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

Protocol No.: RACE3002

STATISTICAL ANALYSIS PLAN

Version: 3.0
Date: 25.Aug.2020
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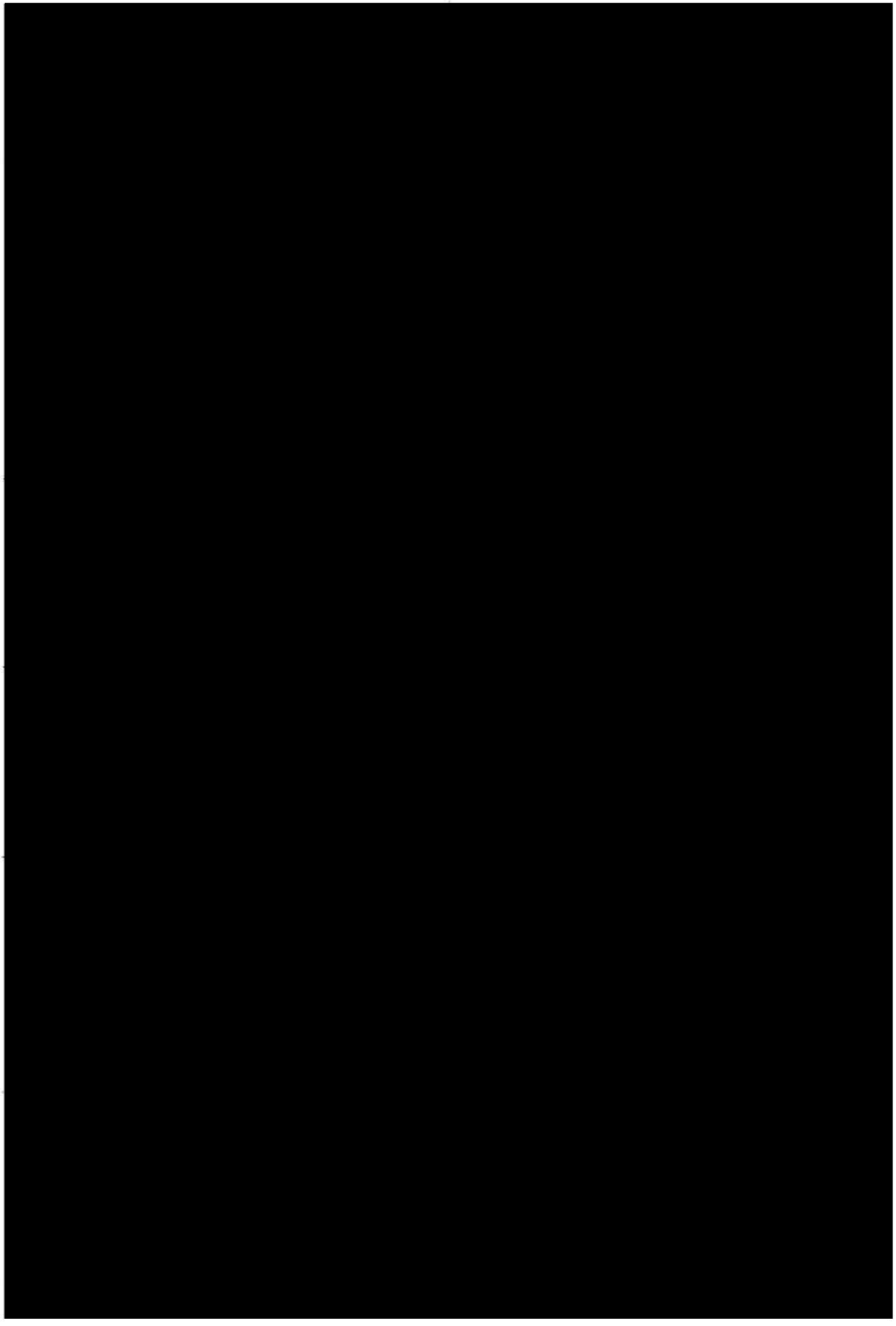
Confidentiality Statement



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1. INTRODUCTION

This statistical analysis plan (SAP) is based on protocol RACE3002 Version Date 09 OCT 2017, Amendment 1 Date 07 NOV 2018, Amendment 2 Date 22 NOV 2019, TFDA Official Letter (No. 1096009485) dated 08-Jun-2020 as well as Abbott Clarification Letter for Interim Analysis dated 20-Aug-2020. The SAP provides details of data handling procedures, statistical analysis methods for efficacy and safety evaluations. It also outlines statistical programming specifications for tables and listings, and other details on the analyses not provided in the study protocol.

All data of these enrolled and randomized subjects using Protocol Version Date 09 OCT 2017 will be listed only. A note to file (NTF), Racecadotril dosage per sachet dated on 21-Mar-2019 is adapted for Racecadotril dosage collection.

2. STUDY OBJECTIVE

2.1 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.

2.2 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. 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.

2.3 Safety Objective(s)

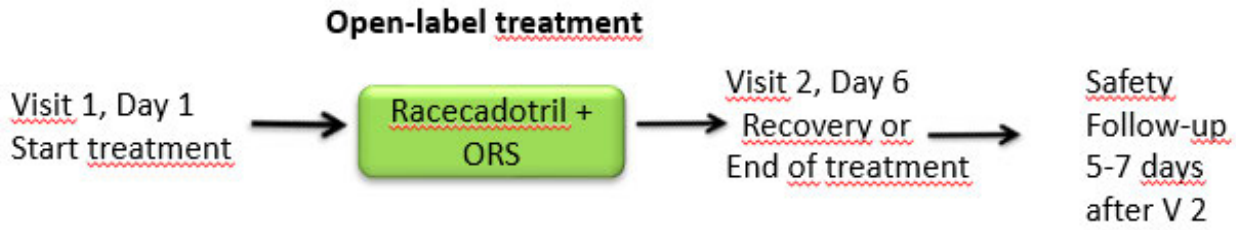
To evaluate the safety and tolerability of Racecadotril together with oral rehydration solution (ORS) in infants and children (3 months until 60 months) with acute diarrhea by adverse events, physical examination and vital signs.

3. STUDY DESIGN

3.1 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.

Figure 3-1 Overall Study Design



3.2 Selection of Study Population

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).

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 Protocol 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.

3.3 Blinding and Treatment Code Information

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

3.4 Method of Assigning Subjects to Treatment Groups

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).

Approximately 50 subjects should be screened.

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.

3.5 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.

3.6 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.

3.7 Safety Variables

Adverse Events

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.

Requirements for collecting, recording and reporting of AEs are described in Protocol 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: 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.
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 calendar day.

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.

3.8 Flow Chart of Study Assessments

Table 1: Flow Chart of Study Assessments

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		
Inclusion/exclusion criteria	X		
Demographic data	X		
Medical history including vaccination history	X		
Physical examination	X	X	

Period	Screening	End of Treatment period	Safety follow-up (phone call, 5-7 days after Visit 2)
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

3.9 Interim Analysis

No interim analysis will be performed for protocol Amendment 2, but there will be a dry run of Table, Listing and Figures (TLFs) based on Study Date Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets to Abbott at a time when 25 randomized subjects complete the study and 40 randomized subjects complete the study. While the subjects enrolled using protocol version date 09 OCT 2017 will be excluded from dry run analysis. Dry run tables will be prepared and reviewed in the blinded fashion.

[redacted]

3.10 Subgroup Analysis

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

An additional subgroup analysis which is not included in the protocol will be summarized across subgroups defined by weight group (in infants less than 9 kg, in infants from 9 kg to < 13 kg, in

children from 13 kg to 27 kg, and in children of more than 27 kg). Subgroup analysis by weight groups will be only conducted in the demographics and efficacy.

4. GENERAL STATISTICAL ISSUES

4.1 Continuous Endpoints

Descriptive statistics for quantitative and ordinal variables including number of observation (n), mean, standard deviation (SD), median, minimum (Min) and maximum (Max) will be presented for the raw data as well as change from baseline. The mean will be represented one more decimal than the raw number, and SD as two more decimals than the raw number.

4.2 Categorical Endpoints

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. Percentages will be presented with 2 decimals. Partial date(s) will be listed as provided in the listings.

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

4.3 Time-to-event Endpoints

The time-to-event endpoint will be analyzed by Kaplan-Meier method and presented as mean, median and 95% confidence interval for median.

4.4 Sample Size Estimation and Power

In total, 40 subjects will be allocated to receive Racecadotril treatment. 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 48 subjects will be recruited. Recruitment will be stopped once 40 subjects have completed the study**.**

5. DATA HANDLING PROCEDURES

5.1 Coding System

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 dictionary, using the most recent version.

Concomitant medications will be classified according to active drug substance using the World Health Organization (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.

5.2 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. When a patient doesn't recover beyond the study cutoff date, survival duration is stopped at the study cutoff date and it will be regarded as a censored data. The cut-off date will be the end of study (treatment duration maximal 5 days).

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

6. ANALYSIS OF 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.

7. DISPOSITION OF PATIENTS AND STUDY COMPLETION

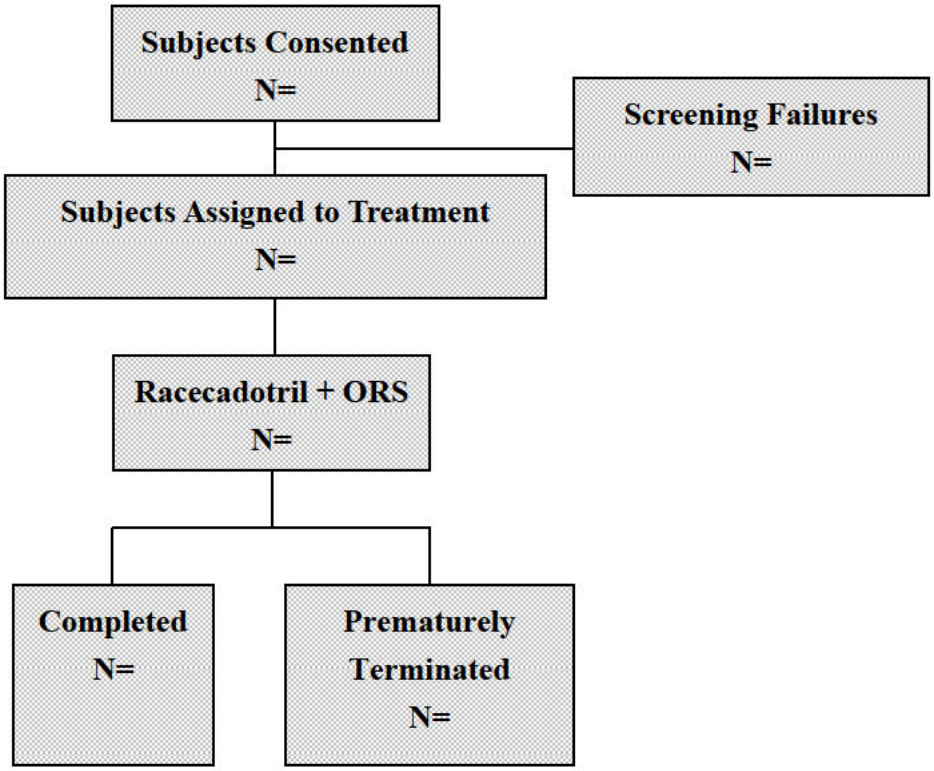
The assignment of subjects to subject samples, the disposition of subjects with respect to premature termination, reason for premature termination will be summarized for the treatment group as Table 14.1.1. The flow chart of subject disposition is shown as Figure 7-1.

Data on visit date and the completion status with primary reason for premature termination will be listed in Listing 16.2.1.1.

Individual subject inclusion/ exclusion criteria not met at screening will be listed in Listing 16.2.1.2. Only the exceptions are to be listed, that is, subjects with a response to the inclusion criteria of "No" and/or subjects with a response to the exclusion criteria of "Yes". Subjects with a missing response to inclusion/exclusion criteria will also be presented. Eligibility and assignment will be listed in Listing 16.2.1.3.

All minor and major protocol deviation(s) which judged by principal investigator will be listed in Listing 16.2.2. All subjects who excluded from any of the safety sample, FA sample or PP analysis as well as the reason (s) for exclusion will be listed in Listing 16.2.3.

Figure 7-1 Flow Chart of Subject Disposition



8. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Subject demographics and other baseline characteristics will be listed in Listing 16.2.4.1 and Listing 16.2.4.2 and will be summarized as Table 14.1.2.1 using Safety, FA and PP samples. Subgroup analysis of demographics and baseline characteristics by age group (< 24 months old and ≥ 24 months old) will be also summarized as Table 14.1.2.2 using Safety, FA and PP samples. Subgroup analysis of demographics and baseline characteristics by weight group (in infants less than 9 kg, in infants from 9 kg to < 13 kg, in children from 13 kg to 27 kg, and in children of more than 27 kg) will be also summarized as Table 14.1.2.3 using Safety, FA and PP samples.

8.1 Medical/ Surgery/ Vaccination 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. The medical history recorded will be listed by subject in Listing 16.2.4.3. The Medical history, including coding data will be summarized per primary SOC, per HLT by primary SOC and per PT by HLT and primary SOC as Table 14.1.2.4 using Safety sample.

8.2 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 and will be listed by subject in Listing 16.2.4.4, except for study drug. 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 as Table 14.1.2.5 using Safety Sample.

9. EFFICACY ANALYSIS

FA and PP Samples will be used to all efficacy analysis.

9.1 Primary Efficacy Variable

The primary efficacy variable is the duration (hours) of diarrhea (treatment duration max 5 days). Duration of diarrhea is defined as date and time of the evacuation of the last watery/diarrheal stool before recovery or end of treatment. The duration of diarrhea definition can be referred to Figure 9-1. 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. The KM algorithm will be applied to derive the median duration (hours) and the 95% confidence intervals for the median, and mean duration. The censored number and event number will be presented as counts and percentage as well.

The SAS code is listed as below:

```
PROC LIFETEST DATA=duration METHOD=KM PLOTS=SURVIVAL (FAILURE ATRISK);
TIME T*status (0);
RUN;
```

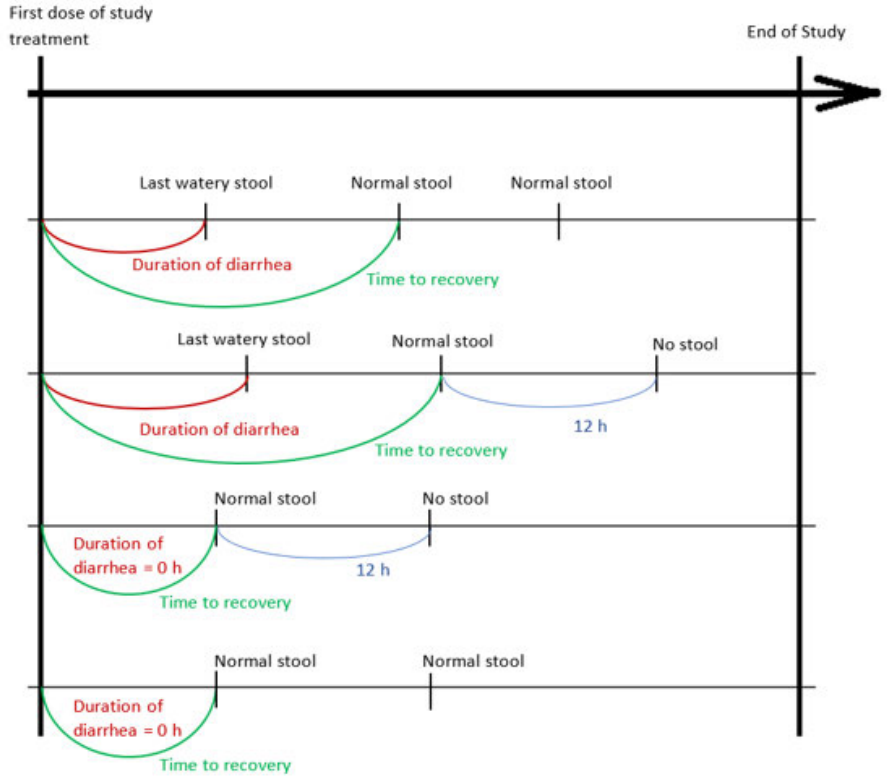
Note:
The proc lifetest analysis will be performed with failure curve (an increasing trend). The duration (hours) of diarrhea or time (hours) until recovery is recorded in the variable T. The variable status is the censoring indicator. A status of 1 indicates an event time, and a status of 0 indicates a censored time. The event is recovery. The censored data are those did not recover during treatment period including drop-outs. When a patient doesn't recover beyond the end of study (treatment duration maximal 5 days), duration is stopped at the end of study date and it will be regarded as a censored data as well. The censored times will be plotted as a plus sign on the Kaplan-Meier.

An event time for the duration of diarrhea is defined as the duration from the date of dosing to the date of the evacuation of last watery/ diarrheal stool before recovery. A censored time for the duration of diarrhea is defined as the duration from the date of dosing to the date of not recovery during treatment period.

An event time for time until recovery is defined as the time from the date of dosing to the date of the evacuation of the first of two consecutive normal stools or no stool within 12 hours after the first normal stool. A censored time for time until recovery is defined as the duration from the date of dosing to the date of not recovery during treatment period.

Individual subject diary card dispensation and subject stool record will be listed in Listing 16.2.6.1 and 16.2.6.2, respectively. The overall duration of diarrhea and additional table of duration of diarrhea for each day of the study will be summarized as Tables 14.2.1 using FA and PP samples. Figures for overall duration of diarrhea can refer to Figure 14.2.1.1 and Figure 14.2.1.2, respectively.

Figure 9-1 Duration of Diarrhea and Time until Recovery Definition



Subgroup analysis of duration (hours) of diarrhea by age group (< 24 months old and ≥ 24 months old) will be also summarized as Table 14.2.6 using FA and PP samples. Figures for overall duration of diarrhea by age group can refer to Figure 14.2.6.1 and Figure 14.2.6.2, respectively.

Subgroup analysis of duration (hours) of diarrhea by weight group (in infants less than 9 kg, in infants from 9 kg to < 13 kg, in children from 13 kg to 27 kg, and in children of more than 27 kg) will be also summarized as Table 14.2.11 using FA and PP samples. Figures for overall duration of diarrhea by weight group can refer to Figure 14.2.11.1 and Figure 14.2.11.2, respectively.

9.2 Secondary Efficacy Variables

9.2.1 Time until Recovery

Time until recovery is 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***. The time until recovery definition and SAS code can be referred to Figure 9-1. The time until recovery and additional table of time until recovery for each day of the study will be summarized using Kaplan-Meier analysis as Tables 14.2.1 using FA and PP samples. Figures for time until recovery at end of treatment can refer to Figure 14.2.1.3 and Figure 14.2.1.4, respectively.

Subgroup analysis of time until recovery by age group (< 24 months old and ≥ 24 months old) will be also summarized using Kaplan-Meier analysis as Table 14.2.6 using FA and PP samples. Figures for time until recovery at the end of treatment can refer to Figure 14.2.6.3 and Figure 14.2.6.4, respectively.

Subgroup analysis of time until recovery by weight group (in infants less than 9 kg, in infants from 9 kg to < 13 kg, in children from 13 kg to 27 kg, and in children of more than 27 kg) will be also summarized using Kaplan-Meier analysis as Table 14.2.11 using FA and PP samples. Figures for time until recovery at the end of treatment can refer to Figure 14.2.11.3 and Figure 14.2.11.4, respectively.

9.2.2 Number of Subjects Recovered

Number and proportion of subjects recovered, in total and until each individual treatment day will be summarized with count and percentage as well as 95% CI as Table 14.2.2 using FA and PP samples.

Subgroup analysis of number and proportion of subjects recovered by age group (< 24 months old and ≥ 24 months old) will be also summarized with count and percentage as well as 95% CI as Table 14.2.7 using FA and PP samples.

Subgroup analysis of number and proportion of subjects recovered by weight group (in infants less than 9 kg, in infants from 9 kg to < 13 kg, in children from 13 kg to 27 kg, and in children of more than 27 kg) will be also summarized with count and percentage as well as 95% CI as Table 14.2.12 using FA and PP samples.

9.2.3 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.

Individual subject global physician assessment is listed in Listing 16.2.6.3. Treatment will be rated as success when the GPA score equals 1 or 2. The assessment of treatment success by the physician will be summarized with count and percentage as well as 95% CI as Table 14.2.3 using FA and PP samples.

Subgroup analysis of assessment of treatment success by age group (< 24 months old and ≥ 24 months old) will be also summarized with count and percentage as well as 95% CI as Table 14.2.8 using FA and PP samples.

Subgroup analysis of assessment of treatment success by weight group (in infants less than 9 kg, in infants from 9 kg to < 13 kg, in children from 13 kg to 27 kg, and in children of more than 27 kg) will be also summarized with count and percentage as well as 95% CI as Table 14.2.13 using FA and PP samples.

9.2.4 Number of Stools and Watery Stools per Day for Toilet-Trained Subjects

Number of stools per day as well as number of watery stools per day from start of treatment and until end of study treatment will be summarized as Table 14.2.4 using FA and PP samples.

Subgroup analysis of number of stools per day as well as number of watery stools by age group (< 24 months old and ≥ 24 months old) will be also summarized as Table 14.2.9 using FA and PP samples.

9.2.5 Number of Stools and Watery Stools (Additional Table Requested by Abbott)

Number of stools as well as number of watery stools from start of treatment and until end of study treatment and for each day of the study will be summarized as Table 14.2.5 using FA and PP samples.

Subgroup analysis of number of stools as well as number of watery stools by age group (< 24 months old and ≥ 24 months old) will be also summarized as Table 14.2.10 using FA and PP samples.

10.EXTENT OF EXPOSURE AND DRUG COMPLIANCE

The randomization (only for Protocol Version dated 09 OCT 2017) will be listed in Listing 16.2.5.1.

All study drug dispensation and retrieve to each subject will be listed in Listing 16.2.5.2. Individual subject study drug administration record will be listed in Listing 16.2.5.2. In listing 16.2.5.2, for data collection of Racecadotril dosage, a NTF (Abbott_RACE3002_NTF_Racecadotril dosage per sachet_20190321) from Abbott is adapted to extract the dosage with unit from column of "Relevant Information Related to Study Drug Dispensation".

10.1 Extent of Exposure

The way of computing the extent of exposure is listed as below,
The extent of exposure = The date of completion/ termination of the study treatment drug intake - The date of the first study treatment drug intake) + 1]

Number of sachets scheduled to be taken during that treatment period is the collected data from diary card before the last dose (last dose was defined the first dose of the next day after recovery). The extent of exposure for the treatment group will be summarized as Table 14.1.3 using Safety, FA and PP Samples.

10.2 Drug Compliance

The way of computing the drug compliance is listed as below,
The study drug compliance = Number of sachets a subject takes during the treatment period / Number of sachets scheduled to be taken during that treatment period)*100%

The drug compliance for the treatment group will be summarized as Table 14.1.3 using Safety, FA and PP samples as well.

11.SAFETY ANALYSIS

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

11.1 Adverse Events

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.

All adverse event data will be listed in Listing 16.2.7. A general summary of all AEs, TEAEs and SAEs will be provided in Table 14.3.1.1.

Other summary tables for adverse events will be summarized:

- Table 14.3.1.2: Incidence of Treatment-Emergent Adverse Events - MedDRA
- Table 14.3.1.3: Incidence of Treatment-Emergent Adverse Events >= 5% of the Subjects in the Treatment Group
- Table 14.3.1.4: Incidence of Treatment - Emergent Adverse Events by Reasonable Possibility for a Causal Relationship - MedDRA
- Table 14.3.1.5: Incidence of Treatment - Emergent Adverse Events by Severity – MedDRA

Subgroup analysis of number of stools per day as well as number of watery stools by age group (< 24 months old and ≥ 24 months old) will be also summarized:

- Table 14.3.1.6: Subgroup of Treatment-Emergent Adverse Events
- Table 14.3.1.7: Subgroup of Incidence of Treatment-Emergent Adverse Events - MedDRA
- Table 14.3.1.8: Subgroup of Incidence of Treatment-Emergent Adverse Events >= 5% of the Subjects in the Treatment Group
- Table 14.3.1.9: Subgroup of Incidence of Treatment - Emergent Adverse Events by Reasonable Possibility for a Causal Relationship - MedDRA
- Table 14.3.1.10: Subgroup of Incidence of Treatment - Emergent Adverse Events by Severity - MedDRA

11.2 Vital Signs

Vital signs including height and weight, body temperature, Systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate will be listed in Listing 16.4.1. 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. Individual subject body temperature in diary card will be listed in Listing 16.4.2.

Vital sign values at each time point collected will be summarized using descriptive statistics (n, mean, SD, median, min and max) as well as the percentage of abnormal results with frequency tables (count and percentage). The change form baseline will be summarized for each measurement using descriptive statistics (n, mean, SD, median, min and max). The overall summary table will be summarized as Table 14.3.5.1. The normal ranges for temperature, heart rate (pulse rate) and blood pressure can be referred to Table 2 and Table 3. While normal ranges of body height and weight will be based on the percentile of World Health Organization (WHO) Child Growth Standards.

Subgroup analysis of vital signs by age group (< 24 months old and ≥ 24 months old) will be also summarized as Table 14.3.5.2.

Table 2 Normal Temperature Ranges

Measurement method	Normal temperature range
Rectal	36.6℃ to 38℃ (97.9℉ to 100.4℉)
Ear	35.8℃ to 38℃ (96.4℉ to 100.4℉)
Oral	35.5℃ to 37.5℃ (95.9℉ to 99.5℉)
Axillary	34.7℃ to 37.3℃ (94.5℉ to 99.1℉)

Source: Temperature measurement in paediatrics, Paediatr Child Health. 2000 Jul-Aug; 5(5): 273 – 276.

Table 3 Normal Heart Rate (Pulse Rate), Body Pressure and Respiratory Rate Ranges according to Age

Age	Heart Rate (Pulse Rate) (bpm)	Blood Pressure (mmHg)
0-3 month	100-150	65-85/45-55
3-6 month	90-120	70-90/50-65
6-12 month	80-120	80-100/55-65
1-3 year	70-110	90-105/55-70
3-6 year	65-110	95-110/60-75

Source: Kliegman, R.M., et al. Nelson Textbook of Pediatrics edition 20.

11.3 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 physical examinations will be listed in Listing 16.4.3.

11.4 Additional Comments

Individual subject additional comments will be listed in Listing 16.4.4.

12.COMPUTER METHODS

All statistical analyses will be conducted using SAS® software, Version 9.3 of the SAS System for Windows 7.