investigator at the study site except under those circumstances described previously. Non-substantial amendments will not require approval by the IEC/IRB unless requested by the IEC/IRB.

## 12.2 Study Monitoring

The study will be monitored by authorized representatives of the Sponsor throughout its duration by means of personal visits to the Investigator's facilities and through other communications (e.g., telephone calls, written correspondence). Monitoring visits will be scheduled at mutually agreeable times periodically throughout the study and at frequency deemed appropriate for the study.

These visits will be conducted to evaluate the progress of the study, ensure the rights and well-being of the subjects are protected, check that the reported clinical study data are accurate, complete and verifiable from source documents, and the conduct of the study is in compliance with the approved protocol and amendments, GCPs and applicable national regulatory requirements. A monitoring visit will include a review of the essential clinical study documents

(regulatory documents, CRFs, source documents, drug disposition records, subject informed consent forms, etc.) as well as discussion on the conduct of the study with the Investigator and staff. The Investigator and staff should be available during these visits to facilitate the review of the clinical study records and resolve/document any discrepancies found during the visit.

## 12.3 Quality Assurance Audits

The Sponsor's (or an authorized representative's) Quality Assurance department may conduct on-site audits of all aspects of the clinical study either during the study or after the study has been completed.

The clinical study may also be subject to inspection by regulatory authorities (national or foreign) as well as the IECs/IRBs to ascertain that the study is being or has been conducted in accordance with protocol requirements, GCPs, as well as the applicable regulatory requirements.

# 13 PUBLICATION POLICY

The data generated by this study are confidential information of the Sponsor. The Sponsor will publicly disclose the results of all applicable clinical trials following legal and regulatory requirements. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

# 14 INSURANCE

The Sponsor has taken out a liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines whichever is applicable.

# 15 REFERENCES