Attachment 1. 200

Date 17/09/86

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. P.K. Bardhan

Trainee Investigator (if any)

Application No. 86-031

Supporting Agency (if Non-ICDDR,B) SANDOZ, SWITZE

Title of Study "DOUBLE BLIND, RANDOMIZED CLINICAL TRIAL OF ICS 205-930 AS AN ANTI-SECRETORY AGENT IN PATIENTS WITH CHOLERA"

Project status:
( ) New Study
( ) Continuation with change
( ) No change (do not fill out rest of form)

Circle the appropriate answer to each of the following (If Not Applicable write NA).

1. Source of Population:
   (a) Ill subjects — (Yes) No
   (b) Non-ill subjects — Yes (No)
   (c) Minors or persons under guardianship — Yes (No)
2. Does the study involve:
   (a) Physical risks to the subjects — Yes (No)
   (b) Social Risks — Yes (No)
   (c) Psychological risks to subjects — Yes (No)
   (d) Discomfort to subjects — (Yes) No
   (e) Invasion of privacy — Yes (No)
   (f) Disclosure of information damaging to subject or others — Yes (No)
3. Does the study involve:
   (a) Use of records, (hospital, medical, death, birth or other) — (Yes) No
   (b) Use of fetal tissue or abortus — Yes (No)
   (b) Use of organs or body fluids — (Yes) No
4. Are subjects clearly informed about:
   (a) Nature and purposes of study — (Yes) No
   (b) Procedures to be followed including alternatives used — (Yes) No
   (c) Physical risks — (Yes) No
   (d) Sensitive questions — (Yes) No
   (e) Benefits to be derived — (Yes) No
   (f) Right to refuse to participate or to withdraw from study — (Yes) No
   (g) Confidential handling of data — (Yes) No
   (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure — (Yes) No
5. Will signed consent form be required:
   (a) From subjects — (Yes) No
   (b) From parent or guardian (if subjects are minors) — Yes (No)
6. Will precautions be taken to protect anonymity of subjects — (Yes) No
7. Check documents being submitted herewith to Committee:
   ___ Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies).
   ✓ Protocol (Required)
   ✓ Abstract Summary (Required)
   ✓ Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
   ✓ Informed consent form for subjects
   ___ Informed consent form for parent or guardian
   ___ Procedure for maintaining confidentiality
   ___ Questionnaire or interview schedule *

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary:
1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Cttee. for review.

(PTO)

I agree to obtain approval of the Ethical Review Committee for any changes involving the rights and welfare of subjects before making such change.

Gradjo Bardhan
Principal Investigator

Trainee

SECTION I - RESEARCH PROTOCOL

1.	TITLE:	DOUBLE BLIND, RANDOMIZED CLINICAL TRIAL OF ICS 205-930 AS AN ANTI-SECRETORY AGENT IN PATIENTS WITH CHOLERA
2.	PRINCIPAL INVESTOGATOR:	Dr. P.K. Bardhan
	CO-INVESTIGATORS:	Dr. A.N. Alam Study Physician (to be named)
	CONSULTANTS:	Dr. A.M. Molla Prof. K. Gyr, Basel, Switzerland
3.	STARTING DATE:	October, 1986
4.	COMPLETION DATE:	June, 1987
5.	TOTAL DIRECT COST:	US $ 30523.00
	SOURCE OF FUNDING	SANDOZ - AG, BASEL, SWITZERLAND
6.	SCIENTIFIC PROGRAMME:	This protocol has been approved by the Clinical Sciences Division.

Signature of Acting Head, Clinical Sciences Division

Date: 11.1.87

7. ABSTRACT SUMMARY

To evaluate the anti-secretory effect of ICS 205-930 in cholera, a prospective placebo-controlled, randomised, double-blind clinical trial is proposed in this protocol. ICS 205-930 has been developed as a potent blocker of 5-Hydroxytryptamine M receptors. In animal studies, this drug has been found to act as an effective anti-secretory agent in diarrhoea induced by cholera toxin or serotonin (5-HT). In human volunteer studies, this drug was found to be fairly safe. In thistrial, 44 male adults cholera patients will receive two I.V. doses of either ICS 205-930 20 mg each dose or a placebo. All the patients will receive I.V. acetate solution for rehydration, but no antibiotics. Response to treatment will be evaluated by comparing base-line purging rate, (stool volume/8 h) purging after treatment, and duration of diarrhoea, between the two groups. Any unpleasant side effects of the treatment will be recorded. All routine tests, including ECG will be done before and after treatment to maintain any sub-clinical side-effect of the drug. Blood will be collected before treatment and plasma levels of 5-HT, motilin, and substance p will be determined. This study will examine the anti-secretory potential of ICS 205-930, as well as likely to provide information about the pathophysiological mechanism involved in cholera.

8. REVIEWS:

(a) Ethical Review Committee: ----------

(b) Research Review Committee: ----------

(c) Director: ----------

A. INTRODUCTION:

Objective: To investigate the effectiveness of ICS 205-930 as an antisecretory agent in cholera.

Background

Development of an useful antisecretory agent will greatly simplify the management of acute dehydrating secretory diarrhoeas such as cholera by reducing the voluminous stool output, and thus minimising the duration of illness as well as the need of fluid replacement.
Of the many potential antisecretory agents tried in cholera, only chlorpromazine (1) and nicotinic (2) acid showed effectiveness, but fell short of clinical usefulness. The search for an effective antisecretory agent is continuing.

It is generally accepted that the cholera toxin induces intestinal secretion by stimulating the adenylate cyclase system in the intestinal epithelial cells, thereby increasing the intracellular cyclic-AMP levels and inducing net secretion (3). However, it was found that blocking the intestinal intramural nerves markedly inhibited the intestinal secretion induced by cholera toxin, suggesting a significant participation of the local nervous mechanisms in the pathophysiology of cholera (4). Later studies showed that cholera toxin causes release of 5-HT from the enterochromaffin (EC) cells in rabbits, cats, and rats (5, 6). It was also shown that 5-HT receptors are involved in the pathophysiology of cholera secretion, since the secretion was inhibited by receptors blocked either by making the experimental animal tachyphylactic against 5-HT (7), or by administering methysergide, a 5-HT receptor blocker (8). 5-HT, produced in excess in the carcinoid syndrome, is considered the cause of watery diarrhoea, a common manifestation of this disease (9). 5-HT itself is a potent stimulator of intestinal secretion as has been shown in the small intestines of different experimental animals in vivo (7, 10-12). Based on these facts, the following hypothesis was suggested (5): the cholera toxin adheres to the EC cells and triggers the release of 5-HT, which in turn, activates dendrites of the local neurons in close contact with the EC cells. These neurons form the efferent part of the intramural reflex(es) ind

in the intestine. According to this hypothesis, about 60% of the effect of cholera toxin on intestinal fluid transport could be ascribed to the nervous mechanism(s).

About 90% of the total body content of 5-HT is found in the gut (13). The majority of the endogenous serotonin in the gut is stored in the EC cell system, The EC cells in the gut have been divided into 3 subgroups (14):

a) EC_1 cells - found throughout the small and large intestine in man. In addition to 5-HT, these cells also contain Substance P.

b) EC_2 cells - occur in large numbers in duodenum, and in smaller quantities in jejunum. These cells are reported to store motilin in addition to 5-HT.

c) EC_n cells - considered a wastebasket type from which further subtypes may emerge. They still contain 5-HT, but are apparently unrelated to the production of Substance P or Motilin.

Besides carcinoid syndrome, high plasma levels of 5-HT has been observed in patients suffering from coeliac disease (15). Among the other 2 peptides co-existing with 5-HT in the EC cells, plasma levels of Substance P has been shown to be raised in patients with carcinoid syndrome (16). Substance P is itself capable of inducing intestinal electrolyte secretion, as was shown in vitro (17). The release of 5-HT, Substance P or Motilin from the GI tract of cholera patients (as reflected in peripheral blood) has not been reported. By looking at the plasma levels of 5-HT, Substance P and Motilin in cholera patients, it may be possible to identify the subgroup(s) of EC cells involved in cholera.

Pharmacology of ICS 205-930

Current research has shown 5-HT to be an enteric neurotransmitter and may play a prominent role in the regulation of G.I. motility and secretion (18). These regulatory actions of 5-HT are elicited by the

activation of a heterogenous receptor system. The early 5-HT receptor classification distinguished neuronally located peripheral 5-HT receptors blockable by morphine called 5-HT-M receptors, from a second class of receptors located on smooth muscles blockable by dibenzyline called 5-HT-D receptors (19). Later analyses showed that 5-HT_2 receptors and 5-HT-D receptors are identical (20). The 5-HT-D receptors seem to be of minor importance in the gut (21). Studies regarding 5-HT-M receptors were lacking because of lack of specific agonists and antagonists. Only recently ICS 205-930, a highly potent and selective 5-HT-M receptor antagonist has been developed (22).

ICS 205-930 in particular blocks the low affinity 5-HT-M receptors, i.e. the ones that operate under high concentrations of 5-HT. The compound, therefore, does not influence the basic (normal) activity of the smooth muscles, as expected (23). The low affinity 5-HT-M receptors are thought to mediate the release of Substance P, as opposed to the high affinity 5-HT-M receptors which control the release of acetylcholine.

The effects of ICS 205-930 on the gastro-intestinal tract have been investigated in different animals (23). ICS 205-930 inhibited 5-hydroxytryptophan (5-HTP) induced diarrhoea in mice regardless of the route of administration. The maximal reduction was 70-80%. When secretory diarrhoea was induced in mice by exposure to cholera toxin, ICS 205-930 was found to inhibit the intestinal secretion in vivo by about 50-60%. However, when a non-specific diarrhoea was induced by castor oil in rats, ICS 205-930 was found to be without any effect, showing that this drug inhibits intestinal secretory process only when 5-HT-M receptors are involved. This specificity of the 5-HT-M receptors' involvement in cholera toxin and 5-HTP induced diarrhoea is further supported by the fact that ketanserin, a specific 5-HT_2 receptor blocker, failed to show any effect on the intestinal secretion induced by cholera toxin in mice. In vitro, ICS 205-930 blocks the spasm and peristaltic activity induced by 5-HT in guinea pig ileum. In contrast, neither the normal peristaltic activity in vitro, nor the normal G.I. motility in mice in vivo, as measured by the passage time of a charcoal meal, is influenced by ICS 205-930, emphasizing the specificity of the drug. Overall,

ICS 205-930 seems to be a highly specific drug which may prove to be a clinically useful antisecretory agent for treatment of cholera and other secretory diarrhoeas, where 5-HT mechanisms may be involved.

Toxicology of ICS 205-930

Acute and chronic toxicity studies in mice, rats and dogs did not reveal any specific drug-induced abnomalities (24). Based on up-to-date available data, the no-toxic-effect level can be set as follows:

a) in dogs: - oral: 5-20 mg/kg/day
- i.v.: 3 mg/kg/day

b) in rats: - oral: 16-45 mg/kg/day
- i.v.: 15 mg/kg/day

Clinical pharmacology of ICS 205-930

The tolerability and safety of ICS 205-930 administered as a single dose orally (2.5 - 200 mg) or i.v. (0.5 - 90 mg) in humans has been the subject of 4 experimental trials (25-28). All trials have been performed under blind conditions in healthy volunteers aged 18-45 years. In total, 72 subjects have taken a single oral dose of ICS 205-930 and 39 a single i.v. dose.

The results are summarized as follows:

a) The most frequent side-effect reported was headache, occuring in 18/72 subjects treated orally and in 14/39 subjects treated i.v., whereas only 4/32 subjects treated with placebo reported this symptom.

G.I. symptoms (abdominal discomfort, nausea, vomiting and diarrhea) were the second most frequent side-effects in those who took the substance orally (occuring in 11/72 subjects), and tiredness in those

who took the injections (5/39 subjects). G.I. symptoms (constipation with abdominal discomfort) were also reported by 3 subjects receiving 20 and 40 mg I.V.

b) The side-effects were dose-related in those who receive ICS 205-930 orally (occuring mainly at doses 60 mg) but dose-independent in those who had the injection.

c) Vital signs, ECG and laboratory investigations did not show any changes indicative of adverse effects.

Preliminary pharmacokinetic data on subjects who received ICS 250-930 orally indicate that the substance is rapidly absorbed, reaches the highest plasma levels in 2 hours and is eliminated in a biphasic manner. The plasma elimination T1/2 of the compound is about 4 hours in the first phase and 14 hours in the second phase.

Rationale

Development of an effective anti-secretory agent will greatly simplify management of acute dehydrating, secretory diarrhoea, such as cholera. This trial is designed to clinically test such a candidate drug, ICS 205-930.

3. Specific aims:

1. To compare the efficacy of ICS 205-930 with that of placebo in reducing the amount of stool output in cholera.

2. To investigate the plasma levels of 5-HT, motilin and substance P in cholera patients, and compare with those of healthy Bangladeshi volunteers.

C. METHODS AND PROCEDURE:

TRIAL DESIGN

Prospective randomised double-blind trial, comparative between ICS 205-930 and placebo in two parallel groups of patients. The trial period will last 48 hours, during which the drugs will be administered in two I.V. doses separated by 8 hours.

PATIENTS

Number of patients

A total of 36 evaluable patients (18 in each treatment group) are required to prove or disprove the clinical usefulness of ICS 205-930. However, an interim analysis on at least 20 patients should decide upon the continuation or the early termination of the trial.

Sex and age

Males aged 15-45 years.

Inclusion criteria

Heavily purging adult cholera patients. Adult patients presenting with acute dehydrating diarrhoea to the outpatient department of ICDDR, B, Dhaka, Bangladesh will be examined. Those patients showing V.cholerea in stool in darkfield microscopy will be transfered to the study ward, where they will be observed for the next 8 hours. Only those patients having stool output more than 200 ml/hour will be included in the study

Exclusion criteria

a) Patients with diarrheoa due to reasons other than V.cholerae.

b) Myocardial infarction within the last 6 months.

c) Patients with severe renal, hepatic or congestive heart failure.

d) Malignancy.

e) Any other systemic disease necessitating antibiotic therapy.

TRIAL DRUGS AND DOSAGE REGIMEN

Coding and labelling of trial drugs

Both trial drugs (active and placebo) will be prepared, coded, packaged and labelled by the sponsor, according to a randomisation list which will be provided by the Department of Biostatistics, Sandoz Ltd., Basle.

Assignment of trial medication

Each eligible patient will be assigned a patient number and the set of ampoules with the trial medication, which will be identified by a patient number. Patients will be assigned to number and medication in sequence. All unused samples (including drop-outs) should be returned to the sponsor after the end of the trial.

Dosage regimen

The trial drugs will be administered in two doses of 20 mg by i.v. infusion. The trial drugs should be disolved in 100 ml saline and the solution should be infused over a period of 20 minutes. The interval between the two infusions will be 8 hours.

CONCOMITANT TREATMENT

During the whole trial period no specific treatment intended to stop the diarrhoea (antisecretory or antimotility compounds), other than the trial drugs, is allowed.
Whenever such treatment is deemed necessary, the administration of trial drugs should be discontinued and the patient withdrawn from the trial.
Similarly, no antibiotics are allowed during the trial.

Other concomitant medication not related to the indication of the trial is permitted and must be recorded in the case report forms.

TRIAL METHOD

General aspects

Soon after admission and initial assessment, the patients should receive the standard management (fluid replacement). Meanwhile the investigator will make the clinical evaluation which will determine the patient's eligibility for participation in the trial, as well as the microscopical examination of the stools for detection of V. cholerae.

Since the present trial will be carried out according to the Tokyo amendment to the Helsinki Guidelines (Federal Reg. 40, 16056-56, 1975), all eligible patients should be informed about the trial and told that they will be able to withdraw from it at any time. Written consent will be obtained from each patient or his relatives prior to entering the trial.

Trial periods

a) Observation period (first 8 hours):

All patients showing V. cholerae in stool in darkfield microscopy will be transfered to the study ward, where they will be observed for the next 8 hours. Only those patients having stool output more than 200 ml/hour will be included in the study.

After a thorough physical examination, blood, urine and stool will be sent for routine laboratory investigations. In addition, during this period, 15 ml of blood will be obtained from the patients, and plasma will be immediately separated, and then stored at -20°C. These plasma samples will be analysed for determining 5-HT, Substance P and Motilin. As controls, blood samples will be obtained from 10 volunteers. Stool will be cultured for V. cholerae, shigella, salmonella campylobacters and ETEC. All hydration, including initial rehydration and subsequent maintenance of hydration will be performed by i.v. Acetat-

b) Main trial period (48 hours):

The eligible patients will be randomly assigned to one of the two groups. One group will receive ICS 205-930 as i.v. infusion (over 20 minutes) in two doses separated by 8 hours, the other group will receive placebo in the same manner.
Vital signs will be monitored to record any untoward effect of the drug. In addition, ECG and routine laboratory investigations should be performed during this period.
All outputs, including stool, urine, and vomitus, will be measured every period of 8 hours for the next 48 hours. No restriction of food take will be made.

c) Follow-up (unlimited):

All patients should be followed up after termination of the trial, until discharge from the hospital. The duration of hospitalization, the daily treatment and any relevant change in the patients condition should be recorded.

Clinical safety testing (see also Annex I)

Physical examination

The physical examination form will be completed by the investigator during the observation period, as well as at 24 and since start of treatment. Any changes between these examinations must be commented on by the investigator.

The standard physical examination will include: general appearance, skin, ears, nose, throat, neck, heart, lungs, abdomen, lymph nodes, extremities, back, and eyes.

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The eligible patients will be randomly assigned to one of the two groups. One group will receive ICS 205-930 as i.v. infusion (over 20 minutes) in two doses separated by 8 hours, the other group will receive placebo in the same manner.
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Clinical safety testing (see also Annex I)

Physical examination

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The standard physical examination will include: general appearance, skin, ears, nose, throat, neck, heart, lungs, abdomen, lymph nodes, extremities, back, and eyes.

Vital signs

Vital signs will include supine blood pressure, radial pulse and temperature. These will be performed at frequent intervals at the observation and main trial periods. Body weight will also be obtained. All vital signs data will be recorded on the appropriate case report forms.

Electrocardiogram evaluation

A standard 12-lead ECG will be performed before and 24 hours after the first i.v. infusion of the trial drugs. The findings will be reported and evaluated by the investigator on the appropriate pages of the case report form.

Laboratory evaluation

Laboratory safety tests will be performed and recorded before and 24 hours after the first i.v. infusion of the trial drugs. The laboratory evaluation consists of the following:

a) Blood cytology: Hemoglobin and/or hematocrit, thrombocytes, red blood cell count, total and differential white cell counts.

b) Blood biochemistry: Serum electrolytes, creatinine, urea, glucose, total bilirubin, alkaline phosphatase, SGOT or SGPT.

c) Standard urine analysis.

Any laboratory tests reported to have an abnormal value that is considered to be clinically significant by the investigator, must be repeated in order to exclude laboratory errors. In tests where there is a persistent abnormality, repeat analysis will be performed at intervals appropriate to the abnormality, until the cause is determined or return to normality occurs.

ADVERSE REACTION REPORTING

Any serious, unusual or life threatening adverse reactions or encountered during the course of the investigation and for a reasonable time thereafter will be reported to Dr. A. Yotis (Tel.: 0041.61.24 91 61), Sandoz Ltd., Clinical Research, Building 386, CH-4002 Basle, or to the local Sandoz Monitor and clinical manifestations as well as laboratory results will be documented.
Clinical, diagnostic and laboratory measures employed to delineate the reaction in question will be performed and the results reported. In tests where there is an abnormality considered to be drug related, repeat analysis will be performed at appropriate intervals until the cause is determined or return to normal occurs. In all cases of serious reactions, the medication will be discontinued and any appropriate supportive or definitive therapy given.

The sponsor will provide the investigator with sealed envelopes labelled with numbers, identical to those of the patients package of trial drugs. Each envelope will contain the name of the drug administered for the corresponding patient, and should be opened only in case of emergency (i.e. indications for severe adverse reactions).
Once the envelope has been opened, the patient must be withdrawn from the trial.
All envelopes should be returned to the sponsor at the end of the trial.

EARLY DISCONTINUATION OF TREATMENT - DROP OUTS

Patients must be excluded from the trial under the following circumstances: protocol violation, intercurrent illness (clinical judgement to be exercised by the investigator), inability to tolerate study medication, failure to take the study medication, patient's uncooperativeness and adverse reactions requiring discontinuation of study drug and/or

necessitating breaking code. If an adverse reaction is involved, the appropriate page in the investigator's report form should also be completed and an explanation should follow in the comments section.

Patients terminated from the study for reasons cited above, except adverse reactions and intolerability to trial drug, are considered non-evaluable. All other cases, i.e. those which have completed treatment and premature discontinuations due to adverse reactions, will be considered evaluable.

STATISTICAL ANALYSIS

The data obtained during the course of this clinical trial will be subjected to analyses by ICDDR, Dhaka and the Department of Biostatistics, Sandoz Ltd., Basle, Switzerland. A randomization list will be provided by the sponsor to ICDDR for that purpose.

The stool outputs of the patients belonging to the two groups will be compared. The stool output during the observation period will be taken as the baseline purging rate, and changes in the next 6-8 hour periods (increase or decrease) will be calculated for at least 48 hours or as long as the patient is hospitalized.

Differences in purging rates between the two groups will be compared by means of a t-test. The sample size has been estimated in order to detect a 50% decrease of liquid loss in the ICS 205-930 group as compared to placebo (significance level 5%, one tailed t-test, propability of type II error: 20%).

The total amount of i.v. fluid required in the two groups, as well as their duration of stay in the hospital will also be compared. Student's t test will be performed, and statistical significance will be accepted at the level of < 0.05.

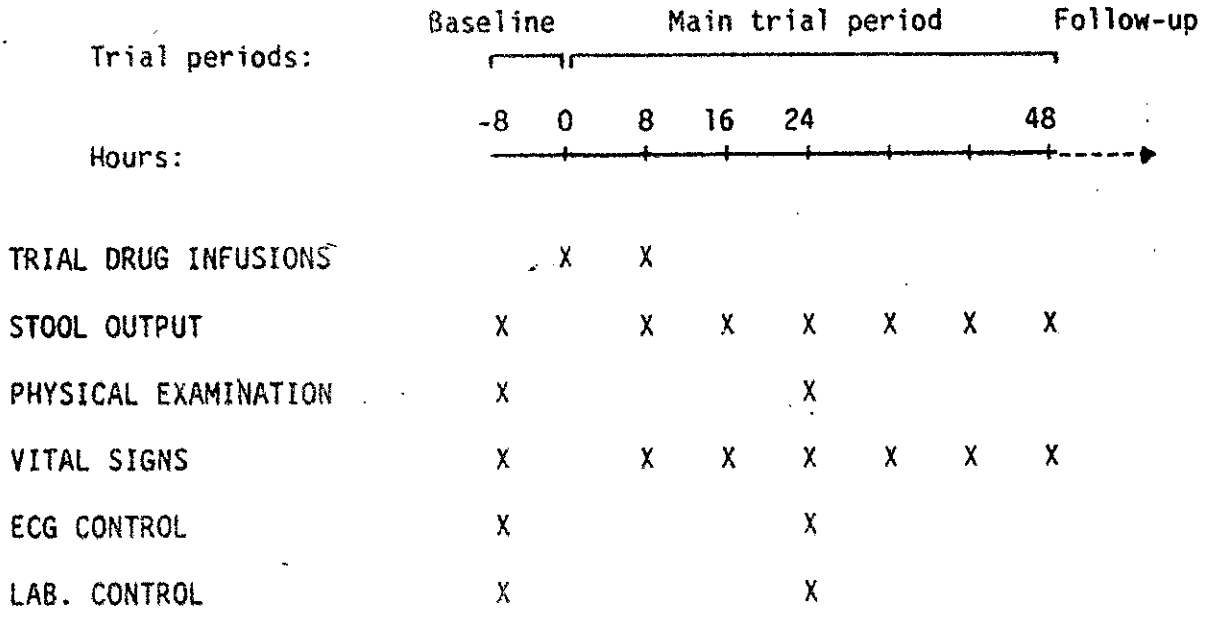
Assessing the tolerability of the drug, treatment comparisons will be done by appropriate statistical tests depending on the level of the data (Wilcoxon-Mann-Whitney-rank sum test, contingency table analysis). The level of significance will be chosen as $p = 0.05$ for each test, i.e. no adjustment will be performed although multiple statistical tests will be performed for these evaluations.

Further data will be analysed descriptively (summary tables, graphics, etc.). Statistical tests will be performed in the sense of exploratory data analysis.

D. Significance

Reducing the magnitude of fluid and electrolyte loss in cholera patients will simplify the management of such patients. Identification of a drug which will act as an effective, safe and useful antisecretory agent in such patients, thus significantly reducing the overall fluid loss, will be expected to be of immense help in optimal management of diarrhoea. This study aims to test the clinical efficacy of ICS 205-930, which appears to be a promising candidate. Moreover, by determining the plasma levels of several G.I. hormones, important insights into the pathophysiological mechanism in cholera may be gained.

SUMMARY OF TRIAL PLAN



E. FACILITIES REQUIRED:

1. Office space - the present office space will be utilized
2. Laboratory space - ICDDR,B lab. will be utilized
3. Hospital resource - Study ward and outpatient space will be required
4. Animal Resources
5. Logistic support - set up of micro-computer for data processing.
6. ICDDR,B Transport - will be used.

F. COLLABORATIVE ARRANGEMENTS:

Collaborative arrangements will be made between ICDDR,B and Prof. Klaus Gyr, University of Basel, Switzerland and Dr. A.M. Molla, Aga Khan University, Pakistan.

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generally results in the onset of fever and watery diarrhoea within 24 to 72 hours. In many instances this is followed by the dysentery syndrome, including abdominal cramps, tenesmus and bloody mucoid stools. In severe

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ABSTRACT SUMMARY FOR E.R.C.

1. The subject population will consist of patients suffering from cholera. High purging rate remains the major obstacle for simple management of some cholera patients. A pharmacological agent able to reduce the purging rate will greatly simplify this problem. The clinical trial of such an agent is proposed in the protocol.

2. The potential risks involved in this study are those of side-effects, which are minor in the proposed dose range. There will be close 24 hour monitoring of patient condition, and in case of any significant deterioration in the patient's condition, the code will be broken and the patient will be withdrawn from the study. All side effects, even the major ones noted only in very high doses are fully reversible.

3. The only invasive procedure will be drawing of blood, the amount posing no risk to the patient. No significant side-effects are expected in the dose of the drug to be used in this study.

4. All patients enrolled in the study will be assigned a study number and that number will be used during data analysis.

5. Informed consent will be obtained from all patients entered into the study.

6. A standard medical history will be obtained at the time of admission.

7. The major benefit to the patient will be the best available medical care he will receive. If the drug proves useful, then it will help to simplify management of severe cholera, thus providing benefits to the society.

8. The study will require the use of hospital records, stool, and blood.

SECTION III - BUDGET

1. Personnel services

Name	Position	% effort	US $
Dr. P.K. Bardhan	Principal Investigator	50%	2500.00
Dr. A.N. Alam	Co-Investigator	10%	6000.00
Study Physician	Co-Investigator	25%	1100.00
Dr. A.M. Molla	Consultant	-	-
Prof. K. Gyr	Consultant	-	-
3 Staff Nurse (Study ward)		20%	1200.00
Clerk - 1		20%	300.00
Cleaners - 3		20%	500.00
Lab. Technician		10%	250.00

Sub Total=11,850.00

2. Supplies and Materials:

Hospital supplies 1900.00

ICS 205-930 (provided by Sandoz) - Nil

3. Interdepartmental services:

Lab. costs:

Test	Cost/test	No. of test	US $
HCT, TC, DC, Platelets	2.50	88	220.00
Serum chemistry	7.00	88	616.00
LFT	10.00	88	880.00
Stool culture	8.00	44	352.00
Stool D/F	1.32	44	65.00
Stool M/E	2.50	44	110.00
Urine M/E	2.50	44	110.00
EKG	2.50	88	220.00

Sub Total=2573.00

		US $
4.	Equipments - Peristaltic pump	1000.00
5.	Patient hospitalization (44 pts X 7 days X $ 25)	7700.00
6.	Outpatient care - Nil	
7.	Local transport	500.00
8.	International transport of materials	500.00
9.	Rent, communication & utilities - Nil	
10.	Printing and reproduction	500.00
11.	Other contractual services - Nil	
13.	Data analysis	1500.00
14.	Publication & presentation in meetings	2500.00
	Sub Total =	14,200.00

GRAND TOTAL = US $ 30,523

CONSENT FORM

Double -blind randomised trial of ICS 205-930

I understand that I have cholera diarrhoea, and that I may need treatment with intravenous fluids. I also understand that I may be admitted into the hospital research ward until the diarrhoea is over. I will receive treatment with intravenous solution and will eat normal rice and curry diet. In addition, I will be treated either with ICS 205-930 or placebo. Placebo will have no effect on my illness. The reason to give ICS 205-930 is to see whether it is effective in helping to stop cholera diarrhoea. This drug has been found safe when used in healthy humans in Europe, but may cause reversible headache, vomiting, and diarrhoea.

I understand that on admission 15 ml of blood, and after 24 hours another 10 ml of blood will be taken for laboratory tests. I am aware that if I do not agree to participate in this study, or even if I withdraw from the study, I will still get adequate treatment at ICDDR,B. All the records of my treatment will be kept confidential.

Signature of investigator

Signature/thumb impression of patient

Date: ----------

সম্মতি পত্র

কলেরা রোগে আই. সি. এম. ২০৫ - ৬৩০

আমি অবগত আছি যে আমার কলেরা হয়েছে এবং আমাকে শিরায় স্যালাইন দিয়ে চিকিৎসা করা হবে। আমি এও অবগত আছি যে আমাকে হাসপাতালে ভর্তি করা হবে এবং যতদিন পর্যন্ত বমি বন্ধ না হয়, সুচিকিৎসা করা হবে। আমাকে শিরায় স্যালাইন দেয়া হবে এবং স্বাভাবিক খাবার বন্ধ রাখা হবে। এ ছাড়াও আমাকে আই. সি. এম. ২০৫ - ৬৩০ নামক ঔষধি ইনজেকশন দিলে অথবা শিরায় ঔষধি দেয়া হবে। আমার রোগের ওপর শিরায় ঔষধের কোন ক্রিয়া হবে না। কলেরা ডায়রিয়াতে আই. সি. এম. ২০৫-৬৩০ প্রকৃতপক্ষে ডায়রিয়া কমাতে সক্ষম কিনা তা দেখার জন্য এই ঔষধি দেয়া হবে। ইউরোপ আমেরিকার সুস্থ মানুষদের এই ঔষধি দেয়ার পর পরীক্ষায় এই ঔষধিকে নিরাপদ বলে মনে করা হয়েছে। তবে কখনো কখনো মাথা ঝিম, বমি অথবা ডায়রিয়া হতে পারে। তবে এগুলো ক্ষণস্থায়ী। আমি আরো অবগত আছি যে এই গবেষনায় ভর্তি হলে ভর্তির সময় ১৫ মি: লি: রক্ত এবং ভর্তির ২৪ ঘন্টা পরে ১০ মি: লি: রক্ত বিভিন্ন পরীক্ষার জন্য নেয়া হবে। এছাড়া মল, মূত্র ও ই. সি. জি. পরীক্ষা করা হবে।

আমি এও অবগত আছি যে এই গবেষনায় অংশগ্রহন না করলে আমার অংশগ্রহন করার পরও যে কোন সময় সরে আসার অধিকার রয়েছে এবং এই হাসপাতালে আমার যথাযথ চিকিৎসার কোন ত্রুটি হবে না। আমার সমস্ত চিকিৎসা সংক্রান্ত তথ্য গোপন রাখা হবে।

গবেষকের স্বাক্ষর

রোগীর স্বাক্ষর অথবা বুড়ো আঙ্গুলের ছাপ

তারিখ

ANNEX 1

SUMMARY OF TOXICITY DATA

COMMENTS

ICS 205-930 was well tolerated by various species at high dose levels as shown by the results of the acute, subacute and chronic oral and parenteral toxicity studies and the reproduction studies.

The following findings were considered to be related to ICS 205-930 treatment.

In dogs, slight emesis initially frequent, later sporadic, slight to moderate hypersalivation and slightly reduced feed intake concomittently impaired weight gain and body weight losses were observed in some animals, mainly at the high dose levels in all studies. There were no clinical or hematological findings nor was there any evidence of macroscopically or microscopically detectable drug related changes.

At an intravenous dose of 10 mg/kg ICS 205-930, high dose level, one animal of the group died immediately after the bolus injection. The precise cause of death was unclear, however, in view of the ECG-changes which were recorded in the acute tolerance study, at the same dose, it could be due to cardiac arrest.

The abnormal findings which were observed during treatment were all reversible during a five to six weeks recovery phase.

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The abnormal findings which were observed during treatment were all reversible during a five to six weeks recovery phase.

Part A **CLINICAL STUDY SYNOPSIS**

Project: ICS 205-930

Indication: MIGRAINE

cross if appropr.
Part of MC-trial O
Summary of MC-trial O

Final evaluation ☒
If MC-trial, abbrev. of partic. countries:
Study Code(s):

Name and country of main investigator or name of MC-trial:

Mauro Pirovino, M.D., Dept. of Internal Medicine
University of Berne, Berne/Switzerland

Title of study protocol:

Tolerability of ICS 205-930 after single intravenous injection in healthy volunteers

Date of protocol: 09.11.1984

Aim of study, selection criteria and target parameters:

Tolerability of ICS 205-930 after single intravenous application in doses between 0.5 - 40.0 mg

Type of study.		**Design of study** (please cross appropr. circles)					
experimental	☒					normal	
therapeutic	O	randomized	O	single group	O	volunteers	☒
field	O	open	☒	parallel groups	☒	patients	O
PMS	O	single blind	O	cross-over	O		
.....	O	double blind	O	other design	O	in-house	O

No. of pats./volunt. planned: 23 **Begin of study** (Mth., Yr.): January, 1985
Last pat. completed (Mth., Yr.): January, 1985

Trtm. strategies (indicate medication(s), gal. Form(s), dosage(s), duration)

1: ICS 205-930 ampoules 0.5 mg single injection
2: ICS 205-930 ampoules 1.0 mg single injection
3: ICS 205-930 ampoules 2.5 mg single injection
4: ICS 205.930 ampoules 5.0 mg single injection
5: ICS 205-930 ampoules 10.0 mg single injection
6: ICS 205-930 ampoules 20.0 mg single injection
7: ICS 205-930 ampoules 40.0 mg single injection

PREPARATION:	**BNCL:**	**BATCH:**
Ampoules (20 mg / 10 ml)	71479.05	Y 138 G4

Part B, Clinical Study Synopsis

Pat. population:	Total	Fill in this rectangle only for parallel group designs Trtm.1	Trtm.2	Trtm.3	Trtm.4
Entered total	23				
- Drop outs	0				
= Evaluable cases	23				
male/female	23				
age (min/max)	21-31				
age mean	24				
Eval. for efficacy	23				
Discont. safety	ø				
Discont. ineffect.	ø				
Subj. with ADR	15				

Results (Efficacy/Safety):

The tolerability of the used doses of ICS 205-930 given intravenously was very good. The most frequently observed side effect was frontal headache (10/23), generally of mild intensity. Minor side effects were tiredness (4/23), pressure in the eyes (2/23), asthenia (2/23), and pulssynchrone throbbing in the temporal region (1/23). The side effects were dose-independent. Systemic blood pressure and pulse rate and all biochemical laboratory parameters remained unchanged.

Conclusions:

The findings in this study demonstrate the very good tolerability of ICS 205-930 administered intravenously up to 40 mg as a single dose.

Clinical Expert: Klaus Kutz, M.D.

Signature: 

Date: 13.03.1985

Part A

CLINICAL STUDY SYNOPSIS

Project: ICS 205-930

cross if appropr.
Part of MC-trial O
Summary of MC-trial O

Indication:

Final evaluation (Volunteer Study) O

If MC-trial, abbrev. of partic. countries:

Study Code(s): ICS 0003

Name and country of main investigator or name of MC-trial:

Dr. P.M. Dewland
Simbec Research, U.K.

Title of study protocol:

Repeated Dose Tolerance Study of ICS 205-930 Administered orally to Adult Healthy Volunteers

Date of protocol: 25.4.85

Aim of study, selection criteria and target parameters:

Aim: To examine the safety of ICS 205-930 when given in repeated doses to healthy volunteers - in terms of side effects, laboratory data and ECG. To compare the kinetics following a single dose with the following 6 days' treatment (twice daily administration)

Type of study		Design of study (please cross appropr. circles)					
experimental	✓					normal	
therapeutic	O	randomized	✓	single group	O	volunteers	✓
field	O	open	O	parallel groups	O	patients	O
PMS	O	single blind	O	cross-over	✓		
.....	O	double blind	✓	other design	O	in-house	O

No. of pats./volunt. planned: 12 volunteers for 2 doses

Begin of study (Mth., Yr.): AUG 85

Last pat. completed (Mth., Yr.): SEPT 85

Trtm. strategies (indicate medication(s),gal. Form(s),dosage(s),duration)

1: Oral treatment

2: Single dose Day 1, twice daily treatment days 2 to 6, final dose

3: on day 7. Crossover, repeat sequence at Day 10.

4:

5: Doses : 50 and 100 mg b.d. with placebo control.

6:

PREPARATION:	ENGL:	BATCH:
50 mg capsules	71727.03	X 108C5

Part B, Clinical Study Synopsis

Pat. population:	Total	Fill in this rectangle only for parallel group designs Trtm.1	Trtm.2	Trtm.3	Trtm.4
Entered total - Drop outs	12				
= Evaluable cases	12				
male/female age (min/max) age mean	6/6 18/34 25.25				
Eval. for efficacy	12				
Discont. safety Discont. ineffect. Subj. with ADR	3 - 3/6 @ 50 mg, 2/6 Placebo	3/3 100 mg, 2/3 Placebo			

Results (Efficacy/Safety):

ICS 205-930 was reasonably well tolerated at 50 mg b.d. The 2 subjects reporting side effects during placebo had mild experiences. However, on active one subject reported moderate headache and one moderate constipation, ataxia and headache. At 100 mg. b.d. the study was prematurely terminated due to all 3 subjects, initially randomised to active, experiencing hallucinations. These occurred from Day 3, and the medication was stopped on Day 5. One subject did not fully recover until Day 7. The remaining 3 subjects initially randomised to placebo were not crossed over in view of the likely risks.

At 50 mg b.d. 2 subjects were observed to have lowered BP on active therapy, mainly standing systolic pressures. No other significant changes were seen in terms of ECG or laboratory values.

Plasma sample measurements showed increases in Cmax, AUC and $T\frac{1}{2}$ following multiple dose treatment in comparison to single doses, for both dosages, $T\frac{1}{2}$ 50 mg (single dose) 7.09 rising to 18.4 hrs over 7 days. $T\frac{1}{2}$ 100 mg 9.5 risin to 27 hrs over 5 days.

Conclusions:

Very definite evidence of central nervous system side effects seen for ICS 205-9 when given as 100 mg b.d. repeated doses. Greater accumulation of drug seen upon chronic treatment than was predicted from single dose studies. In view of of this it is proposed to undertake further tolerance studies examining repeated dosage using a once daily dosage regime.

Clinical Expert:

Signature: Martin W. Lennon **Date:** 11th December, 1985

Part A CLINICAL STUDY SYNOPSIS

Project: ICS 205-930

Indication: Volunteer Study

cross if appropr.
Part of MC-trial O
Summary of MC-trial O

Final evaluation O YES
If MC-trial, abbrev. of partic. countries:

Study Code(s): ICS 0001

Name and country of main investigator or name of MC-trial:

Dr. P.M. Dewland, Simbec Research Limited, Mid-Glamorgan, UK.

Title of study protocol:

The tolerance of ICS 205-930 administered in rising single oral doses to healthy male volunteers.

Date of protocol: 10.7.84.

Aim of study, selection criteria and target parameters:

Aim: To examine the tolerance of rising single oral doses of ICS 205-930 in healthy male volunteers by assessment of reported side effects, labora parameters, vital signs and clinical examination. Also to gain preliu pharmacokinetic information.

Selection: Males, 18 to 45 years, free from gastro-intestinal disease or ot significant organic dysfunction, no history of hypersensitivity. At l two months since any previous drug trial. No concomitant medication.

Type of study		Design of study (please cross appropr. circles)					
experimental	X					normal	
therapeutic	O	randomized	X	single group	O	volunteers	X
field	O	open	O	parallel groups	X	patients	O
PMS	O	single blind	O	cross-over	O		
.....	O	double blind	X	other design	O	in-house	O

No. of pats./volunt. planned: Ninety-six studied in total.

Begin of study (Mth., Yr.): July 1984

Last pat. completed (Mth., Yr.): June 1985

Trtm. strategies (indicate medication(s),gal. Form(s),dosage(s),duration)

1: Rising doses were: 2.5, 5, 10, 20, 30, 45, 60, 75, 90, 115, 150 and 200

2: ICS 205-930 capsules (2.5, 5, 15 and 50 mg)

3:

4: Single doses.

5:

6:

PREPARATION:	KNGL:	BATCH:
2.5 mg	71426.01	X 095E4
5 mg	71427.01	X 096E4
15 mg	71428.01	X 097E4
50 mg	71727.03	X 108C5

Part B, Clinical Study Synopsis

Pat. population:	Total	Fill in this rectangle only for parallel group designs Trtm.1	Trtm.2	Trtm.3	Trtm.4
Entered total	96				
- Drop outs	No drop outs				
= Evaluable cases	96				
male/female	All male				
age (min/max)					
age mean	See report for individual treatment groups.				
Eval. for efficacy	96				
Discont. safety					
Discont. ineffect.					
Subj. with ADR	46% of all active (total = 72) and 29% of placebo (total 24).				

Results (Efficacy/Safety):
ICS 205-930 well tolerated up to 150 mg with side effects of a mainly mild nature. These side effects were mainly those of headache or gastro-intestinal symptoms. At 200 mg all six subjects on active experienced side effects, two of which gave cause for concern ([i] headache with dizziness and [ii] headache with nausea) and it was decided not to give any higher single doses on this basis. Laboratory findings (urinalysis, biochemistry and haematology) were largely normal. At 60 and 75 mg raised ALT values were seen in certain subjects but were not considered to be of clinical relevance and are probably related to the analytical methodology. No significant changes in vital signs were seen (pulse rate, blood pressure, ECG, respiration rate, body temperature).

Conclusions:

ICS 205-930 showed good tolerance in single doses up to 150 mg. The side effects in two volunteers at 200 mg were sufficiently severe to warrant discontinuation of the study at this level.

Pharmacokinetics:

Great variation in individual plasma levels at each dosage. Correlation seen between Cmax and dose, but not for AUC and dose. t_{max} was two hours in majority of subjects. Certain predicitions able to be made for chronic dosing. Would predict side effects at $\geq$ 100 mg b.d.s.

Clinical Expert: M.W. LUNNON

Signature: M.W. Lunnon **Date:** 12th September 1985.

Part A **CLINICAL STUDY SYNOPSIS**

Project: ICS 205-930
Clinical Indication:

cross if appropr.
Part of MC-trial O
Summary of MC-trial O

Final evaluation O
If MC-trial, abbrev. of partic. countries

Study Code(s): ICS 0004

Name and country of main investigator or name of MC-trial:

DR. P.M. DEWLAND
SIMBEC RESEARCH LIMITED, MERTHYR TYDFIL, MID-GLAMORGAN, UK.

Title of study protocol:
RISING DOSE TOLERANCE STUDY - SINGLE DOSE OF ICS 205-930 ADMINISTERED INTRAVENOUSLY TO HEALTHY HUMAN VOLUNTEERS.

Date of protocol: 15.5.85.

Aim of study, selection criteria and target parameters:
TO EXAMINE SUBJECTIVE AND LABORATORY SAFETY OF RISING I.V. DOSES OF ICS 205-930 GIVEN TO HEALTHY HUMAN VOLUNTEERS. ADDITIONALLY, TO GET PRELIMINARY PHARMACO-KINETIC INFORMATION AND TO SEE IF ICS 205-930 HAS ANY EFFECT UPON THE ICE COLD PRESSOR TEST (ICP) AND VALSALVA MANOEUVRE (VM)
SELECTION: AGE 18 TO 45 YEARS. NO EVIDENCE OF CONCURRENT DISEASE, G.I. DISORDER, FEMALES NOT AT RISK OF PREGNANCY, NO CONCOMITANT MEDICATION OR OTHER CLINICAL TRIAL WITHIN TWO MONTHS, COMPLETION OF SATISFACTORY PRE-STUDY MEDICAL.

Type of study		Design of study (please cross appropr. circles)					
experimental	X					normal	
therapeutic	O	randomized	X	single group	O	volunteers	X
field	O	open	O	parallel groups	X	patients	O
PMS	O	single blind	O	cross-over	O		
.....	O	double blind	X	other design	O	in-house	O

No. of pats./volunt. planned: Begin of study (Mth., Yr.): JULY 1985

TOTAL: TWENTY-FOUR Last pat. completed (Mth., Yr.): AUGUST 1985

Trtm. strategies (indicate medication(s),gal. Form(s),dosage(s),duration)

1: ICS 205-930 INJECTION 20 mg/10 ml
2: ICS 205-930 INJECTION 100 mg/10 ml
3: PLACEBO INJECTION
4:
5:
6:

SINGLE DOSE STUDIES
MEDICATION GIVEN
AS A TWENTY MINUTE INFUSION.

PREPARATION:	KNGL:	BATCH:
ICS 205-930 100 mg/10 ml	71511.01	Y15564
ICS 205-930 20 mg/10 ml	71[illegible]3.05	Y13864
PLACEBO AMPOULES	71[illegible]80.03	Y13964

Part B, Clinical Study Synopsis

Pat. population:	Total	Fill in this rectangle only for parallel group designs Trtm.1 20 mg	Trtm.2 40 mg	Trtm.3 60 mg	Trtm.4 90 mg	Placebo
Entered total - Drop outs	24	4	4	4	4	8
= Evaluable cases	24	4	4	4	4	8
male/female		3/1	1/3	2/2	2/2	4/4
age (min/max)		18/33	22/32	20/23	22/35	21/34
age mean		26.75	28.0	21.5	27.25	27.1
Eval. for efficacy		4	4	4	4	8
Discont. safety		-	-	-	-	-
Discont. ineffect.		-	-	-	-	-
Subj. with ADR		3	4	2	0	2

Results (Efficacy/Safety):

ICS 205-930 WAS WELL TOLERATED IN TERMS OF SUBJECTIVE SIDE EFFECTS. SIDE EFFECTS OF HEADACHE AND CONSTIPATION CONFIRMED EARLIER FINDINGS FROM SINGLE ORAL DOSE TOLERANCE STUDIES; NO DOSE-RELATED TRENDS WERE SEEN. ICS 205-930 WAS ALSO WITHOUT ADVERSE EFFECT IN TERMS OF HAEMATOLOGY AND BIOCHEMISTRY MEASUREMENTS PERFORMED ON THE VOLUNTEERS. NO OBVIOUS EFFECT UPON BLOOD PRESSURE OR THE ECG WAS SEEN. RESULTS FROM THE ICP AND VM TESTS ARE HARDER TO INTERPRET IN VIEW OF THE RELATIVELY SMALL NUMBER OF SUBJECTS STUDIED AT EACH DOSE LEVEL. HOWEVER, THE RESULTS MAY INDICATE AN EFFECT AT THE END OF INFUSION UPON THE TACHYCARDIA PRODUCED DURING VM. THE EFFECT IN THE ICP WAS TO SUPPRESS THE HR INCREASE AT LOWER DOSES, BUT APPARENTLY TO HAVE AN OPPOSITE EFFECT AT THE HIGHEST DOSE.

Conclusions:

RESULTS FROM THIS STUDY SHOW SATISFACTORY TOLERANCE OF ICS 205-930 GIVEN INTRAVENOUSLY UP TO 90 MG IN HEALTHY HUMAN VOLUNTEERS. THE COMPOUND MAY WELL HAVE AN EFFECT UPON CARDIAC REFLEXES IN RESPONSE TO CERTAIN PHYSIOLOGICAL TESTS AND THIS NEEDS TO BE INVESTIGATED WITH HIGHER NUMBERS AND ALSO ANY DOSE/RESPONSE EFFECT INVESTIGATED.

Clinical Expert: MARTIN W. LUNNON

Signatu[illegible] Date: 2.1.85