

Study Title : "A prospective, randomized, double-blind, placebo controlled, parallel group, multi-centre trial to assess the efficacy and safety of in subjects with"

Clinical study protocol number/version:

Development phase:

Study initiation date :

Study completion date :

Date of protocol :

Amendment number(s) and date :

Author(s) :

Author's and Reviewer's signature and date:

Protocol Author	Reviewed and approved by
Signature:	Signature:
Date:	Date:

This protocol incorporates the following amendment(s):

Amendment No.	Date of Amendment	Initials of CRC coordinator

Confidentiality Statement
May not be used, divulged, published or otherwise disclosed without the written consent of

1 SYNOPSIS

Title of study:

"A prospective, randomized, double-blind, placebo controlled, parallel group, multi-centre trial to assess the efficacy and safety of in subjects with"

Sponsor:

Clinical Phase:

Investigators:

Investigators will be(eg. nephrologists and endocrinologists) practicing in

Study period:years

Planned date of first subject enrolment:

Planned date of last subject completed:

Objectives:

- Primary objective:

To establish efficacy of compared to with respect to in subjects with

- Secondary objectives :

Methodology:

This is a randomised, double blind, placebo controlled, parallel group design.

Number of patients:

It is planned to randomised an estimated total of adult patients with (disease) into this study, with patients randomised into each treatment group.

Number of centres:

Inclusion criteria:

Exclusion criteria:

1.

Test treatment, dose and mode of administration:

Duration of treatment with study medication:

Criteria for evaluation:

1. Efficacy parameter(s)
 - Primary criterion
 - Secondary criteria
2. Safety parameters

Statistical methods:

1. Sample size and power considerations
 2. Efficacy analysis
-

2 SIGNATURE PAGE

I hereby certify that I agree to adhere to the protocol and to all the documents referenced in the protocol.

Trial Clinical Monitor:

Date

Signature

Name:

Organisation/Department:

Trial Statistician:

Date

Signature

Name:

Organisation/Department:

Medical Director:

Date

Signature

Name:

Organisation/Department:

Medical Team Member:

Date

Signature

Name:

Organisation/Department:

Coordinating Investigator:

Date

Signature

Name:

Organisation/Department:

3 TABLE OF CONTENTS

1	<u>SYNOPSIS.....</u>	2
2	<u>SIGNATURE PAGE</u>	3
3	<u>TABLE OF CONTENTS</u>	4
4	<u>LIST OF ABBREVIATIONS</u>	7
5	<u>GLOSSARY OF TERMS</u>	8
6	<u>ETHICS & REGULATORY CONSIDERATIONS.....</u>	9
6.1	INDEPENDENT ETHICS COMMITTEE	9
6.2	ETHICAL CONDUCT OF THE STUDY	9
6.3	INFORMED CONSENT AND SUBJECT INFORMATION.....	9
6.4	PATIENT PROTECTION PROCEDURES	10
6.4.1	PROCEDURES IN THE EVENT OF EMERGENCY	10
6.4.2	PROCEDURES IN THE EVENT OF PREGNANCY	11
6.4.3	PATIENT DATA PROTECTION	11
6.4.4	INSURANCE	11
7	<u>INTRODUCTION AND BACKGROUND</u>	12
8	<u>OBJECTIVES.....</u>	13
8.1	PRIMARY OBJECTIVE:	13
8.2	SECONDARY OBJECTIVE(S):.....	13
8.3	ANCILLARY OBJECTIVE(S):	13
9	<u>STUDY DESIGN</u>	13
9.1	OVERALL STUDY DESIGN	13
9.2	SCHEMATIC DIAGRAM OF STUDY DESIGN:.....	13
9.3	DISCUSSION OF STUDY DESIGN	14
9.4	STUDY POPULATION	14
9.4.1	INCLUSION CRITERIA	14
9.4.2	EXCLUSION CRITERIA	14
9.4.3	SUBJECT WITHDRAWAL & DROP-OUT	14
9.4.4	PROCEDURES FOR HANDLING WITHDRAWAL.....	15
9.4.5	SUBJECT REPLACEMENT POLICY	15
9.4.6	SCREENING FAILURES	15
10	<u>TREATMENT AND STUDY PROCEDURES</u>	15
10.1	DESCRIPTION OF STUDY DRUG/INTERVENTION.....	15

10.2	COMPARATOR DRUG/INTERVENTION	15
10.3	DOSAGE AND ADMINISTRATION	15
10.4	INVESTIGATIONAL PRODUCT SUPPLY AND HANDLING.....	16
10.4.1	SUPPLY, PACKAGING AND LABELLING.....	16
10.4.2	STORAGE.....	16
10.4.3	DISPENSING.....	16
10.4.4	ACCOUNTABILITY	16
10.5	CONCOMITANT MEDICATION/TREATMENT	17
10.6	TREATMENT ALLOCATION AND RANDOMIZATION.....	17
10.7	BLINDING & EMERGENCY UNBLINDING PROCEDURES	17
10.8	BASELINE ASSESSMENT AND LABORATORY TESTS.....	17
10.9	ASSESSMENT OF COMPLIANCE	18
10.10	DISCONTINUATION AND INTERRUPTION OF TREATMENT.....	18
10.11	ASSESSMENT OF EFFICACY	18
10.12	ASSESSMENT OF SAFETY	18
<u>11</u>	<u>ADVERSE EVENTS.....</u>	<u>18</u>
11.1	DEFINITIONS	19
11.1.1	ADVERSE EVENT (AE)	19
11.1.2	UNEXPECTED ADVERSE EVENT	19
11.1.3	SERIOUS ADVERSE EVENT (SAE).....	19
11.2	DETECTING AND DOCUMENTING AE	20
11.3	REPORTING SAE	21
11.4	TREATMENT AND FOLLOW UP OF AE	22
11.5	SAFETY UPDATE.....	23
<u>12</u>	<u>STUDY CONDUCT</u>	<u>24</u>
12.1	STUDY VISITS AND PROCEDURES	24
12.1.1	SCREENING VISIT	24
12.1.2	BASELINE VISIT	24
12.1.3	RANDOMISATION	25
12.1.4	STUDY TREATMENT AND VISITS	25
12.2	CRITERIA FOR STOPPING SUBJECT TREATMENT.....	28
12.3	DROPOUTS AND WITHDRAWALS	28
12.4	SAMPLE HANDLING AND ANALYSIS	28
12.4.1	COLLECTION	28
12.4.2	LABELLING	28
12.4.3	SHIPMENT OF SAMPLES	28
12.5	LABORATORY ANALYSIS.....	28
<u>13</u>	<u>DATA MANAGEMENT.....</u>	<u>29</u>
<u>14</u>	<u>STATISTICAL METHODS.....</u>	<u>29</u>
14.1	SAMPLE SIZE AND POWER CONSIDERATIONS	29
14.2	RANDOMISATION.....	29
14.3	ANALYSIS	29
14.3.1	ANALYSIS SETS.....	29
14.3.2	BASELINE COMPARABILITY	30
14.3.3	EFFICACY ANALYSIS	30

14.3.4	SAFETY ANALYSIS	30
14.3.5	HANDLING OF MISSING, UNUSED AND SPURIOUS DATA	30
14.3.6	PROCEDURE FOR DEVIATION FROM ORIGINAL STATISTICAL PLAN	30
14.3.7	PLANNED INTERIM ANALYSIS	30

15 ADMINISTRATIVE MATTERS..... 30

15.1	NOTIFICATION OF REGULATORY AUTHORITY(IES).....	30
15.2	NOTIFICATION OF PRIMARY CARE PHYSICIAN	30
15.3	STUDY INITIATION.....	30
15.4	PROTOCOL DEVIATION	30
15.5	STUDY DOCUMENTATION.....	31
15.5.1	ESSENTIAL DOCUMENTS	31
15.5.2	SOURCE DOCUMENTS.....	31
15.6	PATIENT IDENTIFICATION LIST/ENROLLMENT LOG	31
15.7	CURRICULUM VITAE	32
15.8	SITE SIGNATURE/AUTHORIZATION LOG	32
15.9	MONITORING THE STUDY	32
15.10	AUDITS AND INSPECTIONS	32
15.11	RETENTION OF DOCUMENTS.....	32
15.12	FINANCE.....	33
15.13	STUDY TERMINATION AND SITE CLOSURE.....	33
15.14	CONFIDENTIALLY	33
15.15	PUBLICATION POLICY	33
15.16	ANTICIPATED SUBJECT ACCRUAL AND DURATION OF THE STUDY	34
15.17	AUDITS AND INSPECTION	ERROR! BOOKMARK NOT DEFINED.

16 REFERENCES 35

17 APPENDICES..... 35

4 LIST OF ABBREVIATIONS

⁰ C	Degree Centigrade
AE	Adverse event
BP	Blood pressure
CRC	Clinical Research Centre
CRF	Case report form
CV	Curriculum vitae
ENT	Ear, nose and throat
GCP	Good clinical practice
IEC	Independent Ethics Committee
ID	Identification
IRB	Independent Review Board
IUD	Intrauterine device
mmHg	Millimetre mercury
SAE	Serious adverse event

5 GLOSSARY OF TERMS

(Comprehensive list of commonly used terms is found in Malaysian Guidelines for GCP)

Eligible	Qualified for enrolment into the study based on strict adherence to inclusion and exclusion criteria.
Evaluable	Meeting all eligibility criteria, complying with the procedures defined in the protocol and therefore included in analysis.
Investigator	Treating physician
Monitor	An individual assigned by CRC who is responsible for assuring proper conduct of a clinical study.
Protocol amendment	Any change in a study protocol which affects the safety of subjects, the scope, design, assessments or scientific validity of the clinical investigation.
Subject(s)	Individuals enrolled in the clinical study.

6 ETHICS & REGULATORY CONSIDERATIONS

6.1 Independent Ethics Committee

The study protocol and any other documents that the IEC may need to fulfil its responsibilities including the Patient Information Sheet, Consent Form, subject requirement procedures and advertisements to be used, and information on payments and compensation available to subjects, will be submitted to a properly constituted Independent Ethics Committee (IEC). Unconditional approval or a favourable opinion must be received from the IEC before commencement of this study. Approval from the committee must be documented in a letter to the investigator specifying the study title, protocol number, the documents reviewed, the date on which the committee met and granted the approval, the name, occupation and institutional affiliation of the chairman and members of the IEC, and provisions for periodic review if any. Any amendments to the protocol, other than administrative ones, must also be approved by this committee.

The principal investigator will inform the IEC of:

- Any amendment to the protocol, informed consent changes or revisions of other documents originally submitted for review.
- Any serious and/or unexpected events occurring during the study, where required.
- Any new information that may adversely affect the safety of the subjects or the conduct of the study.
- An annual update on the progress of the study and/or request for re-approval, where required.
- Final study report when the study has been completed, where required.

All correspondence with the IEC should be filed by the principal investigator in the Investigator's Study File and a copy forwarded to CRC and sponsor.

6.2 Ethical conduct of the study

The study will be conducted in compliance with the protocol and CRC standard operating procedures. These are designed to ensure adherence to the ethical principles that have their origin in the "World Medical Association Declaration of Helsinki" (see Appendix), "Malaysian Guidelines for Good Clinical Practice" and applicable regulatory Requirements.

6.3 Informed consent and subject information

Freely given informed consent must be obtained from every subject prior to participation in this study. The investigator must inform every subject in detail about the nature of the study, its purpose, the treatments and the probability of random assignment to treatment groups, those aspects of the study that are experimental, the procedures involved including all invasive procedures and the discomfort they may entail, the possible risks including to an embryo,

foetus or nursing infant where applicable, the reasonably expected benefits the expected duration and the approximate number of subjects involved and the subject's responsibilities.

Study subjects must also be informed that:

- Participation in this study is voluntary and that he/she may withdraw from this study at any time for any reason and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.
- They will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the study.
- Alternative procedures or treatments that may be available and the important potential benefits and risks of these available alternative procedures or treatments.
- Any compensation for additional costs and/or injury caused to a subject attributable to participation in the study.
- Financial expenses, if any, to the subject for participating in the study as well as prorated payment, if any, to the subject for participating in the study.
- Any foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.
- The person(s) to contact for further information regarding the study and whom to contact in the event of study related injury.

Written consent will be obtained from each subject involved in the study. If written consent is not possible, oral consent can be obtained if witnessed by a signed statement from one or more persons not involved in the study, stating why the patient was unable to sign the consent form. The informed consent form used to document written or oral consent in the study must be received prior to approval from the IEC. If the subject and his/her parent/guardian are unable to read, the investigator or designee must explain to the subject the content of the Patient Information Sheet and Consent Form point by point in the presence of an impartial witness. The witness should personally sign and date the consent form. The potential study subject and/or his/her parent/guardian should be given the opportunity to ask questions and time for consideration.

A copy of the Patient Information Sheet and signed Consent Form should be given to the subject. The original must be filed by the principal investigator in the Investigator's Study File. A sample of the Patient Information Sheet and Consent Form can be found in the Appendix of this protocol.

6.4 Patient protection procedures

6.4.1 Procedures in the event of Emergency

The investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study. An emergency may constitute an SAE.

6.4.2 Procedures in the event of Pregnancy

The subject must be instructed to inform the investigator if she becomes pregnant during the study and seek advice regarding continuation of the study treatment. The investigator should follow up the pregnancy until the outcome is known.

6.4.3 Patient data protection

The investigator must assure that the subjects' anonymity will be maintained and that the confidentiality of records and documents that could identify subjects will be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

- Subjects must be identified only by their assigned identification number and initial on all CRFs and other records and documents submitted to CRC and sponsor.
- The investigator will keep a Patient Identification List with complete identification information (name, address, contact number, IC#) on each subject.
- Documents not for submission to CRC such as subject's written informed consent form, should be maintained by the investigator in strict confidence.

Monitors and auditors from CRC and sponsor, and representatives of IEC or other regulatory agencies will be granted direct access to subject medical records and other study documents for verification of study procedures and data without violating the confidentiality of the subject. The subject should be informed that by signing a written informed consent form, the subject or his/parent or guardian is authorizing such access.

All electronic data processed at CRC will be identified by patient numbers only, thereby ensuring that patients' identity remains unknown to CRC and the sponsor.

6.4.4 Insurance

With respect to any liability directly or indirectly caused by the investigational products in connection with this study, the sponsor assumes liability by law on behalf of the investigator and his/her staff for possible injury to the subject, provided the investigator and his/her staff have followed the instructions of the sponsor in accordance with this protocol and any amendments thereto, that the investigational products administered to the subject in this study have been supplied by the sponsor and that the investigator and his/her staff have in general performed this study in accordance with scientific practice and currently acceptable techniques and know how.

7 INTRODUCTION AND BACKGROUND

- Condition(s) to be treated - natural history, diagnostic criteria, routine medical management, other variables that influence the progress of the condition
- Name and description of investigational product(s)
- Findings from non-clinical and clinical studies relevant to the trial
- Applicable epidemiological or public health background
- Known potential risks and benefits to human subjects
- Rationale for the study and study design. Include a description of and justification for the route of administration, dosage, dosing regimen, intervention periods, and selection of study population.
- Other relevant literature

7.1 Potential Risks

Include a review of relevant literature, which should be referenced. Add relevant websites, etc from which the information could be drawn.

If a package insert is available, it should be used as the primary source of risk information. If the product is investigational, the Investigator's Brochure (IB) should be the primary source of the risk information. In addition, literature searches can also provide relevant risk information. If the risk profile cannot be described from any of the above sources, the risk information discussion will result from the literature search and review.

Describe in detail any physical, psychological, social, legal, economic, or any other risks to subjects, as to each of the following:

- Immediate risks
- Long-range risks
- Rationale for the necessity of such risks
- Alternative data gathering procedures that have been considered or will be considered
- Why alternative procedures may not be feasible
- Why the value of the information to be gained outweighs the risks involved.

7.2 Potential Benefits

If the research is beneficial, describe in detail any physical, psychological, social, legal, economic, or any other benefits to subjects.

Note: Payment to subjects, whether as an inducement to participate or as compensation for pain and inconvenience, is not considered a "benefit."

8 OBJECTIVES

8.1 Primary objective:

To assess the efficacy of compared to in patients with

8.2 Secondary objective(s):

- relate to subsidiary end points
- relate to subgroup hypothesis eg. other than overall contrast between each arm of trial

8.3 Ancillary objective(s):

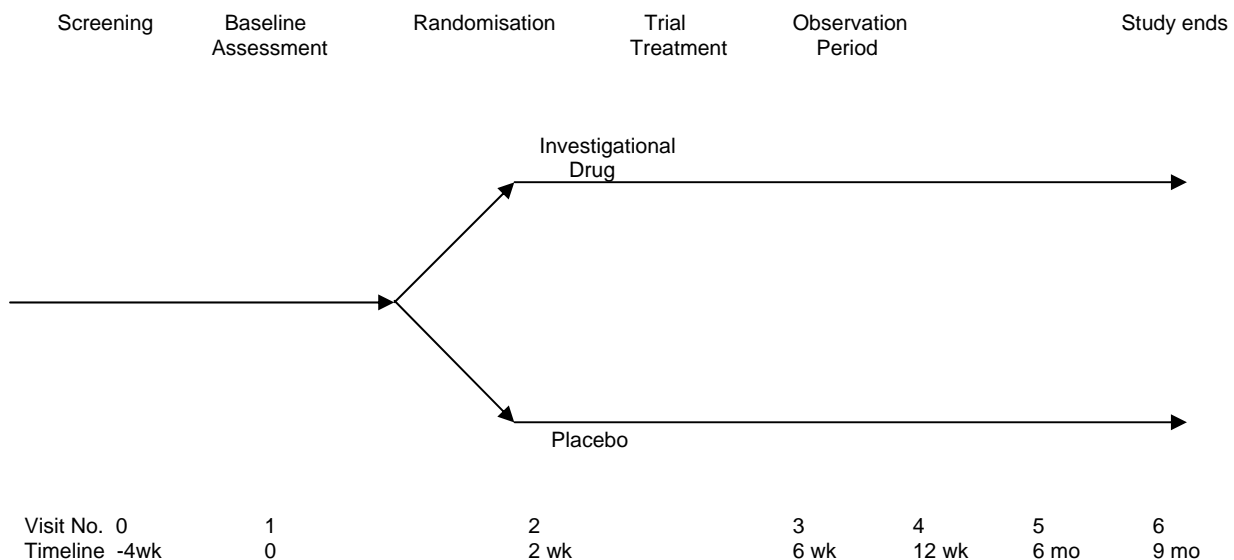
Do not bear directly on the intervention being tested but which are also of interest; eg. natural history of disease in the control group, risk factor analysis.

9 STUDY DESIGN

9.1 Overall study design

9.2 Schematic diagram of study design:

Design of a randomized, controlled, double-blind clinical trial



9.3 Discussion of study design

Discussion includes justification of design, choice of control groups

9.4 Study population

9.4.1 Inclusion criteria

- a) Provision of written consent by subject or guardian.
- b) Subject of either sex, to years of age (inclusive)
- c) Female patients will either be
 - post-menopausal for ≥ 2 years
 - surgically sterile
 - or, if of childbearing age, using double contraception, with at least one method being barrier contraception. Women of childbearing potential must have a negative pregnancy test at screening and at randomisation. Pregnancy tests will be repeated during each visit.

9.4.2 Exclusion criteria

- a) Inability or unwillingness to provide written consent.
- b) Inability or unwillingness to comply with the requirements of the protocol as determined by the investigator.
- c) Pregnancy, breastfeeding or use of non-reliable method of contraception.
- d) Other medical condition which, in the investigator's judgement, may be associated with increased risk to the subject or may interfere with study assessments or outcomes.
- e) Participation in another clinical trial and/or receipt of investigational drugs within 4 weeks prior to screening visit.
- f) Use of medications prohibited prior to first randomization.

9.4.3 Subject withdrawal & drop-out

Subjects are free to withdraw from the study at any time for any reason. Subjects may also be withdrawn from the study at any time at the discretion of the investigator. It should be understood that an excessive rate of withdrawals may render the study difficult to be interpreted. Missing data on efficacy assessments may significantly affect the interpretation of the study results. Should a subject withdraw or is withdrawn, every effort must be made to complete and report the observations as thoroughly as possible.

Possible reasons for withdrawal:

- Adverse event(s)
- Abnormal laboratory values
- Improvement of subject's condition such that he/she no longer requires study treatment
- Insufficient therapeutic effect
- Protocol violation (eg. incorrectly enrolled or randomised)
- Subject requires use of unacceptable concomitant medication
- Subject not compliant with protocol procedures
- Subject develops a condition during the study that violates the inclusion/exclusion criteria

- Lost to follow-up
- Administrative problems
- Death
- Any other reason, in the investigator's opinion, that would impede the subject's participation in the study

9.4.4 Procedures for handling withdrawal

Subjects who withdraw or are withdrawn from the study should:

- Have the reason(s) for their withdrawal recorded
- Be asked about the presence of any AEs and if so should be followed up by regular scheduled visits, telephone contact, correspondence or home visits until satisfactory clinical resolution of AEs is achieved.
- Be seen by an investigator and all final assessments will be performed and recorded in the Termination page of CRF.
- Be encouraged to continue coming for regular visits and assessments
- Have at least one follow-up contact (scheduled visit, telephone contact, correspondence or home visit) for safety evaluation during the 30 days following the last dose of study treatment.
- In the event of pregnancy, the subject should be monitored until conclusion of the pregnancy and the outcome of pregnancy reported.
- Have study treatment returned.

9.4.5 Subject replacement policy

9.4.6 Screening failures

Patients who fail to meet the inclusion and exclusion criteria are defined as screening failures. The investigator will maintain a Screening Log which includes screen failures. The log will document the subject number, subject initials, demographics and the reason(s) for excluding the patient from the study. This log will be kept in the Investigator's Study File. It will be used to determine systematic bias in selection of patients for entry into the study.

10 TREATMENT AND STUDY PROCEDURES

10.1 Description of study drug/intervention

10.2 Comparator drug/intervention

10.3 Dosage and administration

10.4 Investigational product supply and handling

10.4.1 Supply, packaging and labelling

Each study drug box will be labelled with the following information:

- Sponsor identification
- Manufacturer's identification
- Protocol number
- Caution statement
- 'For Clinical Trial Use Only' statement
- Investigational product identification (name/treatment no.) and batch number
- Quantity of bottles
- Storage conditions
- Expiry date

10.4.2 Storage

The investigational product must be stored in accordance with the manufacturers' instructions. Required conditions for storage will be printed on the medication label. Until the investigational product is dispensed, it must be kept under refrigeration at °C. The minimum requirement for temperature monitoring will be for a thermometer that measures maximum and minimum temperatures to be placed within the load. The thermometer should be read and reset daily, preferably in the mornings and the maximum and minimum temperatures are to be recorded in the Storage Temperature Log.

Investigational product should be kept under adequate security by the investigator and only accessible to authorised study personnel.

10.4.3 Dispensing

Each patient will be dispensed sufficient medication for weeks of therapy. Upon dispensation, the investigator must write the following in the Investigational Product Dispensing Log: subject ID and initials and date dispensed, the total dose given weekly/monthly and frequency of dosage, total bottles dispensed, batch number and expiry date of product.

10.4.4 Accountability

The investigator or designee must maintain current and accurate record of the receipt, inventory and dispensing, including shipping invoices, of all study supplies. The Investigational Product Accountability Log must include:

- Date received
- Delivery order (D.O.#) reference number and amount received and placed in storage
- Name of study medication and dosage
- Amount currently in storage area
- Label ID number or batch number/Lot number

- Name and initial of person responsible for each investigational product inventory entry/movement
- Amount dispensed to and returned by each subject, including unique subject identifiers
- Amount transferred to another area for dispensing or storage
- Non-study disposition (eg. Lost, wasted, broken)
- Amount returned to sponsor or CRC
- Amount destroyed at study site

Accountability logs must be available for inspection by CRC monitor at any time. Upon completion/termination of the study, unused investigational product must be returned to the sponsor or CRC for reconciliation and destruction.

10.5 Concomitant medication/treatment

10.6 Treatment allocation and randomization

10.7 Blinding & emergency unblinding procedures

All study personnel and subjects will be blinded to the study medication during the trial. In the event that an AE or pregnancy occurs for which knowledge of the identity of the test drug is necessary to manage the subject's condition, the sealed emergency code key for that subject may be broken and the test drug identified by the medical monitor. The medical monitor will have a set of sealed emergency code keys (one for each subject) kept in a secured location and he/she will be accessible at all times by telephone. Should emergency unblinding be required, the investigator will call the medical monitor who will break the emergency code key for that subject, identify the test drug and inform the investigator. A detailed report with the date and reason for identifying the study drug will be prepared by the medical monitor and attached to the CRF. This report must be signed by the medical monitor and the investigator. All unused sealed code keys will be accounted for at the end of the study.

Except in the case of emergency, the treatment blind will be maintained until all subjects have completed the treatment and the database has been cleaned and locked. Any broken code will be clearly justified and explained by a comment on the case report form, along with the date on which the code was broken.

10.8 Baseline assessment and laboratory tests

- Social demographics, weight and height

- Co-morbid factors
- Primary disease
- Drug history
- Laboratory data

10.9 Assessment of compliance

Accountability and subject compliance will be assessed by maintaining adequate "drug dispensing" and return forms. Subjects will be required to return all unused study medication, and the pill count will be entered into the CRF.

10.10 Discontinuation and interruption of treatment

10.11 Assessment of efficacy

Specify what outcomes are expected and what criteria are to be applied to determine success or failure of the trial. Outcomes may include prevention of a condition, cure, improvement, alleviation of symptoms, improved physical or mental health.

Specify efficacy parameter:

- Primary end-point(s): Rx effect for primary objective
- Secondary end-point(s): supportive measures related to Rx effect for secondary objective
- Global assessment variable: overall safety; Rx effect and usefulness
- Surrogate variable: predictor of clinical benefit

10.12 Assessment of safety

Safety and tolerability assessments will consist of:

- Regular performance of physical examinations
- Regular monitoring of laboratory tests
- Monitoring and recording all adverse events and serious adverse events

11 ADVERSE EVENTS

There should be criteria for observing, recording and reporting AE. If AE would endanger a patient, he/she should be excluded from the study and treated appropriately. The trial should also be stopped if too many AE are observed.

11.1 Definitions

11.1.1 Adverse event (AE)

Any untoward medical occurrence in a subject administered an investigational product and which does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavourable and unintended sign, symptom, laboratory observation or disease temporally associated with the use of the investigational product, whether or not related to the investigational product.

The following should be reported as AE:

- Treatment emergent symptoms which include:
 - Medical conditions or signs or symptoms that was absent before starting study treatment.
 - Medical conditions or signs or symptoms present before starting study treatment and worsen (increase severity or frequency) after starting study treatment.
- Abnormal laboratory values or tests that induce clinical signs or symptoms or require therapy.
- Any adverse experience even if no drug has been administered, for example during run in or wash out phase of the study.
- For studies involving a marketed drug in an established indication, AE includes significant failure of expected pharmacological or biological action.
- Any doubtful event should be treated as an AE.

11.1.2 Unexpected adverse event

Any adverse event not reported in the safety section of the Investigator's Brochure or if the event is of greater frequency, specificity or severity.

11.1.3 Serious adverse event (SAE)

Any adverse event occurring that:

- Results in death
- Is a life threatening adverse experience defined as any adverse event that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. Note that this does not include a reaction that had it occurred in a more severe form, it would have caused death.
- Results in subject hospitalisation or prolongation of existing hospitalisation.

The following hospitalisations are not considered to be SAEs:

- Those planned before entry into the study
- Elective treatment for a condition unrelated to study indication or study treatment
- Occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria in SAE definition)

- Part of normal treatment or monitoring of the study indication and are not associated with any deterioration in condition.
- Results in a significant or persistent disability or incapacity defined as any event that results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.
- Is a congenital anomaly or birth defect
- Is any instance of overdose, either accidental or intentional (suspected or confirmed)
- Is any other important medical event, based upon appropriate medical judgement, that may jeopardise the subject or may require medical or surgical intervention to prevent or avert one of the outcomes listed above.

11.2 Detecting and documenting AE

Information about all AEs, whether volunteered by the patient, discovered by investigator questioning or detected through physical examination, laboratory test or other means, would be recorded on the Adverse Event Page of the CRF and followed up as appropriate.

When eliciting experiences of AE from a subject, ask a standard non-leading question like "Do you feel different in any way since starting the new treatment/the last visit?" This question will be put to the subject in his/her own language at each study visit.

Each AE should be described by:

a) Nature of AE

This should be documented in terms of a medical diagnosis(es). When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject.

b) Duration

Start and end dates

c) Assessment of causality

The investigator should attempt to explain each AE and assess its relationship, if any, to the study treatment. Causality should be assessed using the following definitions:

- Very likely
 - The AE follows a reasonable temporal sequence from study treatment administration
 - Abates upon discontinuation of study treatment
 - Reappears on repeated exposure (re-challenge)
- Probable
 - The AE follows a reasonable temporal sequence from study treatment administration
 - Abates upon discontinuation of study treatment
 - Cannot reasonably be explained by known characteristics of the subject's clinical state

- Possible
 - The AE follows a reasonable temporal sequence from study treatment administration
 - But could have been produced by the subject's clinical state or other mode of therapy administered to the subject
- Doubtful
 - The temporal association between study treatment and AE is such that the study treatment is not likely to have any reasonable association with the observed event
- Very unlikely
 - The AE is definitely produced by the subject's clinical state or other mode of therapy administered to the subject

The degree of certainty with which an AE is attributed to study treatment or alternative cause like natural history of disease or concomitant treatment should be guided by the following considerations:

- Time relationship between treatment and occurrence of AE
- De-challenge and re-challenge information, if applicable
- Known pharmacology of the drug
- Dose response relationships
- Lack of alternative explanations i.e. no concomitant drug used and no other inter-current disease
- Reaction of similar nature being previously observed with this drug or class of drug
- Reaction having often been reported in literature for similar drug

d) Severity of AE

- Mild: awareness of signs or symptoms, but they are easily tolerated
- Moderate: enough discomfort to cause interference with usual activity
- Severe: incapacitating, with inability to work or do usual activity

Note that a severe AE is not necessarily serious. The term severe is a measure of the intensity while a serious AE is determined based on regulatory criteria. A life threatening AE is an SAE.

11.3 Reporting SAE

Information about all SAE will be recorded on the Serious Adverse Event Page of the CRF. All events documented in the SAE Form must be reported within 24 hours to the Clinical Research Centre (CRC)/sponsor by fax (see below for contact person and fax no.). The investigator should not wait to receive additional information to fully document the SAE before notifying CRC. A fax SAE form detailing relevant aspects of the SAE in question should follow telephone report of SAE. The investigator should also comply with the applicable regulatory requirements related to the reporting of unexpected serious drug reactions to the regulatory authorities. Where applicable, information from relevant medical records and autopsy reports should be obtained.

Any death or congenital abnormality, if brought to the attention of the investigator within 6 months after cessation of study treatment, whether considered treatment related or not, should be reported to CRC.

Study contact for reporting SAE:

Name:

Department:

Tel:

Fax:

E-mail:

Mobile phone:

24 hour contact information for physicians on call will be provided to each site prior to study initiation.

11.4 Treatment and follow up of AE

Treatment of any AE is at the sole discretion of the investigator who should follow up subjects with AE until the event has resolved or until the condition has stabilised. Otherwise appropriate medical care should be arranged for the patient. Abnormal tests should be repeated until they return to baseline levels or an adequate explanation of the abnormality has been found. Any follow up information should be reported to CRC monitor as soon as it becomes available.

➤ Treatment of over-dosage

➤ Pregnancy

Information on effects of trial drug in pregnancy. A female subject must be instructed to stop taking study medication and immediately inform the investigator if she becomes pregnant during the study. The medical monitor must be contacted immediately to break the blind. The investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject should continue until conclusion of the pregnancy. The investigator should report all pregnancies to the sponsor within 24 hours of being notified of the pregnancy.

Pregnancies occurring up to 90 days after completion of the study medication that come to the attention of the investigator must also be reported to the sponsor.

Pregnancy occurring in the partner of a subject participating in the study should also be reported to the investigator and sponsor. The partner should be counselled and followed as described above.

Pregnancies will be formally reported as SAEs.

11.5 Safety update

Sponsor will notify investigators of all AEs that are serious or unexpected and very likely, probably or possibly related to the investigational product. The investigator must retain such notice with the Investigator's Brochure and immediately submit a copy of this information to the IRB/IEC. The IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

12 STUDY CONDUCT

12.1 *Study visits and procedures*

Any deviation from the study procedures described below will be noted in the CRFs and the sponsor and CRC will be notified.

12.1.1 Screening visit

- Assess subject for eligibility to enter study according to the inclusion and exclusion criteria.
- Women of child bearing potential should have a negative test (the type of test should be stated) within 1 week prior to beginning study medication. Study medication should not be initiated until a report of a negative pregnancy test has been obtained. Contraception methods will be discussed and 2 reliable forms of contraception must be used simultaneously unless abstinence is the chosen method. Effective methods of contraception are oral contraception, Norplant, surgical sterilization, IUD, or diaphragms in conjunction with spermicidal foam and condom on the male partner.
- Obtain written consent from subject or parent/guardian.
- The following screening tests are done:
- For subjects enrolled into the study, complete relevant section/page of CRF.
- Record all screened subjects in the Screening Log regardless of whether or not the subject has been enrolled in the study.

Baseline evaluation and randomization can be performed during the screening visit or another visit.

12.1.2 Baseline visit

The following data will be collected at baseline:

- Subject's demography: date of birth/age, sex, race, height (cm) and weight
- Background and medical history which includes any diagnosed medical conditions within the previous 12 months, history of medication and medical procedures within the previous 30 days of entry into the study.
- Physical examination:
Complete physical examination, performed by a licensed physician, will include examination of general appearance, skin, neck (including thyroid), eyes (including fundi), ENT, lungs, heart, abdomen, back, lymph nodes, extremities and neurological examination.
- Vital signs
The following vital signs assessments will be performed:
 - Body weight (kg) and height (cm), no shoes in light clothing
 - Pulse in beats/min, taken at the radial artery over 60 seconds, after 5 minutes rest prior to BP measurements, once in the sitting position.
 - Blood pressure will be measured with a mercury sphygmomanometer, once in the sitting position after 5 minutes rest. At least 2

measurements should be taken with a 2 minute interval between measurements.

- BP should be measured by the same study personnel whenever possible and on the same arm. All measurements should be to the nearest 2 mmHg. Diastolic BP is determined at Phase V (i.e. disappearance of the Korotkoff sound).

➤ Laboratory evaluations

The following laboratory evaluations will be done: (list tests to be done).

State which laboratory will be performing the tests. The investigator will have a set of reference ranges for tests performed at the local lab. The monitor should be informed if these ranges have changed, or if tests were conducted by an alternative lab, a relevant set of reference ranges should be provided.

Refer to Section for instructions regarding collection and transport of samples.

- Complete relevant section/page of the CRF.

12.1.3 Randomisation

- Complete the Randomization Sheet
- Describe the procedure for randomization
- The following information will be recorded during randomization:
 - Study ID (assigned during study initiation)
 - Site ID (assigned during study initiation)
 - Investigator password (assigned during study initiation)
 - Subject's screening status
 - Date of informed consent signed by subject
 - Subject's ID no. (eg. Last 4 digits of IC)
 - Upon successful randomization, the subject will be assigned a randomization number and treatment. Document the subject's ID no. and randomization no. on the Patient Enrolment Log and Patient Identification List.

12.1.4 Study treatment and visits

Study visits will occur at weeks for efficacy and safety assessments for the duration of the study. There will be a total of visits.

The investigator will perform the following procedures at each visit where applicable:

- Medical history taking
- Record any concomitant medication
- Record any change of dose administration of study treatment
- Perform physical examination including vital signs

- Obtain blood sample for lab evaluations
- Record any AE or SAE
- Complete relevant section/page of CRF
- Dispense study treatment

Study visits schedule and procedures are summarised in the table below:

	Screening & Baseline	Treatment				End	Post trial
Visit	1	2	3	4	5	6	7
Timeline	0	2wks	6wks	12 wks	6 mo	9 mo	12 mo
Procedures							
Check eligibility	X						
Blood sample for screening	X						
Informed consent	X						
Randomisation	X						
Patient demographics & medical history	X						
Clinical examination	X	X	X	X	X	X	X
Lab. test 1	X			X		X	X
Lab. test 2	X	X	X	X	X	X	X
Lab. test 3	X		X	X		X	X
Efficacy assessment	X	X	X	X	X	X	X
Report AE and SAE	X	X	X	X	X	X	X
Dispense study treatment	X	X	X	X	X	X	X
Complete relevant section of CRF	X	X	X	X	X	X	X

12.2 Criteria for stopping subject treatment

12.3 Dropouts and withdrawals

12.4 Sample handling and analysis

12.4.1 Collection

12.4.2 Labelling

- The standard labels provided by central lab should be used to label each sample.
- Any hand written additions to the labels should be made using indelible ink
- Labels should not be attached to caps.

12.4.3 Shipment of samples

- Storage of samples before and during shipment
- Timeframe for shipment
- The investigator or designee should complete the sample request form specifying the samples being shipped and tests required for individual subjects at each shipment. A copy of this form should be retained at the study site while the original should be sealed in the specimen carrier bag and shipped with the samples.
- Samples should always be sent by the designated courier service. Do not ship sample to arrive over weekends or holidays.

12.5 Laboratory analysis

Describe methods used for each test.

#	Test	Method
1		
2		
3		
4		

13 DATA MANAGEMENT

Data management will be conducted using appropriate database and validation programmes. Accurate and reliable data collection will be assured by verification and cross-check of 100% of the CRFs against the investigator's records (source document verification). The data collected will be entered into a computer database and subject to quality assurance procedures as dictated by Standard Operating Procedures of

Describe procedures for the following:

- Data entry
- Data validation and Data Query
- Clean File and Database Lock

14 STATISTICAL METHODS

There should be epidemiological and statistical talent on the research team. Detailed plans for analysis must be made prior to the trial.

14.1 Sample size and power considerations

To compare continuous variable between the two treatment groups, the unpaired 2-tailed student's *t* test will be used. The chi-squared and Fischer's exact test methods will be used for comparison of categorical variables between the 2 groups. The expected efficacy is ___% with drug A and ___% with drug B. Based on literature, the standard deviation of the efficacy parameter is __%. Consequently the sample size is calculated to be ___ in each arm for a power of 80%. Allowing for 20% drop out rate, the sample size required is therefore ___ per arm. A *P* value of 0.05 is considered significant.

14.2 Randomisation

14.3 Analysis

14.3.1 Analysis Sets

Selection of subjects to be included in the analyses (e.g. all randomised subjects, all dosed subjects, all eligible subjects, evaluable subjects)

- 14.3.2 Baseline Comparability**
- 14.3.3 Efficacy Analysis**
- 14.3.4 Safety Analysis**
- 14.3.5 Handling of missing, unused and spurious data**
- 14.3.6 Procedure for deviation from original statistical plan**
- 14.3.7 Planned Interim analysis**

15 ADMINISTRATIVE MATTERS

15.1 Notification of regulatory authority(ies)

All necessary arrangements for the registration and approval of this study with the responsible authorities and the disposition of the required data and document will be undertaken by the Principal Investigator.

15.2 Notification of primary care physician

Investigators should ask patients if they wish for their general practitioner or primary care physician to be notified about their involvement in this study. This is so that if the patients need to see their own physician for any reason, the physician will be aware that they are taking a study drug,

15.3 Study initiation

Investigators involved in this study must not enrol any patient prior to completion of a formal meeting conducted by the Clinical Research Associate of CRC. This meeting will include an inventory of study supplies, a detailed review of the protocol and CRF, training on study procedures and other procedures required of GCP. Investigators who are not GCP certified will undergo GCP training during the study.

15.4 Protocol deviation

Any protocol deviation will be documented by the CRC monitor with rectification as soon as possible. The investigator should be notified immediately. With the exception of emergency situations, no changes or deviations in the conduct of this protocol will be permitted without the prior approval from CRC. In the event of any emergency, the investigators will institute any medical procedures deemed appropriate. All such procedures must be promptly reported to CRC.

15.5 Study documentation

The investigator must maintain adequate and accurate records to document the conduct of the study and substantiate the study data. These documents are Essential Documents and Source Documents.

15.5.1 Essential documents

These are documents that permit evaluation of the study and the quality of the data produced. The Essential Documents are:

- Signed protocol amendments
- Sample CRFs
- IRB/IEC approval letter, including a dated list of IRB/IEC membership and members' affiliation
- Informed consent form
- CV of investigator and co-investigator
- Correspondences with IRB/IEC, sponsor and CRC
- Interim reports to IRB/IEC
- Investigational product accountability and shipping records
- Site signature log
- Monitor visit log
- Other appropriate documents in accordance with GCP guidelines.

The investigator will maintain an Investigators Study File. This file shall be used to facilitate and ensure filing of all relevant and Essential Documents during and after the study. The investigator will be responsible for keeping the Investigator's Study File updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

15.5.2 Source documents

These are original hospital records, clinical charts, subject screening checklist, original laboratory reports, memoranda, pharmacy dispensing records, recorded data from automated instruments, transcriptions certified after verification as being accurate, microfiches, photographic negatives, microfilm, magnetic or electronic media, x-rays, subjects' files, and records kept at the pharmacy, at the laboratories and at medico-legal departments involved in the study.

The investigator must maintain source documents for each patient in the study. All information on CRFs must be traceable to these source documents:

- Patient identification list
- Curriculum vitae
- Site signature/authorization log

15.6 Patient identification list/Enrolment log

The investigator has to maintain a list of all enrolled patients containing the full name, date of birth, date of enrolment, and the randomization number. The

list has to show an unequivocal study identification number. The list will be filed in the Investigator's Study File on site.

15.7 Curriculum vitae

The investigator will provide curriculum vitae showing his/her experience in the area of the proposed study. These should be filed at CRC as well as in the Investigator's Study File on site.

15.8 Site signature/authorization log

The investigator must maintain a Signature Log to document signatures and initials of all staff authorized to make entries and/or corrections on CRFs and other study related records or documents. The log will be filed in the Investigator's Study File.

15.9 Monitoring the study

The monitor from the sponsor company will at frequent intervals inspect the CRFs to verify adherence to the protocol and the completeness, consistency and accuracy of the data. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

15.10 Audits and Inspections

The investigators should make available the various records of the trial to qualified personnel from the sponsor company or its designees, or to health authority inspectors after appropriate notification. The verification of CRFs data will be made by direct inspection of source documents.

15.11 Retention of documents

The investigator shall arrange for the retention of all study documents and records, including subject records, CRFs, drug inventory/accountability log, signed informed consent forms and the patient identification list for at least 3 years after completion or discontinuation of the study.

If the investigator moves or retires, he/she must nominate someone in writing to be responsible for archiving. Archived data may be held in microfiche or electronic record, provided a back up exists and a hard copy can be obtained from it if required.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made with the sponsor or CRC to store these in a sealed container(s) outside of the site so that they can be returned sealed to the investigator in case of a regulatory

audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

15.12 Finance

The Clinical Research Centre of Penang Hospital and the Sponsor company will support the work of the investigator and supply the required investigational product for the study.

15.13 Study Termination and Site Closure

The sponsor and CRC reserve the right to terminate this study and remove all study materials from the study site at any time. Reasons that may require termination of the study include:

- It becomes apparent that patient enrolment is unsatisfactory with respect to quality or quantity.
- Date recording is inaccurate and/or incomplete
- Deliberate violation of the signed protocol
- The incidence and/or severity of adverse events in this or other studies indicate a potential health hazard caused by the treatments under trial.

Should CRC or the sponsor decide to terminate the study, the investigator will complete the CRFs as far as possible. The completed CRFs and any study material will then be collected by CRC.

15.14 Confidentially

The investigator agrees that all information communicated to him/her is the exclusive property of the sponsor company or CRC, and ensure that the same will be kept strictly confidential by the investigator or any person connected with the work and shall not be disclosed to any third party without the prior written consent of the sponsor company and CRC.

15.15 Publication policy

Sponsor company and CRC agree that the investigator shall have the right to publish or permit the publication of any information or material relating to or arising out of the work.

However, any proposed publication or presentation (eg. manuscript, abstract or poster) for submission to journal or scientific meeting should be sent to the sponsor company and CRC at least 45 days prior to submission for manuscripts, and at least 21 days prior to submission to publishers for abstracts.

If the sponsor company notifies CRC during this period that it proposed to file patent applications relating to matters contained in such disclosure, disclosure will be delayed up to an additional 60 days from such notice to permit such filings.

The investigator and CRC also agree to withhold publication in the event there were any unresolved issues over interpretation of the results. The resolution of any outstanding issues over publication however should not be unreasonably delayed.

Any formal publication of the study in which input of CRC exceeded that of conventional monitoring and data management will be considered as a joint publication by the investigator and the appropriate CRC personnel.

The investigators involved shall form a Writing Committee prior to commencing the study. The committee is responsible for writing the final study report and preparing the manuscript for journal submission. It is mandatory that the first publication is based on data from all centres, analysed as stipulated in the protocol by the statistician at the Trial Coordinating Centre, and not by the investigators themselves. Investigators in this trial agree not to present data gathered from one centre or a small group of centres before the full initial publication, unless formally agreed to by all other investigators, CRC and sponsor company.

Authorship will be determined by mutual agreement prior to the start of the study and will include # lead authors for the primary presentation and publication of this study. Criteria for selection of additional authors will be agreed prior to the start of this study. As it will not be possible for all investigators to be named as authors in the primary publication, other investigators who have enrolled patients in the included in the list will be acknowledged as being part of the study team. Investigators who do not enrol any patients into the study will not be included in the list.

15.16 Anticipated subject accrual and duration of the study

This study is expected to start in The projected study timetable for the study is as follows:

- First patient enrolled is expected in
- Last patient enrolled is expected in
- The last patient enrolled is projected to complete the treatment period in

These accrual rates are based on reasonable planning expectations. The investigator should however continually compare the actual and expected accrual rates, and make every effort to ensure that they are as closely matched as possible. If the investigator anticipates major problems with recruitment, or delay in the expected completion date, he/she should discuss this with the CRC staff as early as possible.

16 REFERENCES

17 APPENDICES

- Declaration of Helsinki
- Study Procedures
- Questionnaire and CRF (*if applicable*)
- Investigational product labels
- Elements of informed consent
- Sample informed consent form (in different languages)
- Patient information sheet (in different languages)
- Letter of indemnity
- Investigators' curriculum vitae