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ICDDRB: Centre for Health & Population Research RRC APPLICATION FORM

RESEARCH PROTOCOL

<2001-009>

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Protocol No: Date received:

RRC Approval: Yes/ No Date:

ERC Approval: Yes/No Date:

Project Title: A single centre, open, phase II study to evaluate the population pharmacokinetics and safety of racecardotril in the treatment of acute diarrhoea in children aged one to five years in Bangladesh

Theme: *(Check all that apply)*

- ☐ Nutrition
- ☐ Emerging and Re-emerging Infectious Diseases
- ☐ Population Dynamics
- ☐ Reproductive Health
- ☐ Vaccine evaluation
- ☐ Environmental Health
- ☐ Health Services
- ☐ Child Health
- X Clinical Case Management
- ☐ Social and Behavioural Sciences

Key words: Racecadotril, Acute watery diarrhoea, Childhood, Pharmacokinetcis

Principal Investigator: **Wasif Ali Khan** **Division: CSD** **Phone: 880-2-8821751-60 / 2333 (Ext)**
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GPO Box -128, Dhaka-1000

Co-Principal Investigator(s): Prof. George J Fuchs

Co-Investigator(s): Mr. MA Wahed

Student Investigator/Intern:

Collaborating Institute(s):

Population: Inclusion of special groups *(Check all that apply)*:

Gender
- X Male
- X Females

Age
- ☐ 0 – 5 years
- ☐ 5 – 9 years
- ☐ 10 – 19 years
- ☐ 20 +
- ☐ > 65

- ☐ Pregnant Women
- ☐ Fetuses
- ☐ Prisoners
- ☐ Destitutes
- ☐ Service providers
- ☐ Cognitively Impaired
- ☐ CSW
- X Others (specify age **1 year to 5 years**)

Project / study Site *(Check all the apply)*:

- X Dhaka Hospital
- ☐ Matlab Hospital
- ☐ Matlab DSS area
- ☐ Matlab non-DSS area
- ☐ Mirzapur
- ☐ Dhaka Community
- ☐ Chakaria
- ☐ Abhoynagar
- ☐ Mirsarai
- ☐ Patyia
- ☐ Other areas in Bangladesh _____
- ☐ Outside Bangladesh
  name of country: _____
- ☐ Multi centre trial
  (Name other countries involved)

Type of Study *(Check all that apply)*:

- ☐ Case Control study
- ☐ Community based trial / intervention
- ☐ Program Project (Umbrella)
- ☐ Secondary Data Analysis
- ☐ Clinical Trial (Hospital/Clinic)
- ☐ Family follow-up study
- ☐ Cross sectional survey
- ☐ Longitudinal Study (cohort or follow-up)
- ☐ Record Review
- ☐ Prophylactic trial
- ☐ Surveillance / monitoring
- X Others - **Pharmacokinetic**

Revised on: 17 October 2000

RECEIVED 10 OCT 2004

Targeted Population *(Check all that apply)*:

X No ethnic selection (Bangladeshi)
☐ Bangalee
☐ Tribal groups
☐ Expatriates
☐ Immigrants
☐ Refugee

Consent Process *(Check all that apply)*:

X Written
☐ Oral
☐ None
X Bengali language
X English language

Proposed Sample size: Total sample size: 90

Sub-group _____ ☐ _____ ☐

_____ ☐ _____ ☐

Determination of Risk: Does the Research Involve *(Check all that apply)*:

☐ Human exposure to radioactive agents?
☐ Fetal tissue or abortus?
☐ Investigational new device?
(specify_____)
☐ Existing data available from Co-investigator
☐ Human exposure to infectious agents?
X Investigational new drug
☐ Existing data available via public archives/source
☐ Pathological or diagnostic clinical specimen only
☐ Observation of public behavior
☐ New treatment regime

Yes/No

X ☐ Is the information recorded in such a manner that subjects can be identified from information provided directly or through identifiers linked to the subjects?

☐ X Does the research deal with sensitive aspects of the subject's behavior; sexual behavior, alcohol use or illegal conduct such as drug use?

Could the information recorded about the individual if it became known outside of the research:

☐ X a. place the subject at risk of criminal or civil liability?

☐ X b. damage the subject's financial standing, reputation or employability; social rejection, lead to stigma, divorce etc.

Do you consider this research *(Check one)*:

☐ greater than minimal risk
☐ no risk
X no more than minimal risk
☐ only part of the diagnostic test

Minimal Risk is "a risk where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical, psychological examinations or tests. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as a part of routine physical examination".

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Yes/No	
X ☐	Is the proposal funded? If yes, sponsor Name: **GlaxoSmithKline (GSK)**

Is the proposal being submitted for funding? Not Applicable

☐ ☐ If yes, name of funding agency: Not Applicable

Do any of the participating investigators and/or their immediate families have an equity relationship (e.g. stockholder) with the sponsor of the project or manufacturer and/or owner of the test product or device to be studied or serve as a consultant to any of the above?

IF YES, submit a written statement of disclosure to the Director.

Dates of Proposed Period of Support	**Cost Required for the Budget Period ($)**
(Day, Month, Year - DD/MM/YY)	*a. Ist Year 2nd Year 3rd Year Other years*
Beginning date As soon as Possible	
End date Patient recruitment 6 months	*b. Direct Cost :* US$ 105,053 *Total Cost :* US$ 131,316

Approval of the Project by the Division Director of the Applicant

The above-mentioned project has been discussed and reviewed at the Division level as well by the external reviewers. The protocol has been revised according to the reviewer's comments and is approved.

Prof. George J Fuchs
Name of the Division Director

Signature

26 Mar 01
Date of Approval

Certification by the Principal Investigator

I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

Signature of PI

Date: 26/03/2001

Name of Contact Person (if applicable)

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[X] Check here if appendix is included

PROJECT SUMMARY: Describe in concise terms, the hypothesis, objectives, and the relevant background of the project. Describe concisely the experimental design and research methods for achieving the objectives. This description will serve as a succinct and precise and accurate description of the proposed research is required. This summary must be understandable and interpretable when removed from the main application. **(TYPE TEXT WITHIN THE SPACE PROVIDED).**

Principal Investigator: WASIF ALI KHAN

Project Name A single centre, open, phase II study to evaluate the population pharmacokinetics and safety of racecardotril in the treatment of acute diarrhoea in children aged one to five years in Bangladesh.

Total Budget: US$ 131,316 Beginning Date: As soon as possible Ending Date: 6 months patient recruitment

Acute watery diarrhoea (AWD) is still a major problem in developing countries including Bangladesh and other countries around the globe. Patients suffering from acute diarrhoea may have profuse fluid and electrolyte loss resulting in severe dehydration, hypovolamic shock and ultimately death unless timely and proper management is not initiated. At present oral rehydration therapy (ORT) for rehydration has been the only choice for treatment and been accepted worldwide. Many antisecretary drugs have been tried in AWD, however, considering the merits and disadvantages of those agents, no drug have been found acceptable for widespread use in acute diarrhoea.

Recently, an enkephalinase inhibitor "racecardotril", that acts on the opiate receptors and by preventing degradation of enkephalin has shown some exciting hope for future use in adjunct to ORT in the management of all acute diarrhoeal illness among children. Although, racecardotril has already been proven clinically to be safe for children. The pharmacokinetic (Pk) parameters of racecardotril in children with acute diarrhoea are very limited. We propose to study the Pk parameters of racecardotril in mild to moderate malnourished (weight for length 70% to 89%) children, age 1 to 5 years, either sex, duration of diarrhoea ≤ 3 days, presenting with signs and symptoms of some dehydration, having no chronic illness, received no antimotility, antisecretary or antimicrobial agent within the last seven days, written informed consent obtained from the parents or guardian. Racecardotril will be administered per oral 1.5 mg/kg every 8 hourly in children hospitalised for acute watery diarrhoea until diarrhoea cease (maximum 9 dose). We will measure the plasma concentrations of the active metabolite, ""thiorphan" by means of enzyme immunoassay in 90 children. Four blood samples will be taken at varying times from every patient during the study to charecterise the population PK of thiorphan following oral administration of racecadotril. The influence of various patient characteristics, such as age, weight and gender, on thiorphan PK will be examined if data permit. The primary endpoint is the characterisation of the population pharmacokinetics of thiorphan following oral administration of racecadotril in this paediatric population. Secondary endpoints are the safety parameters and time taken to recovery of diarrhoea.

The Pk profile of racecardotril in childhood acute diarrhoea will constitute an important advancement for selecting the optimal dose and interval in adjunct to fluid replacement. This is important because many or most children with AWD in developing countries (where problem is most) are mild to moderately malnourished.

SmithKline Beecham

International Medical Department

CONFIDENTIAL

52607/RACECADOTRIL (HIDRASEC™)

A single centre, open, phase II study investigating the population pharmacokinetics and safety of racecadotril in the treatment of acute diarrhoea in children aged one to five years in Bangladesh

Protocol number	52607/ 016
Final Draft	14.02.2001

SmithKline Beecham

Clinical Unit :	Tropical Medicines, International Medical Department.
Drug Name :	Racecadotril , Hidrasec ™
Compound No :	SB 52607
Protocol Title:	A single centre, open, phase II study investigating the population pharmacokinetics and safety of racecadotril in the treatment of acute diarrhoea in children aged one to five years in Bangladesh
CPMS No :	52607 / 016
Principal Investigator	Dr Wasif Ali Khan
Co Principal Investigator	Prof. George Fuchs
Co Investigator	Mr M.A. Wahed

Authors:

Dr Wasif Ali Khan
Dr George Fuchs
Mr M.A. Wahed
Sally Coulden
Dr. John Horton
Dr Sarah Siederer
Dr Jagdev Sidhu

SB Site Monitor :

I, the undersigned, have reviewed this protocol, including Appendices and I will conduct the study as described and will adhere to the Ethical and Regulatory Considerations stated. I have read and understood the Investigator Brochure.

Investigator ..... **Date** .....

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List of Appendices

SYNOPSIS

Compound / Protocol No. SB – 52607 / 016

Protocol Title A single centre, open, phase II study investigating the population pharmacokinetics and safety of racecadotril in the treatment of acute diarrhoea in children aged one to five years in Bangladesh

Rationale

Acute watery diarrhoea (AWD) remains a major problem in developing countries. Patients suffering from acute diarrhoea may have profuse fluid and electrolyte loss resulting in severe dehydration, hypovolamic shock and ultimately death unless timely and proper management is not initiated. At present oral rehydration therapy (ORT) for rehydration has been the only choice for treatment and been accepted worldwide. The use of adjunct therapy in oral rehydration remains controversial, but agents that effectively inhibit the net secretion of fluid and electrolytes by the intestine without serious side effects may have a place. They will, of course, only be effective if there is a secretory component to the diarrhoea.

Within the last decade, an enkephalinase inhibitor "racecadotril" has been developed. Racecadotril is the pro-drug of thiorphan, which acts on the opiate receptor of the digestive tract preventing degradation of enkephalin, this has shown some exciting hope for future use as an adjunct to ORT in the management of all acute diarrhoeal illness among children. Racecadotril has already been proven clinically to be safe for children. However, information on the paediatric pharmacokinetics (PK) of thiorphan following racecadotril administration in acute watery diarrhoea is very limited.

In this proposed study the population PK of thiorphan will be characterised in mild to moderately malnourished children administered racecadotril, to date there is insufficient information on this pharmacokinetic aspect.

The pharmacokinetic profile of thiorphan in childhood AWD will constitute an important advancement in dosing of racecadotril in malnourished children as an adjunct to fluid replacement. This is important because many or most children with AWD in developing countries are less well nourished or malnourished.

Objectives(s)

Primary To characterise the population pharmacokinetics of thiorphan following oral administration of racecadotril dosed according to body weight bands ~ equivalent to 1.5mg/kg in children with acute watery diarrhoea aged 1 to 5 years suffering from mild to moderate malnutrition.

Secondary To evaluate the safety profile (adverse experiences, laboratory safety parameters and concomitant medication) of racecadotril in children aged 1 to 5 years with acute watery diarrhoea and to measure time taken to recovery of diarrhoea. *(12hours with no loose or watery stools or two consecutive soft / formed stools)*

Study Population

90 children aged between 1 and 5 years will be enrolled at the International Centre for Diarrhoeal Disease Research Dhaka, Bangladesh. This centre treats more than 100,000 diarrhoeal patients each year. This is a single centre study.

Study Design

This is a single centre, open, phase II study to characterise the population pharmacokinetics and safety of racecadotril in the treatment of acute diarrhoea in children aged one to five years in Bangladesh

Children who fulfil the study entry criteria and have written, dated, informed consent will nominally receive racecadotril 1.5mg/kg three times daily po, this treatment will be given as an adjunct to standard fluid replacement therapy for a maximum of 3 days and each patient will be randomised into one of two pharmacokinetic sampling regimes. All children will be admitted to hospital for the course of the study.

Pharmacokinetic Sampling

Four blood samples will be taken at varying times during the study to charecterise the population PK of thiorphan following oral administration of racecadotril. The influence of various patient characteristics, such as age, weight and gender, on thiorphan PK will be examined if data permit.

Endpoints

The primary endpoint is the characterisation of the population pharmacokinetics of thiorphan following oral administration of racecadotril in this paediatric population.

Secondary endpoints are the safety parameters and time taken to recovery of diarrhoea. *(12hours with no loose or watery stools or two consecutive soft / formed stools)*

SAFETY PARAMETERS:

The following will be evaluated:
Adverse experiences, laboratory safety parameters and concomitant medication. To note that this compound 'Racecadotril' is currently licensed for use in patients with acute watery diarrhoea it is nevertheless of paramount importance to continue to collect all safety data.

1.0 INTRODUCTION

Infections of the gastrointestinal tract, especially infectious diarrhoea, are amongst the most common debilitating infectious diseases, afflicting people of all ages around the world. Although an etiologic agent is not found in many cases, the infectious nature of most acute diarrhoeal diseases is suggested by their epidemiological behaviour showing case clustering. On a global scale, diarrhoeal diseases are second only to cardiovascular diseases as a cause of death [1]; they are the leading cause of childhood death, and, in some populous, developing areas, they are responsible for more years of potential life loss than all other causes combined. [2] In developing countries, estimates of the annual incidence of diarrhoea vary from 3.3 episodes,[3] to 7.9 episodes,[4] to 10 episodes in a peri-urban area in Lima.[5]

Gastro-enteritis exerts its greatest toll in children under 5 years old. Estimates are that 4,600,000 - 6,000,000 children die each year (> 12,600/day) in Asia, Africa and Latin America [6-9] and that over 10,000 die from diarrhoea each year in the United States. [10,11] Over 13 percent of the children born in certain parts of Latin America die before their fifth birthday. In more than half, diarrhoea is the major or associated cause of death.[2] In addition to the morbidity and mortality associated with diarrhoeal disease, it is also a major drain on health resources in developing countries. For example, it has been estimated that in Indonesia the per capita health budget is $5.41 per annum and that $2.50 per annum is spent per child in the management of diarrhoeal disease.[12]

In general, paediatric diarrhoea is most often due to viral enteropathogens. Approximately 60% of the cases in most hospital-based surveys are due to virus. Bacterial enteropathogens are responsible for the majority of the remaining cases where a pathogen is found. An institutional setting in which hygiene is difficult and enteric infections are increasingly appreciated is in day care centres. Numerous outbreaks have been reported in association with virus, bacteria or parasites. [13-18] For the majority of the pathogens causing non-inflammatory diarrhoea, their principal site of action is the upper small intestine. Since the transit time is so rapid through the small intestine, an important pathogenic factor is the ability to adhere to the small intestine mucosa. The mechanisms more commonly employed in producing diarrhoea are osmotic and secretory.

The mainstay of management of diarrhoeal disease is the assessment of dehydration and the appropriate replacement of fluid and electrolytes. [19] Originally, rehydration was exclusively intravenous. A major advance was made when an effective oral rehydration regimen was devised. Glucose-electrolyte solutions are highly effective in treating dehydration in acute diarrhoea by stimulating glucose coupled sodium transport in the small intestine. [20-22] However, despite this important contribution to treatment, acute diarrhoea remains a cause of considerable morbidity and appreciable mortality, mainly in developing but also in developed countries of the world. In a survey that used the new PAHO/WHO methodology for data collection and conducted in 9 state capitals in Northeast Brazil has shown that few diarrhoea patients received care that strictly followed the PAHO/WHO/Ministry of Health treatment guidelines. The procedure to assess the patient's hydration status was correct only in 8% of the time and only 1% of the health workers provided correct advice to the caretaker on prevention and home care aspects of diarrhoeal diseases. The procedure used to rehydrate patients with oral rehydration solutions (ORS) was correct in only 6% of the cases.[23]

The use of adjunct therapy in oral rehydration remains controversial, but agents that effectively inhibit the net secretion of fluid and electrolytes by the intestine without serious side effects may have a place. They will of course only be effective if there is a secretory component to the diarrhoea. The value of loperamide as an adjunct in treating diarrhoea in children has been demonstrated [19] , probably as a result of reduced gastrointestinal motility, the effect being dose-dependent is of questionable clinical importance. Abdominal distension has been reported in infants and young children treated with loperamide and as a result, the manufacturer has halted the sale of loperamide drops and restricted the distribution of loperamide syrup in developing countries. [24] A study conducted in cholera patients in which chlorpromazine was added to a routine treatment regimen, including antibiotics and oral rehydration therapy (ORT) showed no overall difference between treatment groups; however, there was a suggestion that chlorpromazine did have some antisecretory effect in severely purging children. [25] Unfortunately, patients taking chlorpromazine also developed somnolence which interfered with the administration of oral rehydration fluid; hence, chlorpromazine is not recommended. If another drug could be identified which shows an antisecretory activity without producing somnolence, it might still be useful. Other drugs have been tested in-patients [26-29]; however, they showed either minimal or no benefit. In summary, for many decades there has been a search for an agent that will inhibit intestinal secretion and thereby reduce stool volume and the volume of fluid required for rehydration, none so far have proved to be of use in routine clinical management.

The enkephalins, the endogenous opiate substances first discovered in 1975, play an important physiological role acting as neurotransmitters most notably along the digestive tract. After their release and the stimulation of opiate receptors, the enkephalins are rapidly inactivated by enkephalinase. It was assumed that preventing this degradation would provide a therapeutic means to protect endogenous enkephalins and thereby reinforce their physiological actions. The discovery and characterisation of enkephalinase in brain and the demonstration that this peptidase was responsible for the inactivation of endogenous enkephalins paved the way for the novel therapeutic approach.[30,31]

Enkephalinase is present all along the gastrointestinal tract. Enkephalins are endogenous opioids which elicit intestinal antisecretory activity without affecting intestinal transit or motility. Tiorfan™, by the inhibition of enkephalinase reinforces the physiological activity of endogenous enkephalins and shows intestinal antisecretory activity [32-34] without affecting intestinal transit. This approach is novel: although other antidiarrhoeals also act on the enkephalin receptor pathway, they act by mimicking endogenous enkephalins at both lambda and mu receptors. This approach results in decreased motility and intestinal transit, and causes the side effects of drugs such as loperamide. In diarrhoeal disease states the lambda receptor is upregulated, and thus reduction of enkephalin breakdown by inhibition of enkephalinases will promote lambda-type activity at the expense of mu activity. This will lead to a reduction of salt/water excretion without any transit effects.

Pharmacokinetic profiles of racecadotril were studied using the level of plasma enkephalinase activity as a measure. After a single oral administration of racecadotril, the maximal inhibition (C_{max}) of enkephalinase was 80%. The peak inhibition (T_{max}) is observed between 1 and 2 hours after the administration of the drug. The biological half-life was three hours. With 300 mg, enkephalinase is significantly inhibited for up to 8 hours. Kinetic parameters are identical after a single and after multiple administration. A study of the pharmacokientics of thiorphan, the active metabolite of racecadotril, was carried out in 6 children with diarrhoea

aged 1.5 to 12 months. They received a single dose of racecadotril 1% granulated powder, average dose 1.4 mg/kg just before food intake. In this data set the absorption/ conversion racecadotril to thiorphan was rapid (average Tmax 2.5 hour) and concentrations of thiorphan generally greater than 60 nmol/l, were observed for at least 4 hours. Thiorphan was still detectable in the majority of children 8 hours after the drug intake. (Data on File) However, this dataset was limited (n=6 infants) and further information is required to consolidate the pharmacokinetics in a wider paediatric population presenting with variariable nutritional deficits.

Studies of pharmacodependence and tolerance (rat, monkey) demonstrated the absence of addictive properties of racecadotril. Racecadotril is distributed in peripheral organs and does not cross the blood barrier after oral administration. Pharmacological studies in animals have demonstrated the activity of racecadotril on several experimental models of diarrhoea. The intestinal antisecretory effect is observed only in the case of hypersecretion and not in the basal state, and is inhibited by naloxone demonstrating the enkephalin/enkephalinase pathway of racecadotril activity. [32]

Clinical studies demonstrated, both against placebo and loperamide, the efficacy of racecadotril in acute diarrhoea. The efficacy of racecadotril has been demonstrated in three double-blind studies against placebo [35-37] and in two double-blind studies against loperamide. [38,39] Its antidiarrhoeal effect seems to result primarily from an antisecretory mechanism. This may explain both the more rapid resolution of symptoms related to fluid accumulation in a distended bowel and the much lower occurrence of constipation in racecadotril -treated patients. In addition to the improved patient comfort (and social cost) that can be expected from the use of antidiarrhoeal agents acting via a purely antisecretory mechanism, these drugs are likely to prevent several side effects associated with the use of antimotility drugs. These include facilitation of bacterial colonisation, invasion of *Shigella*, extension of the period of excretion of bacterial pathogens, and precipitation of ileus and bowel dilatation ('toxic megacolon')[37-39]

A double blind, multicentric study was conducted in 102 children suffering from acute diarrhoea, comparing the efficacy and the safety of racecadotril and loperamide in children older than 2 years, as loperamide is contra-indicated in children below 2 years. The study showed a similar efficacy for racecadotril and loperamide; however, racecadotril was significantly better than loperamide for two important criteria related to tolerance: number of associated treatments needed and the frequency of secondary constipation, both significantly lower with racecadotril.[40] A double-blind, placebo-controlled study was conducted in children aged between 3 months and 4 years old with acute diarrhoea. This multicentric study included 172 children hospitalised for acute diarrhoea in 13 centres in France. This study demonstrated that racecadotril significantly reduced stool output during the first 24 - 48 hours of treatment, duration of diarrhoea, duration of treatment and frequency of dehydration in children with acute diarrhoea. [41] In the most recently published paediatric study,[42] 135 children took part in a single centred, double blind, placebo-controlled study, comparing racecadotril to standard treatment. The mean stool output at 48hrs demonstrated a 46% reduction in stool output within the racecadotril group compared to placebo. Clinical safety data were collected in 3 studies involving 280 patients, of whom, 147 received racecadotril. The frequency of side-effects is similar for racecadotril and placebo, thus suggesting that they are possibly related to acute diarrhoea and not to racecadotril. The frequency of side effects is significantly lower for racecadotril (11.5%) than loperamide (30%). An episode of secondary constipation was observed more frequently with loperamide than racecadotril confirming the

lack of transit inhibition under racecadotril. In children from 1 month to 2 years, the frequency of side effects with racecadotril does not differ from placebo and shows the lack of CNS side effects. [43] Please refer to the Investigator Brochure for a review of pre-clinical and clinical studies of racecadotril.

The objective of this study is to characterise the population pharmacokinetics of thiorphan, following racecadotril administration, in paediatric patients aged 1 to 5 years old, suffering from mild to moderate malnutition. The results will add significant pharmacokinetic and safety data support to the already existing data in paediatrics.

2.0 OBJECTIVES

2.1 Primary

To characterise the population pharmacokinetics of thiorphan following oral administration of racecadotril dosed according to body weight bands ~ equivalent to 1.5mg/kg in children with acute watery diarrhoea aged 1 to 5 years suffering from mild to moderate malnutrition.

2.2 Secondary

- To evaluate the safety profile of racecadotril in children aged 1 to 5 years with acute watery diarrhoea.
- To measure time taken to recovery of diarrhoea.
  (12hours with no loose or watery stools or two consecutive soft / formed stools)

3.0 STUDY SITE & POPULATION

This study will be undertaken at the Dhaka hospital of the International Centre for Diarrhoea Disease Research, Bangladesh (ICDDR,B). Reknowned globally as a centre of excellence for diarrhoeal disease research the centre admits an average of > 100,000 patients annually, of which there are on average > 25,000 children in the 1 to 5 year age range annually. In 2000, 107,474 patients have been admitted for treatment of their diarrhoea. The high season for diarrhoea in Dhaka falls into two seasons April to June and September to November.

The study population will be drawn from the normal population of patients entering the hospital for treatment, the patients and their parent/guardian will have the details of the study explained to them and if eligible, will be asked to give consent/assent for participation. The study start is planned for June 2001.

Recruitment procedures

Before the study begins the principle Investigator will fully brief the study team on the objectives and procedures involved in carrying out this study. The study team will comprise

of the principle investigator and a full time paediatrically trained medical officer, there will be a research officer and assistant in addition to three full time study nurse, two ward attendants and a data manager. All medical staff will be dedicated full time to this project excepting the principal Investigator who has allocated 70% of his time for this study.

This treatment will be given as an adjunct to standard fluid replacement therapy for a maximum of 3 days. Once randomised onto the study all children will admitted to hospital for the course of the study.

All children will be evaluated by the clinician to determine if they meet the entry criteria of the study, they will then participate in a short screening period when observations will be taken and blood specimens taken for analysis. Children requiring only ORS as rehydration therapy will be admitted onto this study. Once randomised they will be observed closely and all observations will be documented in the CRF up until 24 hours following resolution of their diarrhoea, (defined as 12 hours with no stools or 2 consecutive formed stools), or until the patient is discharged from the study.

4.0 STUDY POPULATION

4.1 Number of subjects

90 clinically evaluable patients, aged ≥1 years to ≤5 years inclusive, presenting with acute diarrhoea having started less than 72 hours prior to being enrolled at the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B) in Dhaka.

4.2 Inclusion Criteria

Patients may be included into the screening of this study if the following criteria are satisfied:

1. Patients aged ≥1years to ≤5 years.
2. Gender: Male or female
3. Nutritional status : mild to moderate malnutrition (weight for length : 70 to 89%)[44]
4. Duration of illness: A clinical history of acute watery diarrhoea without faecal blood or mucus ≤3 days.
5. Clinical signs and symptoms of some dehydration entering screening. (refer to Appendix D)
6. Written informed consent for participation in the study from either of the parents, or guardian.

4.3 Exclusion Criteria

Patients should be excluded from the screening of this study if any of the following criteria apply:

1) Patients presenting with severe dehydration according to WHO guidelines (refer to Appendix D)

2) Patient presenting with severe malnutrition (weight for length: <70%)

3) Patient with chronic or iatrogenic diarrhoea or dysenteric syndrome characterised by blood in the stool.

4) History of receiving an antimotility, antisecretory or antimicrobial agent within the past seven days.

5) Concomitant infection requiring antimicrobial therapy.

6) Patient has a concomitant infection, any known chronic illness or other underlying disease that could compromise the pharmacokinetic evaluation of racecadotril.(clinicians opinion)

7) Patients previously participating in the study

8) Patients participating in any clinical study within one month prior to study entry.

9) Patients parents/guardians refusing informed consent

5.0 CONDUCT OF THE STUDY

5.1 Ethics and Regulatory Considerations

The study will be conducted according to Good Clinical Practice and the Declaration of Helsinki (Protocol Appendix A) and relevant institutional guidelines.

5.1.1 Ethics Review Committee/Institutional Review Board (ERC/IRB)

ERC/IRBs must be constituted according to the local laws/customs of the participating country.

This protocol will be submitted to an appropriate Committee or Board and their written unconditional approval obtained and submitted to the sponsor before commencement of the study. SB will supply relevant data for the investigator to submit to the hospital /university/independent ERC/IRB for the protocol's review and approval. Verification of the ERC/IRB unconditional approval of the protocol and either the written informed consent statement or sample oral witnessed consent form with written information to be given to the subjects will be transmitted to the SB Study Monitor prior to shipment of drug supplies and CRFs to the site. This approval must refer to the study by exact protocol title and number, identify the documents reviewed and state the date of review.

The ERC/IRB must be informed by the investigator of all subsequent protocol amendments and of serious or unexpected adverse experiences occurring during the study which are likely to affect the safety of the subjects or the conduct of the study. Approval of such changes must be transmitted in writing to the SB Study Monitor via the investigator.

5.1.2 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki (Protocol Appendix A) should be implemented in each clinical study before protocol-specified procedures are carried out.

Information should be given in both oral and written form whenever possible and deemed appropriate by the ERC/IRB. Subjects, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

The consent form generated by the investigator with the assistance of SB, must be approved (along with the protocol) by the ERC/IRB and be acceptable by SB. Consent forms must be in a language fully comprehensible to the prospective subject. Informed consent shall be documented by the use of a written consent form approved by the ERB/IRB and signed by the subject or the subject's legally authorised representative.

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations. This form may be read to the subject or the subject's legally authorised representative, but, in any event, the investigator shall give the either the subject or the representative adequate opportunity to read it before it is signed.

Consent must be documented either by the dated signature of the subject or by the subject's legally authorised representative. The signature confirms the consent is based on information that has been understood. Each subject's

signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or SB professional and Regulatory Compliance persons.

In countries where written informed consent contravenes local custom, informed consent may be gained orally. Full and comprehensive information must be communicated to the potential subject (or his legal representative) in the presence of a witness. The witness will be an independent third party, i.e., not a nominated co-investigator. The witness will sign the informed consent form (testifying that informed consent has been given orally) along with the investigator (or his/her nominated representative).

5.2 General Instructions

A case report form (CRF) should be completed for each patient entered into the study.

Patients will receive study medication under supervision of the study physician or nurse. At the end of the study, the investigator, assisted by the SB Clinical Research Scientist, will return the used and unused medication together with a completed drug accountability form.

5.3 Study Flow

See Appendix E for the outline of study flow.

5.3.1 Screening (Day 1, Hour -4 to 0)

The screening visit will consist of the following assessments; all information will be recorded in the Case Report Form.

- The patient will be checked for compliance with the Inclusion/Exclusion criteria
- Informed written consent will be obtained from the parent / legal guardian by the investigating physician before study specific procedures are undertaken before entry into the study.
- A patient demography, comprising of age, sex and race.
- Evaluation of vital signs (supine pulse, weight & height) will be performed and where possible the same person should take these measurements on each occasion during the study.
- A medical/surgical history will be taken as well as performing a full physical examination.

- Documentation of any baseline signs or symptoms eg. Episodes of vomiting.
- Duration of diarrhoea prior to inclusion into the study and the number of stools in the preceding 24 hours will be recorded.
- Assessment of dehydration category as defined in section *5.4.1.*
- Assessment of nutritional status will be recorded
- Documentation of prior or concomitant medication
- A blood sample will be obtained to measure Haematocrit, Complete blood count, Platelets, Serum specific gravity, Serum total protein, Serum sodium, potassium, chloride and bicarbonate, LFT's and Serum creatinine. These will be recorded in the Case Record Form and if abnormalities are found they will be followed up daily until complete resolution or until the results are no longer considered clinically significant.
- A stool sample will be obtained to identify pathogens.

5.3.2 Randomisation into the study (Day 1, Hour 0)

At this timepoint, which can lie between 1-3 hours after completing screening the following assessments/procedures will be carried out:

- Number of loose / watery stools
- Number of vomiting episodes
- Vital signs (Weight, heart rate and temperature)
- Assessment of dehydration status
- Collection of information on concomitant medication
- Collection of information on adverse experiences
- Assessment of eligibility for inclusion into the study.
- Randomisation and administration of study medication.

5.3.3 Patient randomisation

All patients entered into this study will receive an oral administration of racecadotril dosed according to body weight bands ~ equivalent to 1.5mg/kg, in

addition to standard ORS rehydration solution. Treatment will be continued until resolution, *(12hours with no loose or watery stools or two consecutive soft / formed stools)* or treatment for a maximum of 3 days.

Patients will be randomised into 2 groups for the pharmacokinetic sampling.
Group 1 or 2

GROUP 1		GROUP 2	
PK SAMPLE	**TIME AFTER 1st dose**	**PK SAMPLE**	**TIME AFTER 1st dose**
Sample 1	**0.5 hrs**	**Sample 1**	**1 hour**
Sample 2	**2 hrs**	**Sample 2**	**4 hours**
Sample 3	**6 hrs**	**Sample 3**	**8 hours**
Sample 4	**6 hrs after last dose of study medication**	**Sample 4**	**8 hrs after last dose of study medication**

A randomisation code will be generated by the data management company. Approximately equal numbers of patients being allocated to each weight band. Each eligible patient will be assigned the next patient number available at the centre and thereby will be assigned randomly to one of the two groups. (see 6.3 for blinding) If the patient vomits ≤ 1 hour of the first dose of medication being administered the patient must be withdrawn from the study (see 5.4.3). If the patient vomits within 10 minutes of any subsequent administrations they should be redosed. If the patient vomits on 2 consecutive occasions they must be withdrawn from the study. (see 6.3 for redosing)

Diet:

All patients will receive the standard hospital diet, major meals will be provided at three times a day. However, fluids (ORS, plan water, milk etc) will be provided to the study patients (ad. lib) at all time.

Breakfast (7am) – bread, sugar and banana;

Lunch (12.30pm) – rice, lentils and fish/meat.

Supper (7pm) rice, lentil /vegetables and meat or fish.

All food eaten by the child must be recorded in the CRF

5.3.4 On-Therapy Evaluations

Patients will be observed by study staff continuously, observations will be recorded four hourly until the 8 hour timepoint after which 8 hourly observations will be recorded until resolution of diarrhoea, *(12hours with no loose or watery stools or two consecutive soft / formed stools)*, or until the patient is discharged from the study. All patients will have a maximum of 3 days treatment.

Clinical Assessments:

- Assessment body weight
- Assessment of body temperature
- Assessment of heart rate

- Assessment of number of watery stools
- Assessment of number of formed stools
- Assessment of vomiting
- Assessment of dehydration
- Assessment of routine blood sampling if appropriate
- Collection of pharmacokinetic specimens at designated timepoints
- Collection of information on concomitant medication
- Collection of information on adverse experiences

5.3.5 End of Therapy

Patients will remain in the hospital for a minimum of 12 hours after diarrhoea resolution, *(12hours with no loose or watery stools or two consecutive soft / formed stools)* or a maximum of 3 days treatment followed by 12 hour observation period, final observations must be performed prior to discharge.

FINAL PK SAMPLE TO BE TAKEN

GROUP 1 - 6 HOURS AFTER LAST DOSE OF MEDICATION
GROUP 2 - 8 HOURS AFTER LAST DOSE OF MEDICATION

5.3.6 Study Conclusion

The following assessment will be performed at study conclusion

- Assessment of weight and vital signs
- Study medication compliance
- Collection of information on concomitant medication
- Collection of information on adverse events
- Assessment of dehydration
- Collection of stool sample (if possible)
- Collection of blood sample (safety)
- Evaluation of clinical response (see section 5.4.6)
- Did the patient complete the study as planned

5.3.7 Follow-up Evaluation

All patients randomised into the study including those that were withdrawn from the study prior to the end of therapy will be required to attend a follow up safety assessment at 7 days ±1 day after the last dose of study medication. Adverse events and concomitant medication(s) will be recorded and assessed at this visit.

Note:
Any patient that completes the study period but fails to attend the follow up visit will be classified as completing the study period as planned.(CRF p.26)

5.4 Details of study procedures

5.4.1 Dehydration Category

On admission to the hospital and once considered suitable for screening, the patient will be placed in a cholera cot, weighed and their clinical signs recorded to permit a correct assessment of dehydration. Some dehydration corresponds to 5-9%, and severe +10% dehydration, respectively. (Fluid deficit relative to body weight after hydration). Patients with severe dehydration will not be randomised. If a patient becomes severely dehydrated during the study they must be withdrawn (section 8.2)

5.4.2.Pharmacokinetic Samples

A total of 4 blood samples will be collected from each patient (unless they have been withdrawn from the study due to vomiting; see Section 5.4.3). Patients will be randomised into one of two PK sampling groups (see Section 5.3.3). Three samples will be collected after administration of the first dose as follows: 0.5, 2 and 6 hours for **Group 1** and 1, 4 and 8 hours for **Group 2**. In addition, one sample will be collected from all patients in Group1 at 6 hours after administration of their last dose and Group 2 at 8 hours after administration of their last dose.
The **date** and **exact** time of each blood sample must be recorded in the CRF. The **exact** date and time of administration of all doses administered must also be recorded in the CRF. It is **extremely important** that this information is accurately recorded.

5.4.2.1 Sample Preparation

Blood (1.5 ml) will be collected from anticubital vein following aseptic condition. A total of 4 blood samples will be collected as per schedule 5.3.3. Blood will be collected in heparinized glass tubes and directly treated with an equal volume of 1mg/ml N-ethyl-maleimide (NEM) in Phosphate buffer. Blood samples will be left for 30 minutes prior to centrifuging for 10 minutes at 800g. The plasma collected will transferred into clean polypropylene tubes, clearly labelled with patient identification and sampling time and date. Plasma samples will be stored at -20°C until analysis.

5.4.2.2 Drug Analysis

Plasma concentrations of thiorphan will be determined as per following principals:

The biologically active moiety of acetorphan, a chemical product by hydrolysis of both the ester and thioester functions of this drug. Thiorphan presents a thiol group that is easily oxidizable.

An Enyzme immunoassay has been developed at INSERM, France, using antibody raised in rabbits after immunization with NEM-thiorphan, coupled with carrier protein and using NEM-thiorphan, coupled to acetylcholinesterase as trace. A 250 µl aliquot of NEM treated plasma will be treated with 4N Perchloric acid and left at 4°C for 30 minutes. A 200 µl supernatant will be taken off after centrifugation and will be adjusted to neutral pH with 2.5M triethanolamine.

Microplates (96 wells) will be coated with specific antibodies for rabbit IgG diluted 200 times in 0.05M phosphate buffer. Assays for standard or 50 µl-diluted samples will be run in triplicates. ODs (optical densities) will be obtained at 405 nm in Microplate reader and concentrations of samples will be calculated against plot for standards of various concentrations.

5.4.3 Assessment of Vomiting

- If a patient vomits ≤ 1 hour after the time of first dose of study medication then the patient must be withdrawn from the study. The patient upon withdrawal will receive standard care for their diarrhoea by the Investigator responsible. The patient will be asked to return for a follow up visit at 7 days after discharge from hospital.
- If the patient vomits within 10 minutes of any subsequent administrations they should be redosed. Each individual episode of vomiting must be recorded in the CRF.
- If the patient vomits ≤10 minutes following a redose the patient must be withdrawn from the study. (refer to 8.2 & 8.3)

5.4.4 Assessment of Diarrhoea

5.4.4.1 Duration of diarrhoea is defined as:

The time (in hours) from randomisation and initiation of study medication to resolution of diarrhoea: *(12hours with no loose or watery stools or two consecutive soft / formed stools)*, calculated as the time of last abnormal (liquid or watery) stool.

5.4.4.2 Frequency of Diarrhoea

Number of liquid or watery stools passed during the course of the study until discharge.

Definition of stool consistency:

Watery/Liquid stool:	Stool that can be poured from one container to another.
Soft stool :	Stool that takes the shape of the container where it is poured.
Formed stool :	Stool that remains in its original shaped wherever it is poured.

5.4.5 Laboratory Evaluations

The following parameters will be measured at screening before randomisation into the study. They will then be repeated on the day of discharge if the initial tests are considered by the Investigator to be clinically normal. If the values are found to be out of range and clinically abnormal for that patient at any point during the course of the study they must then be repeated daily until the values return to a clinically normal state.

Haematology and Clinical Chemistry

The following will be evaluated:

- Haematocrit, Complete blood count, Platelets
- Serum specific gravity, Serum total protein, Serum sodium, potassium, chloride and bicarbonate, LFT's and Serum creatinin.

5.4.6 Stool Examination

On admission, stool samples will be obtained. An initial microscopic examination for semi quantitive estimation of erythrocytes leukocytes and demonstration of parasites and ova will be performed.in addition to sending a specimen to culture for *V cholerae, Shigella, Salmonella, Camphylobacter jejuni and Rota virus* species.
A repeat culture will be taken on day of discharge if this is achievable.

5.4.7 Assessment of Response at the End of Therapy

All patients will be observed closely up until resolution of diarrhoea. *(12hours with no loose or watery stools or two consecutive soft / formed stools).* Clinical response to the study drug will be assessed as follows:

Clinical success
Resolution of diarrhoea within 72 hours from the first dose of study drug administration.

Clinical failure
Patient who continued to have watery stools beyond 72 hours from the first dose of study drug administration.

Clinical Relapse
Patient whose diarrhoea had resolved before 72 hrs but recorded further watery stools (relapse) in the 12 hours observation period.

Clinical Outcome Indeterminate:
A valid assessment of clinical efficacy can not be made or a response cannot be obtained due to the patient being withdrawn from the study because of an adverse event, poor patient co-operation or extenuating circumstances.

5.5 Study Conclusion

The study conclusion page in the CRF must be completed for all patients registered onto the study irrespective of whether they have completed the treatment period or were withdrawn from the study.
All patients that enter the study must have this page completed.

6.0 STUDY MEDICATION

6.1 Dosage and Formulation

Racecadotril / Hidrasec™ will be supplied in 6mg granulated powder sachets for oral administration.

6.2 Oral rehydration Solution

A rice based oral rehydration solution will be administered as per hospital regime to all patients on the study.

6.3 Study drug administration

This study is an open label study in which all patients will receive Hidrasec + ORS

On admission to the hospital, patients will be weighed and their clinical signs recorded to permit a correct assessment of dehydration as described in Section 5.4.1. Patients for whom informed consent was obtained from the parent or legal guardian and who meet the study entry criteria will be entered into the study.

Patients will be stratified into three groups according to body weight. Hidrasec is supplied as an apricot flavoured granulated powder and is not soluble in water; therefore each sachet of Hidrasec will be administered via a clean spoon directly into the child's mouth. All medication must be swallowed completely, if it is acceptable to the patient encourage a drink of water following dosing.

Group	Body Weight	Study Drug Administration
A	6 – 9.9 kg	2 x 6 mg sachets tid po
B	10 – 13.9 kg	3 x 6 mg sachets tid po
C	14 - 25 kg	5 x 6 mg sachets tid po

Oral Rehydration Therapy will be administered as described in Section 5.4.3.

Treatment will be continued until recovery, *(12hours with no loose or watery stools or two consecutive soft / formed stools)*, or for a maximum of 3 days.

Re-dosing:

NB: This applies only for dose 2-9
If the patient vomits within 10 minutes of administering the study medication they must be re-dosed; this must be documented clearly in the CRF. Refer to section 6.2 regarding the issue related to vomiting and collection of blood sampling for pharmacokinetic purposes.
Reminder:
If a patient vomits ≤ 1 hour after the time of first dose of study medication then the patient must be withdrawn from the study.

6.4 Packaging

Hidrasec will be supplied in 6 mg sachets. ICDDR,B will be supplied with sufficient study medication to meet the planned patient enrolment. Each individual patient pack will contain enough medication for a child in weight group C, required to take the

maximum number of sachets for 3 days, with an additional 5 sachets incase of vomiting. Therefore each patient pack will contain 50, 6mg sachets of Hidrasec.

6.5 Labelling and preparation

PATIENT PACK LABEL: DAY 1 - 3

Study No: 52607/016 **Patient Number: XXX**
Contains : 50 sachets
Batch No: **Expiry Date:**
Manufacturing Date:

Administer sachets by mouth as directed.

For Clinical Trial Use Only
KEEP OUT OF REACH OF CHILDREN
PROTECT FROM LIGHT
STORE IN DRY CONDITIONS BETWEEN 15 ° C - 30 ° C
SmithKline Beecham Pharmaceuticals
Wallis House, Great West Road
Brentford, Middlesex, England.

TEAR-OFF PORTION OF LABEL

Study No: 52607/016 **Patient No: XXX**

Dispense on Day 1

Instructions: Tear off this portion of label and fix it securely to the designated area of the CRF.

6.6 Storage

All medication must be stored in a locked cabinet under controlled room temperature.

6.7 Drug Accountability

The Investigator or pharmacist will sign to indicate that the clinical supplies for the study have been received. The investigational products must be handled and

described in the sections 6.2 to 6.6 and dispensed only to those patients enrolled in the study.

At the end of the study it is necessary to reconcile delivery records with those of usage and returned stock. Account must be given of any discrepancies. A drug Disposal Form must be signed with the assurance from the Investigator /Pharmacist that all unused medication for the study will be returned, or destroyed locally, including all opened and unopened packages (according to the directions of the SB Monitor)

6.8 Assessment of Compliance

A record of the number of sachets dispensed, taken and returned for each patient must be documented in the CRF. Compliance will be assessed from information recorded in the CRF, including sachet count and start and end date of therapy.

6.9 Treatment of Overdosage

The dosage of Racecadotril considered to be an overdose in humans has not been defined. Acute overdosage of Racecadotril in humans has not been reported and no specific treatment is known. If overdosage is suspected, patients should be treated as clinically indicated.

6.10 Concomitant Medication/Treatment

During the course of the trial, there should be no concomitant medication(s) administered, except in the case of a child with an oral/rectal temperature ≥38.5c may receive oral acetaminophen.

If, in the investigators judgement a patient does require alternative therapy for an intercurrent illness during therapy they should be treated accordingly but are, by definition, "unevaluable", but will be included in the "intent to treat" analysis.

Antibiotics will <u>not</u> be used routinely during the study, but if such medication is deemed necessary by the investigating physician, the patient will be considered a treatment failure and must be withdrawn from the study. These patients will be considered 'unevaluable', but will be included in the 'intent to treat' analysis.

Antiemetics, such as prochlorperazine and chlorpromazine, cause sedation that can interfere with ORT and for this reason, antiemetics should **<u>not</u>** be given to children with diarrhoea.

No additional antidiarrhoeal therapy should be administered during the course of the study. If such therapy does become necessary the patient must be withdrawn from the study and considered unevaluable. If any child falls ill, as a result of taking part in this research, medical treatment will be provided and its expenses will be borne by the company.

All concomitant medication taken during the study must be recorded in the CRF

with indication, the name of the preparation, the date(s) of administration, the route of administration and the total daily dose.

7.0 ADVERSE EXPERIENCES

The recording of adverse experiences is an important aspect of study documentation. Detailed guidelines are given below.

7.1 Eliciting, and documenting adverse experiences

It is responsibility of the investigator to document all adverse experiences, which occur during the investigation.

An adverse experience includes any noxious, pathological or unintended change in anatomical, physical or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical study whether associated with the study medication, active comparator or placebo and whether or not considered drug related. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the disease under investigation that is not recorded elsewhere in the case report form under specific efficacy assessments. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered adverse experiences. Discrete episodes of chronic conditions occurring during a study period should be reported as adverse experiences in order to assess changes in frequency or severity.

Adverse experiences should be documented in terms of a medical diagnosis(es). When this is not possible, the adverse experience should be documented in terms of signs and/or symptoms observed by the Investigator or reported by the patient at each study visit.

Any pre existing conditions or signs and/or symptoms present in a patient prior to the start of the study should be recorded on the Medical/Surgical history form within the patients' case report form (CRF).

Adverse experiences that occur after informed consent is obtained, but prior to starting active or randomised treatment will be documented on the 'Baseline signs and symptoms' page in the CRF. All adverse experiences occurring after administration of the first dose of study medication (i.e. active drug, placebo, comparator drug) must be reported on the Adverse Experience page in the subjects CRF. All subsequent adverse experiences, whether no drug (i.e. during reference 'run-in' or 'wash-out' period) or when active drug or placebo is being administered, must be reported **REGARDLESS OF WHETHER OR NOT THEY ARE CONSIDERED DRUG RELATED.**

Serious adverse experiences which occur during the clinical study or within 30 days

or five half lives, whichever is the longer of receiving the last dose of study medication, whether or not related to study drug, must be reported.

Instances of death, cancer or congenital abnormality if brought to the attention of the Investigator after cessation of study medication and considered by the Investigator to be POSSIBLY RELATED TO STUDY MEDICATION, should be reported to the site monitor.

At each visit/assessment, the investigator will evaluate adverse experiences. Adverse experiences not previously documented in the study will be recorded in the adverse experience section of the subject's CRF. The nature of each experience, date and time (where appropriate) of onset, outcome, course (i.e. intermittent or constant), duration, severity and relationship to treatment should be established. Details of changes to the dosage schedule or any corrective treatment should be recorded on the appropriate pages of the CRF.

Adverse experiences already documented in the CRF, (i.e.at a previous assessment) and designated as "continuing" should be reviewed at subsequent visits as necessary. If these have resolved, the documentation in the CRF should be completed. NB: If an adverse experience changes in frequency or severity during a study period, a new record of the experience will be started.

As a consistent way of soliciting adverse experiences, ask the subject a non-leading question such as:

"Have you felt or appeared different in any way since starting the new treatment/ or since the last visit?"

7.2 Assessment of Severity

Maximum severity should be assigned to one of the following categories:

Mild
An adverse experience, which is easily tolerated by the subject, causing minimal, discomfort not interfering with everyday activities.

Moderate
An adverse experience which is sufficiently discomforting to interfere with normal everyday activities.

Severe
An adverse experience which prevents normal everyday activities.

7.3 Assessment of causality

Every effort should be made by the investigator to explain each adverse experience and assess its relationship, if any, to study drug treatment. Causality should be assessed using the following categories: not related, unlikely, suspected (reasonable

possibility) or probable.
Not related: The adverse experience is definitely not related to the test drug.

Unlikely: There are other, more likely causes and the drug is not suspected as the cause.

Suspected (reasonable possibility): A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but *there is a reasonable possibility that the experience was caused by the drug.*

Probable: There *probably* is a direct cause and effect relationship between the adverse experience and the study drug.

The degree of certainty with which an adverse experience is attributed to drug treatment (or alternative causes, e.g., natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of one or more of the following:

- Known pharmacology of the drug
- Reaction of similar nature being previously observed with this drug or class of drug
- The experience having often been reported in literature for similar drug as drug related, e.g., skin rashes, blood dyscrasia.
- The experience being related by time to drug ingestion terminating with drug withdrawal (dechallenge) or reproduced on rechallenge.

7.4 Following-up of adverse experiences

Investigators should follow-up subjects with adverse experiences until the event has subsided (disappeared) or until the condition has stabilised. Reports relative to the subject's subsequent course must be submitted to the clinical study monitor.

7.5 Serious Adverse Experiences

7.5.1 Definition of Serious Adverse Experiences:

A serious adverse experience is any event which is fatal, life threatening, disabling/incapacitating or results in hospitalisation, prolongs a hospital stay or is associated with congenital abnormality, cancer or overdose (either accidental or intentional). In addition, any experience which the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug should be reported as a serious event.

Life threatening definition:

An adverse experience is life threatening if the subject was at immediate risk of death from the event as it occurred (i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death). For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug- induced hepatitis can be fatal.

Disability/incapacitating - definition:

An adverse experience is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

Hospitalisation – definition

An adverse experience requiring hospitalisation should be considered serious. Hospitalisation for elective surgery or routine clinical procedures that are not a result of an AE (e.g. elective surgery for a pre-existing condition) need not be considered AE's and should be recorded on the medical/ surgical procedures form. If anything untoward is reported during the procedure, that occurance must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

In general, hospitalisation signifies that the subject has been detained (usually involving at least one overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. When in doubt as to whether 'hospitalisation' occurred or was necessary, the adverse experience should be considered serious.

7.5.2 Reporting Serious Adverse Experiences

Any serious adverse experiences which occur during the clinical study or within 30 days (or five half-lives, whichever is longer) of receiving the last dose of medication, whether or not related to the study drug, must be reported by the investigator to the study monitor by telephone within 24 hours.

All serious adverse experiences must be reported to the RRC, ERC and by telephone within 24 hours to the study monitor:

Name: **Namitha.K**

Address:

No.71, Cunningham Road,
Bangalore 560 052
India

Tel: 91-80-2285700 (Extn.2312)
Fax: 91-80-2280880.

Investigators should not wait to receive additional information to fully document the event before notifying SmithKline Beecham of a serious adverse experience.
The telephone report should be followed by a full written summary detailing relevant aspects of the adverse experience in question. Where applicable, information from relevant hospital case records and autopsy reports should be obtained.

Instances of death, cancer or congenital abnormality if brought to the attention of the investigator after the cessation of study medication **and** considered by the investigator to be **possibly related to** study medication, should be reported to the study monitor.

If the Investigator is notified of a childs death or any severe event and he believes it is **possibly related to the study medication** the Investigator is requested to report this to the SB study monitor.

7.6 Reporting of Overdose

Any instance of overdosage (suspected or confirmed and irrespective of whether or not it involves study medication) must be communicated to SmithKline Beecham within 24 hours and be fully documented as a serious adverse experience. Details of any signs or symptoms and their management (see section 6.9) should be recorded including details of any antidote(s) administered.

8.0 SUBJECT COMPLETION AND WITHDRAWAL

8.1 Definitions

A patient is defined as having completed the study if they have:

- Completed the treatment period by concluding complete resolution of diarrhoea *(12hours with no loose or watery stools or two consecutive soft / formed stools)*), or
- Completed a maximum of 3 days study medication followed by a 12

hour-observation period.

A patient is defined as having withdrawn from the study if they were:

- Randomised to receive study medication but did not complete the study (irrespective of whether they actually received study medication).

8. 2 Procedures for handling withdrawals

When a patient is withdrawn, the investigator should carry out all the assessments that would have been carried out at the next scheduled visit (unless the patient is lost to follow-up).

Patients withdrawing from the study should attend a follow-up visit 7 days after discharge from hospital for the monitoring of adverse experiences and changes in concomitant medication. Every effort will be made to follow-up patients who withdrew due to drug related adverse experiences in order to determine the final outcome. This must then be recorded in the CRF and reported to SB pharmaceuticals. The study conclusion page of the CRF must be completed for all patients taking part in this study.

8.3 Reasons for withdrawal

The investigator may stop medication and withdraw the patient or the patient may withdraw him/herself from the study at any time. The reason for withdrawal must be recorded in the CRF.

Reasons for withdrawal include:

- **Adverse Experience:**
  Patient has any adverse experience deemed sufficiently severe to warrant withdrawal. This must be recorded in the CRF and all adverse experiences followed-up until resolution.

- **Insufficient therapeutic effect:**
  In the opinion of the investigator there has been a clinical failure of study medication on-therapy and further treatment is required.

- **Protocol deviation**
  Non compliance with study medication or visit schedule.

- **Patient is lost to follow up**

- **Termination by sponsor**

- **Intolerence to study medication**

- **Other**
  Patient withdraws consent or requests cessation of treatment

9.0 DATA EVALUATION

There will be two sets of analysis performed on data in this study. 'Statwood', Hitchin, Hertfordshire, England, will perform data management for SmithKline Beecham, United Kingdom, and ICDDR,B will perform an independent analysis within their hospital. Every effort will be made to ensure that both sets of data are identical, at both locations. In the event of any discrepancies occurring, both parties (Statwood and ICDDR,B) in the presence of SmithKline Beecham will review the data file and come to a reasonable solution which is scientifically valid.

9.1 Planned Pharmacokinetic Evaluation

Plasma thiorphan concentration-time data will be displayed in tables and/or graphs. Individual plasma thiorphan concentration-time data will be pooled and population pharmacokinetics will be performed using software such as NONMEM or other currently acceptable methods as permitted by the data. The influence of various covariates (e.g, age, weight, gender and concomitant medications) on the pharmacokinetic parameters will be examined. Pharmacokinetic analysis will be carried out in or under the management of the Department of Clinical Pharmacokinetics, Clinical Pharmacology and Experimental Medicine SmithKline Beecham , Research and Development.

9.2 Criteria for Efficacy

9.2.1 Primary Efficacy Variable

The primary efficacy variable is the duration of diarrhoea, defined as the time from the start of study medication (racecadotril) until the last loose or watery stool.

9.2.2 Secondary Efficacy Variable

The following outcomes are secondary efficacy variables:

- The number of watery stools passed from baseline until recovery, or the end of study whichever is the sooner
- The incidence of cure, relapse or failure

At the end of the study, the investigator will evaluate each patient's clinical response to the study medication with reference to the signs and symptoms at

baseline, as follows:

Clinical success

Patients whose last loose or watery stool occurs within 72 hours of the first dose of study drug administration.

Clinical failure (F) / Relapse (R)

(F) Patients who continue to pass watery stools beyond 72 hours from the first dose of study drug administration.

(R) Patient whose diarrhoea resolves before 72 hrs but who record further watery stools (relapse) in the 12 hour observation period.

Unable to determine:

A valid assessment of clinical efficacy can not be made (e.g., patient did not attend the end of therapy visit) or a response cannot be obtained due to poor patient co-operation or extenuating circumstances.

9.3 Statistical Methods

9.3.1 Comparisons of interest

Since all patients are receiving racecadotril, no statistical hypotheses are being tested.

9.3.2 Sample Size Determination

As no formal statistical hypothesis will be tested, the sample size is based on faesibility and not on formal power calculations.

9.3.3 Interim Analysis

There will be no interim analysis.

9.4 Efficacy Analysis

9.4.1 Methods of Analysis

9.4.1.1 Primary Efficacy Variable

The duration of diarrhoea will be calculated, in hours, as the time elapsing between the start of medication (baseline) and the time of the last watery stool. Where a patient does not recover and continues to pass loose or watery stools, the time until the final observation will be calculated and the data will be considered censored at that point. Patients with indeterminate outcome, or failures will therefore generally provide censored data.

Kaplan-Meier estimates of the time to last stool will be calculated in order to estimate the median recovery time. Baseline variables, namely duration of diarrhoea, the number of loose stools passed in the preceding 24 hours and baseline bodyweight will be considered as explanatory variables. The presence of rotavirus will also be investigated as a prognostic factor if numbers allow. Standard model fitting procedures (see Collett, 1994, chapter 3) will be used to select the best model for estimating the hazard function. Results will be expressed according to the final model selected.

9.4.1.2 Secondary Efficacy Variables

The number of watery stools passed during the study will be summarised using descriptive statistics. No further analysis will be performed.

The incidence of cure will be summarised as the percentage of patients whose diarrhoea resolves within 72 hours. Patients who relapse will be considered as cured in the first instance, but a summary table will also show the number of patients who relapse, and the number who never achieve a cure during the study. If numbers allow, exploratory analysis of cure rates incorporating the explanatory variables described above will be performed.

The change in weight from baseline to the final assessment will be summarised in tables of descriptive statistics. No formal statistical analysis will be performed.

9.4.2 Patient Population/Data Sets to be Evaluated

Two populations will be defined:

- Intent-to-treat population, comprising all patients who take any racecadotril and who have any efficacy data recorded after baseline
- Safety population, comprising all patients who take at least one dose of study medication

The Intent-to-treat population will form the primary analysis population. All available data from this population will form the Full analysis set.

9.5 Safety Evaluation

All adverse experiences reported following enrolment of a patient into the study will be documented. Signs and symptoms (other than those of the disease under investigation) which occur prior to the first dose of study medication will also be recorded.

Evaluation of safety data will be based on descriptive summaries of adverse experiences, with particular attention to the occurrence of constipation, defined as no stools during 36 or more consecutive hours since the last stool, and vomiting. Concomitant medication will also be summarised in tables.

For adverse experience data the incidence of each experience will be described, but no formal analysis will be performed. Tables classifying events by body system, by severity, and by relationship to study drug will be produced where appropriate.

Clinically significant laboratory findings will be summarised in tables if appropriate. The results of stool sample analyses will be summarised in tables and listings.

Information regarding concomitant medication will be presented as listings and tables.

10.0 ADMINISTRATIVE MATTERS

To comply with Good Clinical Practice important administrative obligations relating to investigators responsibilities, monitoring, archiving data, audits, confidentiality and publications must be fulfilled as given in Appendix B.

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WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Recommendations guiding physicians in
biomedical research involving human subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964,
Amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975,
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly Hong Kong, September 1989
and the
48th General Assembly, Somerset West, Republic of South Africa,
October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded with careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE
(Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

(Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers -- either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

APPENDIX B: ADMINISTRATIVE MATTERS

ADMINISTRATIVE MATTERS

I RESPONSIBILITIES OF THE INVESTIGATOR

- To ensure that he/she has sufficient time to conduct and complete the study and has adequate staff and appropriate facilities which are available for the duration of the study and to ensure that other studies do not divert essential subjects or facilities away from the study at hand.
- To submit an up-to-date curriculum vitae and other credentials (e.g. medical license number in the United States) to the sponsor and - where required - to relevant authorities.
- To acquire the normal ranges for laboratory tests performed locally and, if required by local regulations, obtain the Laboratory Licence or Certification.
- To prepare and maintain adequate case histories designed to record observations and other data pertinent to the study.

II PROTOCOL AMENDMENTS

No changes to the study protocol will be allowed unless discussed in detail with the SmithKline Beecham (SB) Medical Monitor and filed as an amendment/modification to this protocol.

Any amendment/modification to the protocol will be adhered to by the participating centre (or all participating centres) and will apply to all subjects following approval as appropriate by the Ethical Review Committee or Institutional Review Board.

III SPONSOR'S TERMINATION OF STUDY

SmithKline Beecham (SB) may discontinue the clinical study at any time for medical or administrative reasons, subject to the agreement of the ICDDR,B, such agreement not to be unreasonably withheld. SB shall provide reasonable explanation to the ICDDR,B of the reasons for discontinuing the clinical study.

IV CASE REPORT FORM INSTRUCTIONS

Prior to screening the first potential participant, the investigator will provide a list showing th signature and hand-written initials of all individuals authorised to make or change entries on cas report forms (CRFs). If the authorised individuals should change during the study, th investigator is to inform SB.

CRFs (and subject diary cards, if applicable), will be supplied by SB for recording all data. It

the responsibility of the investigator or co-investigator to ensure that CRFs (and subject diary cards) are legible and completely filled in with a black ink ball-point pen. Include the subject's identification (2-3 alphabetic letters representing the subject's initials or the first 2-3 letters of subject's first or last name), the patient identification (PID) if not already pre-printed and the visit date, will be entered on the CRF Header Pages as required.

Errors must be corrected by drawing a single line through the incorrect entry and writing in the new value/data positioned as close to the original as possible. The correction must then be initialled, dated and justified by the authorised individual making the change. Do not obliterate, write over, or erase the original entry when making a correction.

When a subject completes a visit, it is anticipated that relevant sections of the CRF will be completed by the investigator (or designated staff) within 24 hours of the last data becoming available, but in no case later than 5 days. Similarly, when a subject completes a study, it is anticipated that all relevant CRF pages will be completed within 24 hours of the last data becoming available, but in no case later than 5 days. This also applies to forms for potential study participants who were not randomised to a treatment group.

As soon as the subject has completed/withdrawn from the study and the CRF is completed the principal investigator or designated physician(s) under his/her supervision will sign the adverse experience page(s) as well as study conclusion page of the CRF to confirm that they have reviewed the data and that the data are completed and accurate. If sections of a CRF are to be brought into SB prior to study conclusion, a section conclusion signature is required.

An original (top copy) of the CRF must be submitted for all subjects who have undergone protocol specific procedures, whether or not the subject completed the study.

While completed CRFs will be reviewed by a SB professional monitor at study site, errors detected by subsequent in-house CRF review may necessitate clarification or correction of errors and documentation and approval by the investigator.

Any questions or comments related to the CRF should be directed to the assigned study monitor.

V MONITORING BY SMITHKLINE BEECHAM

Monitoring visits by a professional representative of the sponsor will be scheduled to take place before entry of the first subject, during the study at appropriate intervals and after the last subject is completed.

These visits are for the purpose of verifying adherence to the protocol and the completeness and exactness of data entered on the CRF and Drug Inventory Forms. The monitor will verify CRF entries by comparing them with the hospital/clinic/office records which will be made available for this purpose. The monitor will retrieve completed CRF sections at each visit. Adequate time and space for these visits must be made available by the investigator.

Investigator must ensure provision of reasonable space and adequate qualified personnel for monitoring visits.

VI ARCHIVING OF DATA

The investigator must retain subject records and CRFs as well as drug disposition records in an easily retrievable form until disposal has been agreed in writing with SB. The investigator must have a 'key' linking the subject's study identification number (i.e. treatment number) to the subject's clinical file. If the investigator moves or retires, he/she must nominate someone in writing to be responsible for record keeping. Archived data may be held on microfiche or electronic record, provided that a back-up exists and a hard copy can be obtained from it if required.

SB agrees to retain a copy of the protocol, documentation, approvals and all other documents related to the study, including certificates that satisfactory audit and inspection procedures have been carried out.

VII AUDITS

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for SB or a Drug Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When an investigator signs the protocol, he agrees to allow the Drug Regulatory Agency and SB auditors to inspect his/her study records. Furthermore, if an investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application.

SB has a substantial investment in clinical studies. Having the highest quality data and studies are essential aspects of drug development. SB has a Regulatory Compliance staff who audit investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that SB sponsored studies are in accordance with the relevant Good Clinical Practices regulations/guidelines are being followed.

To accomplish these functions, Regulatory Compliance selects investigational sites to audit. These audits usually take 1 to 2 days. The SB audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation required to be maintained, and checks on drug accountability. The SB audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring SB of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Log of visits from the sponsor's representatives
- ERC/IRB approval
- Test article accountability
- Approved study protocol and amendments
- Informed consent of the subjects (written or witnessed oral consent)
- Medical records supportive of CRF data
- Reports to the ERC/IRB and the sponsor
- Record retention

SB will gladly help investigators prepare for an inspection.

VIII CONFIDENTIALITY AND PUBLICATION

You agree that all information communicated to you by SB is the exclusive property of SB and you will ensure that the same shall be kept strictly confidential by you or any other person connected with the work and shall not be disclosed by you or such person to any third party without the prior written consent of SB. You shall communicate the results of the work promptly to SB

We agree that you shall have the right to publish or permit the publication of any information or material relating to or arising out of the work after prior submission to us provided that if we shall so request you will delay publication for a maximum of six months to enable us to protect our rights in such information or material. Any proposed publication or presentation (e.g. manuscript, abstract or poster) for submission to a journal or scientific meeting, should be sent to the study monitor prior to submission. SB will undertake to comment on such documents within four weeks.

All rights and interests world-wide in any inventions, know-how or other intellectual or industrial property rights which arise during the course of and/or as a result of the clinical study which is the subject of the Protocol or which otherwise arise from the information or materials supplied under this Agreement, shall be assigned to, vest in and remain the property of SmithKline Beecham

APPENDIX C Voluntary Consent Form

Voluntary Patient Information Sheet and Consent Form
International Centre for Diarrhoeal Disease Research, Bangladesh

Title of the Research Project:
A single centre, open, phase II study to evaluate the population pharmacokinetics and safety of racecadotril in the treatment of acute diarrhoea in children aged one to five years in Bangladesh

Principal Investigator: Dr. Wasif Ali Khan

Prior to participating in this study, the study subject should know about the aims, procedures, potential benefits and risks involved in this study. Details of all procedures, including their risks, utility, duration, frequencies and severity, must be provided to the participant. Participation in the project is completely voluntary and all questions raised by the subject must be answered to his complete satisfaction. For children, consents should be obtained from their parents or legal guardians. The study subject must indicate his consent to participate in the study by signing or giving a thumb impression on this form.

Your child is suffering from acute watery diarrhoea. The mainstay treatment of this disease is the appropriate replacement of fluid and electrolytes. There is a drug called racecadotril (Hidrasec™) which has shown some promising benefits over loperamide (commonly prescribed drug or available over the counter for acute diarrhoea) when given together with oral rehydration solution (ORS). It reduces stool output, the duration of the diarrhoea and has reduced side effects. Acute watery diarrhoea is more common in developing countries where the majority of the children are either less well-nourished or malnourished. ICDDR, B is carrying out a study to measure the drug concentration after dosing of racecadotril, the concentrations will be measured at different time periods. This information is going to be beneficial to ascertain whether the drug concentration varies when compared to well nourished children. The safety profile of racecadotril has shown that it is well tolerated and is known to be safe for use in children.

ICDDR, B is inviting about 90 children to take part in a research study which would determine whether racecadotril (Hidrasec™) would help reduce stool output and duration of diarrhoea. We would be grateful if you would agree for your child to take part in this study. We cannot guarantee them any personal benefits by participating in the study. However, the study will provide us with further data on the absorption, safety and tolerability of Hidrasec™. It is hoped that the drug will lessen the severity of the disease and aid in quick recovery.

If you are happy for your child to take part in this study, they will be required to stay in hospital for a maximum of 4 days, it is possible that this will be shorter and then followed by an outpatient visit at 7 days after discharge. Your child will also need to undergo certain observations and tests:

You will be asked some questions about your child's medical history and then they will have a thorough physical examination performed by the doctor.

Blood (1.5 ml) will be drawn from your child's veins on a total of 5 preassigned occassions over the treatment period. To prevent repeated puncture an indwelling-canulae maybe introduced into one of the upper extremity veins of your child. A stool sample will also be taken for culture on admission and at discharge if possible.

Rehydration will be maintained with rice based ORS together with fluid (plan water, milk) and the usual hospital diet will be provided. Your child will be given the study medication based on body weight

racecadotril (Hidrasec™) every 8 hourly until the diarrhoea stops or a maximum of 3 days (9 doses). All children on this study will receive racecadotril.

Hidrasec™ has demonstrated that it is well-tolerated and is known to be safe at this time. Previous studies have shown that some patients who have taken racecadotril have experienced some minor side-effects like nausea, vomiting, abdominal bloating, constipation, epigastric pains, dizziness, weakness, headache, mood change, insomnia, skin rashes, pruritus, acne and an increase or decrease in urinal frequencies. At present, we do not know of any other side effects of racecadotril. Your childs participation in this study is completely optional. Your unwillingness for your child to participate will not result in any penalty or you being denied of any benefits to which you are entitled. You can withdraw your child from the study at any time without any penalty or reduction in benefits. In such an event, your child will receive treatment from the hospital as usual and your relationship with the doctors and the staff will be as normal as before. Without your prior consent, this study may be stopped at anytime by your doctor, SmithKline Beecham (SB), or the regulators due to administrative or medical reasons. You will be informed of any new findings that become available.

At the time of providing a blood sample, your child may feel a mild discomfort and/or slight faintness, they may have a local infection or blood clot but this is very rare. If you wish to withdraw your child from the study and they are discharged from the hospital, they will be required to attend a follow up visit 7 days after discharge. During this visit, you will be asked about any symptoms they may have experienced since discharge and a physical examination will be conducted by the doctor.

If you have any questions concerning the research, you can contact the people named below:

Name	Telephone No.
Dr. Wasif Ali Khan	2333
Dr. Mahbubul Karim	2310

Your childs participation in the research will be completely confidential. The medical records of the treatment, if necessary, will be reviewed by (SB) personnel, representatives authorised by SB, the hospital, the domestic and foreign regulatory bodies, auditors and the hospital Ethics Committee. The company is committed to abide by any national data protection regulations.

If your child falls ill, as a result of taking part in this research, medical treatment will be provided and its expenses will be borne by the company.

If you agree for your child to take part in this research project, please affix your signature or thumb impression below. A copy of this form will be given to you.

Parent/Guardians statement of consent: The study has been explained to me in detail and I voluntarily give my consent for my child to participate in this research study. I have had an opportunity to ask questions and have received answers which I am satisfied with. I am not waiving my legal rights by signing this consent form.

_____ **Date:**_____

Parent's/Legal Guardian's printed name/thumb impression

(to be entered by the Parent's/Legal Guardian's)

_____

Signature/thumb impression of person giving consent

_____ **Date:**_____

Signature of person obtaining consent (to be entered by signatory)

Or Witnessed Verbal Consent

I certify that I have explained all relevant details to the patient and he has given his verbal consent to participate in the study.

_____

Printed Name (person who conducted consent discussion)

_____ Date: _____

Signature (person who conducted consent discussion) (to be entered by signatory)

I confirm that the investigator has completely described the study to the patient.

_____

Printed Name of Witness

_____ Date: _____

Signature of Witness (to be entered by witness)

A copy of this document has been provided to the patient.

APPENDIX D: ASSESSMENT OF DEHYDRATION

	A	B	C
Condition	Well, alert	***Restless, irritable**	***Lethargic or unconscious; floppy**
Eyes	Normal	Sunken	Very sunken and dry
Tears	Present	Absent	Absent
Mouth and Tongue	Moist	Dry	Very dry
Thirst	Drinks normally, not thirsty	***** Thirsty, drinks eagerly**	***** Drinks poorly or not able to drink**
Skin pinch	Goes back quickly	***** Goes back slowly**	***** Goes back very slowly**
Decide:	The patient has **NO SIGNS OF DEHYDRATION**	If the patient has two or more signs including at least one ***** sign ***** , there is **SOME DEHYDRATION**	If the patient has two or more signs, including at least two ***signs***, there is **SEVERE DEHYDRATION**

The signs in **bold** with **(*)** are the most valuable for assessing dehydration; these are called **'key signs'**

APPENDIX E : SCHEDULE OF ASSESSMENT

PROCEDURE	HOUR -4-0	Day 1 HOUR 0	Day 1 HOUR 4	Day 1 HOUR 8	Day 1 HOUR 16	Day 1 HOUR 24	Day 2 HOUR 32	Day 2 HOUR 40	Day 2 HOUR 48	Day 3 HOUR 56	Day 3 HOUR 64	Day 3 HOUR 72	Day 4 HOUR 84	Day 7 F/U
Informed Consent	X													
Diagnosis	X	X												
Medical History	X													
Physical Examination	X													
Prior/Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	
Baseline signs and symptoms	X													
Assessment of vomiting	X	X	X	X	X	X	X	X	X	X	X	X	X	
Nutritional status	X													
Assessment of weight/vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assessment of stool output *	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assessment of dehydration	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collection of blood samples	Xψ											Xψ	Xψ	
Collection of stool samples	X					X♦	X♦	X♦	X♦	X♦	X♦	X♦	X♦	
Dispense study medication		X		X⊕										
Adverse Experiences		X	X	X	X	X	X	X	X	X	X	X		

* Stool output will be measured 4hrly until discharge.

♦ Stool samples to be collected at screening and then on day of discharge if possible.

ψ Safety assessments (At screening and time of discharge)

⊕ Study medication dispensed 8hrly until resolution

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APPENDIX F : SCHEDULE OF PHARMACOKINETIC SAMPLING

	After 1st Dosing							Following Last Dose	
	0.5 Hour	1 Hour	2 Hours	4 Hours	6 Hours	8 Hours		6 hrs after last dose	8 hrs after last dose
GROUP 1	X		X		X			X	
GROUP 2		X		X		X			X

cilities Available

scribe the availability of physical facilities at the place where the study will be carried out. For clinical and oratory-based studies, indicate the provision of hospital and other types of patient's care facilities and quate laboratory support. Point out the laboratory facilities and major equipments that will be required for study. For field studies, describe the field area including its size, population, and means of mmunications. (TYPE WITHIN THE PROVIDED SPACE).

Site: The Research Ward of the Dhaka Hospital of ICDDR, B will be used for hospitalization of the study patients. This facility has been used for clinical studies, especially clinical studies in acute watery diarrhoea including cholera, rota virus for more than 30 years. It has a full-time trained nursing staff, which will allow for close monitoring of patients.

Study population: The Dhaka Hospital provided treatment to 117,365 patients with diarrhoea in 2000. Thus patient recruitment should not be a problem.

Laboratory facilities: The clinical laboratory service of the Laboratory Sciences Division of ICDDR, B will be used for routine testing. Nutritional Biochemistry Lab under LSD will measure the plasma concentrations of the active metabolite, "thiorphan" by means of enzyme immunoassay.

Data Analysis

Describe plans for data analysis. Indicate whether data will be analyzed by the investigators themselves or by other professionals. Specify what statistical softwares packages will be used and if the study is blinded, when the code will be opened. For clinical trials, indicate if interim data analysis will be required to monitor further progress of the study. (TYPE WITHIN THE PROVIDED SPACE).

Statistical methods

Data will be entered onto computer using SPSS for Windows (Version 8.0). Range checks will be used to insure the validity of data entry. For PK analysis GSK experts will guide and provide training.

Use of Animals

Describe in the space provided the type and species of animal that will be used in the study. Justify with reasons the use of particular animal species in the experiment and the compliance of the animal ethical guidelines for conducting the proposed procedures.

Animal studies will not be undertaken as part of this protocol.

Dissemination and Use of Findings

Describe explicitly the plans for disseminating the accomplished results. Describe what type of publication is anticipated: working papers, internal (institutional) publication, international publications, international conferences and agencies, workshops etc. Mention if the project is linked to the Government of Bangladesh through a training programme.

The findings of the study will disseminated as follows:

1. Presentation(s) at scientific forums, ICDDR,B for dissemination among scientists of the Centre.
2. Presentation at the Annual Scientific Conference (ASCON) of ICDDR, B for dissemination amongst scientists
   and health officials of the Government of Bangladesh and of non-governmental organizations.
3. Presentation at regional and international scientific conferences.
4. Publication in peer-reviewed international medical journal.

ollaborative Arrangements

escribe briefly if this study involves any scientific, administrative, fiscal, or programmatic arrangements ith other national or international organizations or individuals. Indicate the nature and extent of llaboration and include a letter of agreement between the applicant or his/her organization and the llaborating organization. (DO NOT EXCEED ONE PAGE)

his study will be done in collaboration with Glaxo Smith Kline (GSK), UK who are providing the udy drug "Racecardotril", and also sponsoring this study.

Biography of the Investigator

Give biographical data in the following table for key personnel including the Principal Investigator. Use a photocopy of this page for each investigator.

Name	Position		Date of Birth
1. Wasif Ali Khan	Assistant Scientist, CSD, ICDDR, B		19 January, 1963
Academic Qualifications (Begin with baccalaureate or other initial professional education)			
Institution and Location	**Degree**	**Year**	**Field of Study**
1. Chittagong Medical College	M.B.B.S.	1987	Medicine & Surgery

Research and Professional Experience

Concluding with the present position, list, in chronological order, previous positions held, experience, and honours. Indicate current membership on any professional societies or public committees. List, in, chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. **(DO NOT EXCEED TWO PAGES, USE CONTINUATION SHEETS).**

Bibliography

NOTE: THSES ARE THE COMMON PUBLICATION LIST FOR ALL INVESTIGATORS OF THE STUDY

1. Khan WA, Begum M, Salam MA, Bardhan PK, MR, Mahalanabis D. Comparative trial of five antimicrobial compounds in the treatment of cholera in adults. Trans Royal Soc Trop Med Hyg. 1995;89:103-6.
2. Khan WA, Dhar U, Salam MA, Seas C. Bacterial meningitis in a diarrhoeal disease treatment centre in Bangladesh. Acta Paediatr 1995;84:693-4.
3. Khan WA, Bennish ML, Seas C, Khan EH, Ronan A, Dhar U, Busch W, Salam MA. Randomised controlled comparison of sigle-dose ciprofloxacin and doxycycline for cholera caused by *Vibrio cholera* O1 or O139. Lancet 1996;348:296-300.
4. Khan WA, Seas C, Dhar U, Salam MA, Bennish ML. Treatment of shigellosis: V. Comparison of azithromycin and ciprofloxacin. Ann Intern Med 1997;126:697-703.
5. Khan WA, Dhar U, Salam MA, Griffiths JK, Bennish ML. Central Nervous System Manifestations of Childhood Shigellosis: Prevalence, Risk Factors, and Outcome. Pediatrics 1999 103 (2): p. e18 http://www.pediatrics.org/cgi/content/abstract/103/2/e18

6. Kabir I, Khan WA, Haider R, Mitra AK, Alam AN. Erythromycin and trimethoprim-sulphamethoxazole in the treatment of cholera in children. J Diarr Dis Res 1996;14:243-7.
7. Salam MA, Khan WA, Begum M, Bardhan PK, Islam MR, Mahalanabis D. Antimicrobial treatment of cholera. Drugs (Extended abstract). 1995;49 (Suppl.2):466-9.
8. Salam MA, Seas C, Khan WA, Bennish ML. Treatment of shigellosis. IV. Cefixime ineffective in the treatment of shigellosis in adults. Results of a randomized, double-blind trial. Ann Intern Med 1995;123:505-8.
9. Salam MA. Use of quinolones in paediatrics: use in the developing countries. Chemother J 1996;5 (suppl 13):27-35.
10. Salam MA, Dhar U, Khan WA, Bennish M.L. Randomized comparison of ciprofloxacin suspension and pivmecillinam for childhood shigellosis. Lancet 1998;352:522-527.
11. Dhar U, Bennish ML, Khan WA, Seas C, Khan EH, Albert MJ, Salam MA. Clinical features, antimicrobial susceptibility and toxin production in Vibrio cholerae O139 infection: comparison with V. cholerae O1 infection. Trans Roy Soc Trop Med Hyg 1996;90:402-5.

Detailed Budget for New Proposal

Project Title : A single centre, open, phase 11 study to evaluate the population pharmacokinetics and safety of racecardotril in the treatment of acute diarrhoea in children aged one to five years in Bangladesh

Protocol Number: **Name of Division: Clinical Sciences Division**

Funding Source: **Glaxo Smith Kline (GSK)**

Amount Funded (Direct) **US$ 105,053** **Overhead (25%): US$ 26,263**
TOTAL BUDGET COST **US$ 131,316**

Staring Date: As soon as fund is available
Closing Date: 15 months from 1st patient enrollment **(6 months patient recruitment)**

Strategic Plan Prioprity Code (s): **11**

Sl #	Account Description	Salary Support				US $ Amount Requested
	Personnel	Position	Salary (months)	Effort (%)	Time frame (months)	
1	Wasif Ali Khan (PI)	NoB	981	70	12	8,240
2	Prof. George J Fuchs (Co-PI)	D1-06	15716	15	12	28,289
3	MA Wahed (Co-I)	NoC	1778	10	6	1,067
4	Study Medical Officer (2)	NoA	657	100	6	7,884
5	Research Officer (1)	GS6	456	100	6	2,736
6	Data Management Officer	GS5-02	418	40	6	1,003
7	Research Assistant (2)	GS5-05	450	100	6	5,400
	(Mr. Wahed's lab)					-
8	Study Nurse (4)	CSA	170	100	6	4,080
9	Ward attendant (3)	GS-01	160	100	6	2,880
	Sub Total					**61,579**
	International Travel					**4,000**
	Supplies and Materials (Description of Items)					
1	Office supplies					500
2	Non-stock supplies					300
3	Lab. supplies					300
4	Hospital supplies					200
5	Transportation					200
	Sub Total					**1,500**
	Patient Hospitalization					
1	90 patients (complete 3 days @US$ 45/ patient/ day)					12,150
2	~20 Patients (withdrawn / absconded / incomplete study days @US$45/patient/day)					900
3	Follow-up (90 evaluable + ~10 withdrawn = 100 x @US$15/patient)					1,500
	Sub Total					**14,550**
	Other Contractual Services					
1	Repair and Maintenance					200
2	Rent, Communications, Utilities (Email, fax, postal)					500
3	Printing and Publication					300
	Sub Total					**1,000**

Sl #	Account Description	US $ Amount Requested
	Interdepartmental Services	
1	**Pathological Tests** [(4.87 x2 x 90) + (– 10 Patients withdrawn/repeated and another – 10 patients vomited within 1h 1st dose of study medication)]	974
2	**Microbiological tests** [(26 x2 x 90) + (– 10 Patients withdrawn/repeated and another – 10 patients vomited within 1h-1st dose of study medication)]	5,200
3	**Biochemistry Tests** [(30 x2 x 90) + (– 10 Patients withdrawn/repeated and another – 10 patients vomited within 1h-1st dose of study medication)]	6,000
4	**Pharmacokinetics** (Blood - US$ 1370 @ 100 sample.) Total number of samples [1/patient) x 90 total number of patient = 360) + R&D 120 samples + (– 10 Patients withdrawn & – 10 patients vomited within 1h-1st dose of study medication) 360 + 120 + 10 + 10 = 500)]	6,850
5	X-rays	100
6	Medical illustration	100
7	Xerox, Memographs etc	100
8	Staff Clinic Subsidy	100
	Sub Total	19,424
	Other Operating Costs **Capital expenditure** (computer, printer, accessories, file cabinets)	3,000
	Total Direct Cost	105,053
	Overhead cost (25%)	26,263
	TOTAL BUDGET COST	131,316

27-3-2001

Shamima Moin
Controller Budget & Costing

Budget Justifications

Please provide one page statement justifying the budgeted amount for each major item. Justify use of man power, major equipment, and laboratory services.

1. Personnel

This study will enroll 90 evaluable patients in 6 months. The clinical care to these patients must be provided by the investigators of this study, namely Drs. Wasif, and a Medical Officer for this study who will recruit before initiation of the study. The investigator has other commitments and responsibilities, and thus PI will not be able to remain engaged only with this study. For providing care to the study patient on all seven days of the week, assistance of a full time Medical Officer will be required.

The research officer will be responsible to ensure that all routine and special laboratory investigations of the study are done on time and to compile and maintain results of all laboratory tests. These will require 100% time of a research officer. Two full time research assistant will be require to perform the PK assays at the Nutritional Biochemistry lab of the laboratory Sciences Division, ICDDR, B.

Data will be entered twice as soon as they become available. The person will also help in cleaning of data as well as performing some of the basic statistics. All these activities will require 40% time of a data Management officer.

Ward attendants will be required to initially identify potential study patients. Thus it will be essential to recruit three ward attendants.

2. Supply and material; Other contractual and Interdepartmental

These reflect exact cost of supplies and materials, which will be required for the study.

3. International travel

This funding is to allow the results to be presented at an international meeting.

her Support

cribe sources, amount, duration, and grant number of all other research funding currently granted to PI or er consideration. (DO NOT EXCEED ONE PAGE FOR EACH INVESTIGATOR)

Molecular epidemiology of Cryptosporidiosis. The study is in collaboration with New England Medical Center (NEMC), Massachusetts General Hospital (MGH) and University of Virginia, and has a budget of US$10,512

One study, short title "Single-dose ciprofloxacin therapy for childhood cholera". The study is sponsored by New England Medical Center, Boston, MA. and has a budget of about US $ 200,000.

One research protocol, short titled "Diagnosis of pneumonia in children with dehydrating diarrhoea" is currently being reviewed by USAID under the competitive grant agreement. The budget is US $ 50,000.

Ethical Assurance for Protection of Human Rights

Describe in the space provided the justifications for conducting this research in human subjects. If the study needs observations on sick individuals, provide sufficient reasons for using them. Indicate how subject's rights are protected and if there is any benefit or risk to each subject of the study.

Justifications for conducting this research in human subjects

The objective To determine the pharmacokinetic parameters of racecardotril administered per oral 1.5 mg/kg every 8 hourly in children hospitalised for acute watery diarrhoea, aged between 1 year to 5 years, by measuring the plasma concentrations of the active metabolite, ""thiorphan" by means of enzyme immunoassay. To determine area under curve (AUC), maximum concentration (Cmax) and time of maximum concentration (Tmax).

Protection of human rights

The intent of the research program, the study protocol, and the informed consent form to be used in the study will be submitted to the Ethical Review Committee of ICDDR, B. The study will only be initiated only after approval by the Committee.

Informed consent

Informed consent must be obtained from the patient's parents or their guardian in accordance with the Declaration of Helsinki. It will be the responsibility of the investigator to obtain written informed consent from them after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. The investigator must also explain to the patient / guardian that they are completely free to refuse to enter in the study, and also to withdraw them self from the study at any time. This informed consent must be obtained from the patient / guardian in the presence of a witness along with their signature and date.

Check List

After completing the protocol, please check that the following selected items have been included.

Face Sheet Included	√
Approval of the Division Director on Face Sheet	√
Certification and Signature of PI on Face Sheet, #9 and #10	√
Table on Contents	√
Project Summary	√
Literature Cited	√
Biography of Investigators	√
Ethical Assurance	√
Consent Forms	√
10.Detailed Budget	√

ABSTRACT SUMMARY FOR THE ETHICAL REVIEW COMMITTEE

1. Requirement of study population

The aim of the study is to determine the pharmacokinetic parameters of racecardotril administered orally 1.5 mg/kg every 8 hourly in children hospitalised for acute watery diarrhoea. Children of either sex, aged 1-5 years of age, who have a history of acute watery diarrhea of not more than 5 days, some or no signs of dehydrated according to WHO guidelines, weight for length (70% to 89%) will be eligible for enrollment.

2. Potential risk

The only risk to the patients is the rare possibility of infection consequent to venipunctures to be done on four different occasions on the day of admission (5 ml of total blood) to determine the pharmacokinetics of racecardotril. Other than momentary pain during insertion of needles, a small risk of leaking of blood from the puncture site, and a rare chance of infection.

3. Methods for monitoring potential risks

Study patients / parents will be interviewed, and thorough physical examination of the patients will be done on the day of admission at different time period, then on each day of hospitalization. Vital signs of the patients will be recorded by nurses every 4 hourly. These procedures will ensure careful monitoring of the clinical condition of the patients and detection of any untoward events. Patients in whom diarrhoea doesn't stop even after 72 hours of racecardotril if require further investigation or adequate treatment therapy will be given as determined by in vitro susceptibility.

4. Methods for safeguarding confidentiality

Patient information will be kept under lock, and the computer database on the study subjects will not include the name of the patients.

5. Informed consent

At the time of initial screening study health worker(s) will inform the patients parent's or guardian on the nature of the study, and their benefits and potential risks. The investigator will give them the consent form to read or would read out that to patients who are unable to read.

6. Interview

A brief history form will be filled in by the investigator that would require about 10 minutes of the patients' attendant's time. The questions do not depart from the questions that would be asked to make a clinical diagnosis under the usual circumstances.

7. Benefits to individuals and society

The benefits to the patient are that they will be examined by investigators who are well trained for conduction of such studies, and they would have thorough investigation done for their medical problems. The benefits to the general population are that important information may be derived for introduction of racecardotril at a specific dose and at certain intervals in adjunct to oral rehydration therapy that could significantly reduce the volume of watery stool as well as duration of diarrhoea in children (1-5 years) with mild to moderately malnourished (age group and nutritional status where acute watery diarrhoea is most commonly seen in developing countries). If confirmed, this form of treatment will be used in the management of children with acute watery diarrhoea at the ICDDR, B's hospital and hopefully in a further bigger range of population.

8. Samples required

The study will require use of blood and stool samples.