CLINICAL STUDY PROTOCOL

Cover Page

Protocol No.:	RACE3003	**Protocol Date:**	30 May 2017
Study Title:	**Multicenter, open-label, controlled, randomized clinical study to evaluate the efficacy and safety of Racecadotril in infants, children and adolescents with acute diarrhea**		
IND No.:	NA		
EudractCT No:	NA		
Phase of Development:	III		
Sponsor:	Abbott Laboratories GmbH		
Global Clinical Director	[redacted]		
Protocol Author (s)			

SYNOPSIS

Name of Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient(s):**
Abbott Laboratories GmbH	Hidrasec Infants: Granules for Oral Suspension 10 mg Hidrasec Children: Granules for Oral Suspension 30 mg Hidrasec: 100 mg capsules	Racecadotril

Title of Study:
Multicenter, open-label, controlled, randomized clinical study to evaluate the efficacy and safety of Racecadotril in infants, children and adolescents with acute diarrhea

Study Center(s) (Planned):
[redacted]

Study Duration:	Phase of Development:
End of Study is defined as Data Base Lock.	III

Objectives:

Primary objective:

The primary objective is to evaluate the efficacy of Racecadotril in addition to standard treatment oral rehydration solution (ORS) versus ORS alone in infants, children and adolescents with acute diarrhea (3 months until < 18 years) measured as duration of diarrhea (hours) between the start of treatment until final diarrheal/watery stool before recovery or end of study treatment (treatment duration maximal 5 days).
Duration of diarrhea is defined by date and time of the evacuation of the final watery/diarrheal stool before recovery derived from the daily diary.

Secondary objective(s):

- Time until recovery: recovery is defined by date and time of the evacuation of the first of two consecutive normal stools or no stool within 12 hours.

- Number of recovered subjects per treatment group cumulatively and until each individual treatment day. Mean and median time until recovery per treatment group.

- Global Physician Assessment at the end of treatment:
  - 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).

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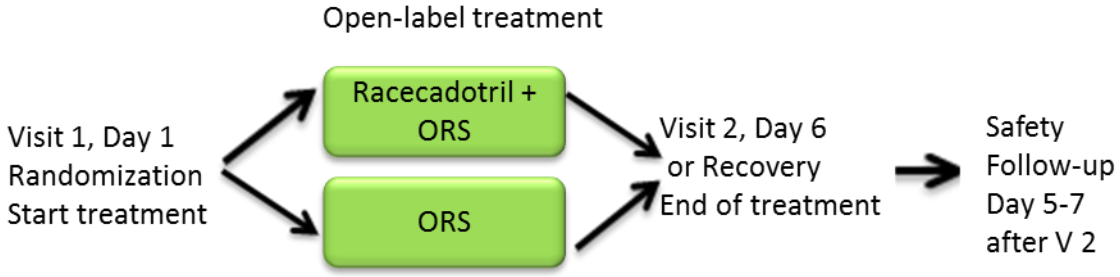
- For toilet trained children and adolescents: number of stools per day as well as number of watery stools per day from start of treatment and until end of study treatment.

Safety objective(s):
To evaluate the safety and tolerability of Racecadotril in addition to ORS versus ORS alone in infants, children and adolescents with acute diarrhea by adverse events, physical examination and vital signs.

Methodology:
This is a controlled, randomized, open-label, parallel-group study evaluating the efficacy and safety of Racecadotril in infants, children and adolescents 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 and concomitant medication. If the subjects are eligible, demographics, number of stools during the last 24 hours will be assessed as baseline values. The subjects will be randomized to Racecadotril plus ORS or ORS alone. On Day 1 the subject will start with study treatment. The starting dose will either be the noon or the 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 or in-patient basis for maximum 5 days in addition to ORS or with

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ORS alone. ORS will be prescribed by the investigator. The parent/caregivers will be instructed to stop treatment when the patient recovered. Recovery is defined by the evacuation of the first of two consecutive normal stools. In the evening of each day, the parent(s)/caregiver(s) will fill in the 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 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) 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) will return the diaries and unused medication.

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

Table 1. Flow Chart of Study Assessments
Note: Any additional medical procedures not included into this study protocol can be performed within routine clinical practice in each medical institution

Period	Screening	End of Treatment period	Safety follow-up (phone call 5-7 days after Visit 2)
Visit	**1**	**2**	**3**
Day	**1**	**6[2]**	**11-13**
Informed consent/assent	X		
Randomization	X		
Demographic data	X		
Medical history	X		
Physical examination[3]	X	X	
In-or outpatient	X		
Stool frequency within the last 24 hours	X		
Inclusion/exclusion criteria	X		

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Vitals signs	X	X	
Dispense study drug	X		
Concomitant medication	X	X	X if applicable
Compliance check		X	
Adverse events	X	X	X
Collect study drug		X	
Dispense diary	X[1]		
Collect diary		X	

[1] Subjects' parent/caregivers have to fill in their daily diaries continuously.
[2] or within 24 h after recovery if this occurs before day 6
[3] including assessment of dehydration level

Number of Subjects (Planned):
A maximum number of subjects to be allocated to treatment: 62 subjects per group, 124 subjects in total. A minimum number of 20 subjects should be available in each age group (3 – < 24 months, 2 years to 11 years, 12 to < 18 years).

A maximum number of subjects to be screened: Approximately 150 should be screened.

Diagnosis and Main Criteria for Inclusion:

- Signed informed consent from one of the parent(s)/caregiver(s) or subject informed assent.
- Children and adolescents, both genders, age from 3 months to < 18 years of age.
- Confirmed diagnosis of acute diarrhea (defined as the passage of three or more unformed or liquid stools within the last 24 hours and lasting for less than three days).
- Females of child-bearing potential should agree to continue using a medically acceptable method of birth control throughout the study and for 30 days immediately after the last dose of study drug. Medically acceptable methods of birth control include bilateral tubal ligation or the use of either a contraceptive implant, a contraceptive injection, an intrauterine device, or an oral contraceptive taken within the past three months where the subject agrees to continue using during the study or to adopt another birth control method, or a double-barrier method which consists of a combination of any two of the following: diaphragm, cervical cap, condom, or spermicide.

Exclusion Criteria:

- Known allergy to Racecadotril or any of its ingredients.
- Subjects suffering from renal or hepatic impairment.

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- Subjects who need treatment for diarrhea other than ORS alone.
- Subjects with fever > 39 degrees Celsius.
- Subjects with bloody and/or purulent stools.
- Subjects suffering from antibiotic-associated diarrhea, chronic diarrhea or iatrogenic diarrhea.
- Subjects with alternating bouts of diarrhea and constipation.
- Diarrhea due to exacerbation of chronic gastrointestinal diseases such as irritable bowel syndrome, inflammatory bowel disease or pancreatic exocrine insufficiency.
- Cystic fibrosis or coeliac disease.
- Subjects suffering from prolonged or uncontrolled vomiting.
- Subjects with rare hereditary problems of fructose or galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption syndrome or sucrase isomaltase insufficiency or primary or secondary lactase insufficiency.
- Subjects having received antibiotic treatment at any time within 30 days prior to inclusion into the study.
- Subjects having received antidiarrheal drugs 48 hours prior to inclusion into the study.
- Subjects with severe dehydration required for intravenous/parenteral rehydration.
- Subjects who have reported angioedema with angiotensin converting enzyme inhibitors (such as captopril, enalapril, lisinopril, perindopril, ramipril)
- Subjects with combined diseases or medical situations that would prevent to be enrolled depending in the judgment of the investigator.
- Intake of experimental drug within 30 days prior to study start.
- Subjects with contraindications to ORS or for whom warnings/precautions of ORS apply.
- Adolescents (≥ 60 kg) not able to swallow capsules.
- Pregnancy and lactation.

Test Product, Dose and Mode of Administration:

Racecadotril Infants Granules for Oral Suspension10mg
Racecadotril Children Granules for Oral Suspension 30mg
Racecadotril Capsules 100 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.

Name of Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient(s):**
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In children or adolescents of 60 kg or higher: 100 mg capsule 3 times daily

Racecadotril will be given three times daily in addition to standard treatment ORS. Other medication to treat diarrhea (see section 7.7) is forbidden.

Duration of Treatment:

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

Reference Therapy, Dose and Mode of Administration:

Standard treatment is oral rehydration solution (ORS) according to the registered local label and the instruction of the investigator. The same brand of ORS and the same age-appropriate standardized treatment pattern for the subjects will be applied throughout the trial. No additional reference therapy will be administered together with oral rehydration in the control arm.

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 by date and time of the evacuation of the final diarrheal stool derived from the daily diary.

Secondary Efficacy Variables:

- Number of recovered subjects per treatment group in total and until each individual treatment day. Mean and median time until recovery per treatment group.
- Time until recovery, defined by date and time of the evacuation of the first of two consecutive normal stools.
- Global Physician Assessment at the end of treatment:
  - 1 = Complete relief of acute diarrhea,
  - 2 = marked improvement of acute diarrhea,
  - 3 = moderate improvement of acute diarrhea,
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- For toilet trained children and adolescents: 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 in both treatment arms.

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 log-rank test will be used to test whether the difference of the duration of diarrhea between two treatment groups is statistically significant, i.e. p-value <0.05.

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 by unique treatment. Severity and drug-event relationship of treatment emergent AEs are summarized separately. Vitals signs, including changes from baseline will be summarized. A frequency table will be presented for markedly abnormal values.

Sample size

The sample size of this study is based on the results obtained with a randomized, double blind, study with Racecadotril in the treatment of hospitalized children aged 3-60 months suffering from acute watery diarrhea (Bio-Projet Study nr. 45, Salazar Lindo et al. 1998). A total of 135 subjects were analyzed in this study. Data of the study showed following recovery rates over time:

Duration of treatment	Percentage of recovered patients		
	Placebo	Racecadotril	Sample size per group required for a power of 80% using log-rank test (+10% drop out rate)
after 1 day (24 hours)	18.3%	46.6%	41 (46)
After 2 days (50 hours)	35.8%	70.1%	36 (40)
After 3 days (72 hours)	59.4%	84.2%	55 (62)

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After 4 days (96 hours)	76.3%	90.1%	119 (132)
After 5 days (120 hours)	80.6%	94.7%	90 (100)

The mean duration of diarrhea was 64 (±4.6) hours in the placebo group (median 64 hours) and 40 (±4.1) hours in the Racecadotril group (median 28 hours). Therefore an appropriate approach to investigate a difference between recovery rates of the two treatment groups would be after a treatment duration of at least 3 days (i.e. 72 hours).When the sample size in each group is 55 (with a total number of recoveries of at least 26), the two-sided log-rank test for equality of survival curves will have 80% power to detect the difference between 84.2% rate of recovery in the Racecadotril group and the 59.4% rate of recovery in the placebo group after a treatment duration of 72 hours. Adding a 10% drop-out rate the sample size per groups would be 62 subjects i.e. 124 subjects in total. A minimum number of 20 subjects should be available in each age group (3 – < 24 months, 2 years to 11 years, 12 to < 18 years). A subgroup analysis per age group (3 – < 24 months, 2 years to 11 years, 12 to < 18 years) will be performed.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	adverse drug reaction
Ae	amount of unchanged drug excreted into the urine
AE	adverse event
ATC	Anatomical Therapeutic Chemical
bpm	beat per minute
CFR	Code of Federal Regulations
CRF	case report form (paper or other media)
DBP	diastolic blood pressure
ECG	electrocardiogram
EDC	Electronic Data Capture
EEG	electroencephalogram
EU	European Union
EudraCT	European clinical trials database
FA	full analysis
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPV	Global Pharmacovigilance
HLGT	high level group term
HLT	high level term
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IXRS	Interactive Voice/Computer/Remote Response System
LLT	lowest level term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities

Min	Minimum
N/A	not applicable
PD	pharmacodynamic
PK	pharmacokinetic
PP	per-protocol
PT	preferred term
SADR	serious adverse drug reaction
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse drug reaction
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/caregiver of each subject prior to performing any study-related procedures. Each parent/caregiver 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/caregiver 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/caregiver has signed an approved informed consent written in a language that is understandable to the subject. The participation of the study should be discussed with the subject <14 years of age according to the child's age and ability and verbal assent should be obtained. The informed consent will be given by the signature of one parent.

Voluntary written informed assent will be obtained from adolescents ≥ 14 years in addition to parent's written informed consent. Each subject will be given both verbal and written information describing the nature and duration of the clinical study. The informed assent process will take place under conditions where the subject has adequate time to consider the risks and benefits associated with the participation in the study. Subjects will not be screened or treated until the subject has signed an approved informed assent written in a language that is understandable to the subject.

The IEC/IRB approved informed consent/assent form will be signed and personally dated by the parent/caregiver (or legally acceptable representative, when appropriate) and the person who conducted the informed consent discussion. Each parent/caregiver 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/caregiver 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 parents/caregivers 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 diarrhoea. 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 antisecretory 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 antisecretory 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.

The trade names are Tiorfan® in France, where it has been approved in capsules since July 1992 and launched in March 1993, and Hidrasec® in other countries. Pediatric dosage form of racecadotril (Tiorfan®sachet 10 mg and 30 mg) were approved in France in October 1999. Hidrasec® capsules were registered in Russia for adult use in 2017. The products are currently approved in 85 countries.

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 antidiarrheals have a positive safety profile and have limited or no effects on motility and basal intestinal secretion.

Racecadotril has been shown to be effective and well tolerated for the complementary symptomatic treatment of acute diarrhea in pediatric subjects older than 3 months.

This study is conducted to assess the efficacy and safety profile of Racecadotril in Russia pediatric and adolescent subjects.

The dosing regimen of Racecadotril is 1.5 mg/kg 3 times daily, via the oral route resulting in the following instruction:

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.
In children or adolescents of 60 kg or higher: 100 mg capsule 3 times daily

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) versus ORS alone in infants, children and adolescents (3 months until <18 years) with acute diarrhea measured as duration of diarrhea (hours) between the start of treatment until final diarrheal/watery stool before recovery or end of study treatment (treatment duration maximal 5 days).

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

3.2 Secondary Objective(s)

- Number of recovered subjects per treatment group in total and until each individual treatment day. Mean and median time until recovery per treatment group.

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

- Global Physician Assessment at the end of treatment:
  - 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 and adolescents: 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) versus ORS alone in infants, children and adolescents 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 controlled, open-label, parallel-group study evaluating the efficacy and safety of Racecadotril in infants, children and adolescents with acute diarrhea. The number of subjects to be screened is 150 in order to enroll 124 subjects for either standard treatment (oral rehydration solution, ORS) alone or 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 the 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.
In children or adolescents of 60 kg or higher: 100 mg capsule 3 times daily

Standard treatment is oral rehydration solution (ORS) according to the registered local label and the instruction of the investigator. The same brand of ORS and the same age-appropriate standardized treatment pattern for the subjects will be applied throughout the trial. ORS treatment and dosing will be documented in the CRF.

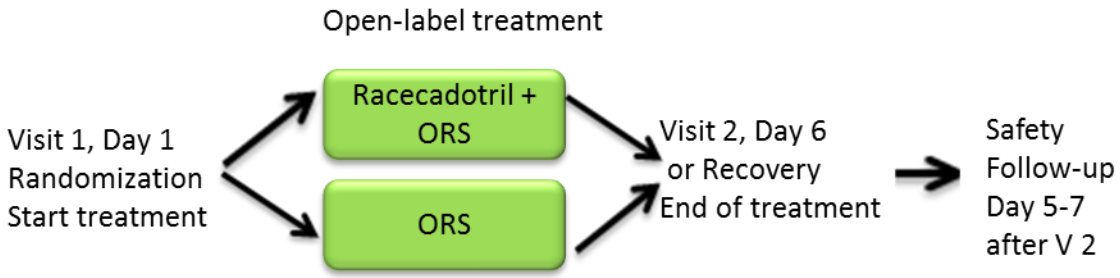
Screening and Enrolment (Day 1, Visit 1)
Subjects presenting with acute diarrhea will be evaluated for eligibility. They will undergo a physical examination including assessment of dehydration level, vital signs, a review of their medical history and concomitant medication. If the subjects are eligible for the study, demographics, number of stools during the last 24 hours will be assessed as baseline values. The subjects will be randomized to Racecadotril plus ORS or ORS alone. On Day 1 the subject will start with study treatment. The starting dose will either be the noon or the evening dose depending on the timing of Visit 1.

Treatment period (until recovery, maximally 5 days)
Subjects will be treated with Racecadotril tid according to the body weight dose requirement on an in- or out-patient basis for maximum 5 days. One arm will be treated with ORS alone as standard treatment, the other treatment arm 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) will be instructed to stop study drug treatment when the patient recovered. On each day, the parent(s)/caregiver(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, the parent(s)/caregiver(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. 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. The same day, or within 24 hours after recovery, the parent(s)/caregiver(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 at 5-7 days after end of the treatment period for the safety follow-up.



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

Standard treatment for pediatric subjects with acute diarrhea is ORS and adequate rehydration is also the basic treatment regimen for adolescents. ESPGHN guidelines (Guarino et al. 2014) and World Gastroeneterology Organization (WGO) guidelines 2012 state that the gold standard of treatment of acute diarrhea in pediatric population is oral rehydration solution (ORS). Thus ORS is considered to be the appropriate control treatment for planned investigation.

An open-label designs of Racecadotril on top of ORS versus ORS alone is appropriate as the primary endpoint can be measured objectively: duration of diarrhea (hours) between the start of treatment until final diarrheal/watery stool before recovery or end of study treatment.

5 SELECTION OF STUDY POPULATION

5.1 Inclusion Criteria

- Informed Consent:
  - For all subjects: signed informed consent from one of the parent(s)/caregiver(s)
  - For subjects ≥ 14 years of age: signed informed assent form in addition to parent's written informed consent
  - For subjects <14 years of age: verbal assent if age and ability allows
- Children and adolescents, both genders, age from 3 months to < 18 years of age.
- Confirmed diagnosis of acute diarrhea (defined as the passage of three or more unformed or liquid stools within the last 24 hours and lasting for less than three days).
- Females of child-bearing potential should agree to continue using a medically acceptable method of birth control throughout the study and for 30 days immediately after the last dose of study drug. Medically acceptable methods of birth control include bilateral tubal ligation or the use of either a contraceptive implant, a contraceptive injection, an intrauterine device, or an oral contraceptive taken within the past three months where the subject agrees to continue using during the study or to adopt another birth control method, or a double-barrier method which consists of a combination of any two of the following: diaphragm, cervical cap, condom, or spermicide.

5.2 Exclusion Criteria

- Known allergy to Racecadotril or any of its ingredients.
- Subjects suffering from renal or hepatic impairment.
- Subjects who need treatment for diarrhea other than ORS alone.
- Subjects with fever > 39 degrees Celsius.
- Subjects with bloody and/or purulent stools.
- Subjects suffering from antibiotic-associated diarrhea, chronic diarrhea or iatrogenic diarrhea.
- Subjects with alternating bouts of diarrhea and constipation.
- Diarrhea due to exacerbation of chronic gastrointestinal diseases such as irritable bowel syndrome, inflammatory bowel disease or pancreatic exocrine insufficiency.
- Cystic fibrosis or coeliac disease.
- Subjects suffering from prolonged or uncontrolled vomiting.
- Subjects with rare hereditary problems of fructose or galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption syndrome or sucrase isomaltase insufficiency or primary or secondary lactase insufficiency.
- Subjects having received antibiotic treatment at any time within 30 days prior to inclusion into the study.
- Subjects having received antidiarrheal drugs 48 hours prior to inclusion into the study.
- Subjects with severe dehydration required for intravenous/parenteral rehydration.

- Subjects who have reported angioedema with angiotensin converting enzyme inhibitors (such as captopril, enalapril, lisinopril, perindopril, ramipril)
- Subjects with combined diseases or medical situations that would prevent to be enrolled depending in the judgment of the investigator.
- Intake of experimental drug within 30 days prior to study start.
- Subjects with contraindications to ORS or for whom warnings/precautions of ORS apply.
- Adolescents (≥ 60 kg) not able to swallow capsules
- Pregnancy or lactation

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.

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 fails to return to the study site for scheduled visits and does not respond to telephone or written attempts to contact.
- Withdrew consent: subject decides to stop his/her 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 with two consecutive temperature measurements of > 39 degrees Celsius during the study should be withdrawn from the study for further diagnosis and alternative treatments. Also subjects whose disease state worsens, e.g. dehydration or increased vomiting, should be withdrawn from the study. An end of treatment visit will be performed.

7 TREATMENTS

Study drug 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 Suspension10mg
Racecadotril Children Granules for Oral Suspension 30mg
Racecadotril Capsules 100 mg

1.5 mg/kg of Racecadotril will be administered, 3 times daily (morning, noon, evening), via the oral route. For more accurate dosing the following formulations will be used for different patient age groups:

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.
In adolescents of 60 kg or higher: 100 mg capsule 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. The same brand of ORS and the same age-appropriate standardized treatment pattern for the subjects will be applied throughout the trial. No additional reference therapy will be administered together with oral rehydration in the control arm.. ORS treatment will be documented in the CRF. Racecadotril will be given in addition to ORS. No drug will be administered together with oral rehydration in the control arm.

7.2 Packaging and Labeling

Packaging and labeling will be controlled by [redacted].

All packaging and labeling as well as the production of study drug will be in compliance with Good Manufacturing Practices (GMP) specifications, as mentioned in the Manufacturing of Investigation and Medicinal Products Volume 4 Annex 13 and in accordance with other applicable laws or local regulations.

Details on the packaging and labeling will be specified in the Packaging and Labeling Specifications and Supply Request.

An Abbott Qualified Person will release all the clinical supplies prior to shipment to investigational sites. A Certificate of Compliance will be issued stating the expiry date of the Racecadotril clinical supplies.

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 randomized to a treatment group by the assignment of a 5-digit randomization number to each subject according to a randomization scheme. The medication will be identified using 6-digit kit randomization numbers.

The randomization scheme will be provided by [redacted]

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.
In adolescents of 60 kg or higher: 100 mg capsule 3 times daily

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 and age appropriate dosing regimen of ORS. In the treatment arm with 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, participants are not allowed to be treated with the following treatments in addition to the study drug:

- Antiperistaltic drugs, e.g. loperamide,
- Antibiotics
- Antipyretics
- Intestinal antiseptics, e.g. 8-hydroxyquinoline
- Respiratory decongestants, e.g phenylephrine
- Antitussive medication, e.g noscapin
- Absorbents, e. g. diosmectite, charcoal, pectin, psyllium
- Zinc-containing medication
- Homemade ORS
- ACE Inhibitors
- Antispasmodics
- Drugs for symptomatic treatment of diarrhea, e.g. pancreatic enzymes, anticholinergic drugs, opiates, diphenoxylate.

Subjects on continuous probiotic treatment (e.g. Lactobacillus, Bifidobacterium, yeast) or probiotic- containing supplements/formula of the same product/brand for at least 4 weeks prior to study start can be included.

The presence of bloody or purulent stool and fever may indicate either the presence of invasive bacteria as a reason for diarrhea or the presence of another severe disease, warranting causal (e.g. antibiotic) treatment or further investigation. 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.

Dietary modifications for thickening of the stools are allowed.

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 last diarrheal/watery stool before recovery or 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 by date and time of the evacuation of the final diarrheal stool derived from the daily diary.

Secondary Efficacy Variables:

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

- Number of recovered subjects per treatment group in total and until each individual treatment day. Mean and median time until recovery per treatment group.

- Global Physician Assessment at the end of treatment:
  - 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 and adolescents: 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.

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. The dehydration level of the subject will be assessed (mild, moderate, severe).

Pregnancy Test

A urine pregnancy test will be conducted on females of child-bearing potential (if child-bearing potential) at Visit 1.

8.3 Other Assessments

Informed Consent

Voluntary written informed consent must be obtained from one parent(s)/caregiver(s) (or their legally acceptable representative) prior to performing any study-related procedures (see Section 1.3) for all subjects. For subjects < 14 years voluntary verbal assent will be obtained if age and ability allows in addition.

Voluntary written informed assent will be obtained from subjects ≥ 14 years of age in addition to parent's written informed consent prior to performing any study-related procedures (see Section 1.3).

Demographic Data

Demographic data (gender, date 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) 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.

The date, time and dose of study drug intake as well as the amount ORS and other liquids (e.g. water, milk formula) consumed has to be recorded.

Fever will be measured once daily by the parent(s)/caregiver(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 by 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 1, which displays the frequency and timing of all measurements.

Table 2: Flow Chart of Study Assessments
Note: Any additional medical procedures not included into this study protocol can be performed within routine clinical practice in each medical institution

Period	Screening	End of Treatment period	Safety follow-up (phone call 5-7 days after Visit 2)
Visit	**1**	**2**	**3**
Day	**1**	**6[2]**	**11-13**
Informed consent	X		
Randomization	X		
Demographic data	X		
Medical history	X		
Pregnancy Test[4]	X		
Physical examination[3]	X	X	

In- or outpatient	X		
Stool frequency within the last 24 hours	X		
Inclusion/exclusion criteria	X		
Vitals signs	X	X	
Dispense study drug	X		
Concomitant medication	X	X	X
Compliance check		X	
Adverse events	X	X	X
Collect study drug		X	
Dispense diary	X[1]		
Collect diary		X	

[1] Subjects' parent/caregivers have to fill in their daily diaries continuously.
[2] or within 24 h after recovery if this occurs before day 6
[3] including assessment of dehydration level

[4] for females of child-bearing potential, urine test

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 as well as the no 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 termination of study drug (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.

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 dyscrasias 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

Any SAE (fatal or life-threatening SAE and other SAEs), whether or not related to the study drug, must be reported immediately within 24 hours of the investigator's awareness of the event by telephone and faxing the appropriate SAE forms to the CRO.

Local reporting requirements other than described, will be taken into account and adhered to.

9.3 Pregnancy

If a subject should become pregnant during the study, the event will be reported on the Pregnancy Form within 24 hours of the investigator's knowledge of the pregnancy. The Pregnancy Form is to be mailed or faxed to the CRO (or an authorized representative).

If pregnancy occurs in a subject from the time of ICF signature who does not qualify for allocation to treatment, i.e. Screen Failure, the pregnancy should be recorded in patient's medical file only, in accordance to local requirements. The pregnancy related medical status change information will not be reviewed by Abbott or delegated staff. The pregnancy will not qualify as a study (S)AE.

If pregnancy occurs in a subject from the time of ICF signature who is not dis-qualified for allocation to treatment, the pregnancy should be recorded in patient's medical file in accordance to local requirements and in Abbott's pregnancy from. The pregnancy related medical status change information will be reviewed by Abbott or delegated staff. The pregnancy will not qualify as a study (S)AE.

The pregnancy evolution and outcome, i.e., the health status of the newborn, is to be reported on the Pregnancy Outcome Form and reported to the CRO (or an authorized representative) within 1 day of the investigator's knowledge of the event.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth, ectopic pregnancy or congenital anomaly is considered a SAE and must be reported to the Sponsor (or an authorized representative) within 24 hours of the investigator becoming aware of the event and followed-up as described in Section 9.1.2.

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 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 Investigator 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 by date of the evacuation of the last diarrheal/watery stool.

In order to compare the primary efficacy parameter, duration of diarrhea, between the treatment groups, a Kaplan Meier analysis will be performed. The log-rank test will be used to test whether the difference between the duration of diarrhea between two treatment groups is statistically significant, i.e. p-value <0.05.

The secondary efficacy variables are

- 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.
- Assessment of treatment success by the physician
- Time until recovery, defined by date and time of the evacuation of the first of two consecutive normal stools.
- Number of subjects recovered per treatment group, in total and until each individual treatment day
- Mean and median time until recovery per treatment group

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.

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.

For each unique treatment, 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 per treatment group.

Demographics and other baseline characteristics will be summarized per 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 (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 (3 – < 24 months, 2 years to 11 years, 12 to < 18 years).

10.7 Interim Analysis

not applicable

10.8 Determination of Sample Size

The sample size of this study is based on the results obtained with a randomized, double blind, study with Racecadotril in the treatment of hospitalized children aged 3-60 months suffering from acute watery diarrhea (Bio-Projet Study nr. 45, Salazar Lindo et al. 1998). A total of 135 subjects were analyzed in this study. Data of the study showed following recovery rates over time:

Duration of treatment	Percentage of recovered patients		
	Placebo	Racecadotril	Sample size per group required for a power of 80% using log-rank test (+10% drop out rate)
after 1 day (24 hours)	18.3%	46.6%	41 (46)
After 2 days (50 hours)	35.8%	70.1%	36 (40)
After 3 days (72 hours)	59.4%	84.2%	55 (62)
After 4 days (96 hours)	76.3%	90.1%	119 (132)
After 5 days (120 hours)	80.6%	94.7%	90 (100)

The mean duration of diarrhea was 64 (±4.6) hours in the placebo group (median 64 hours) and 40 (±4.1) hours in the Racecadotril group (median 28 hours), Therefore an appropriate approach to investigate a difference between recovery rates of the two treatment groups would be after a treatment duration of at least 3 days (i.e 72 hours).When the sample size in each group is 55 (with a total number of recoveries of at least 26), the two-sided log-rank test for equality of survival curves will have 80% power to detect the difference between 84.2% rate of recovery in the Racecadotril group and the 59.4% rate of recovery in the placebo group after a treatment duration of 72 hours. Adding a 10% drop-out rate the sample size per groups would be 62 subjects i.e. 124 subjects in total.
A minimum number of 20 subjects should be available in each age group (3 – < 24 months, 2 years to 11 years, 12 to < 18 years). A subgroup analysis per age group (3 – < 24 months, 2 years to 11 years, 12 to < 18 years) will be performed.

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

[redacted]

Dr. J.M. Vetel.

Double-Blind Comparative Study to Evaluate the Efficacy and Tolerance of Three Doses of Acetorphan versus Placebo in the Treatment of Acute Diarrhoea.

Published as Baumer Ph, Dorval ED, Bertrand J, Vetel JM, Schwartz JC, Lecomte JM. Effects of acetorphan, an enkephalinase inhibitor, on experimental and acute diarrhea. *Gut.* 1992;33:753-758.

Guarino et al. 2014, Euopean Society for Pediatric Gastroenterology, hepatology and Nutrition/European Society for Pediatric Infectious Diseases Evidence-Based Guidelines for the Management of Acute Gastroenteritis in Children in Europe: Update 2014, JPGN, 59: 132-152

World Gastroenterology Organisation Global Guidelines: Acute diarrhea in adults and children: a global perspective, Feb 2012

16 APPENDICES

16.1 Appendix – Participating Countries' National Insurance Requirements

Not applicable

16.2 Appendix – Coordinating Investigator Signature of Clinical Study Report

The following Investigator is regarded to be the coordinating Investigator who should sign the Investigator signature page of the clinical study report:

to be determined

16.3 Appendix – Medical expert for the trial.

[redacted]

16.4 Appendix –Clinical laboratory(ies) involved in the trial

Not applicable