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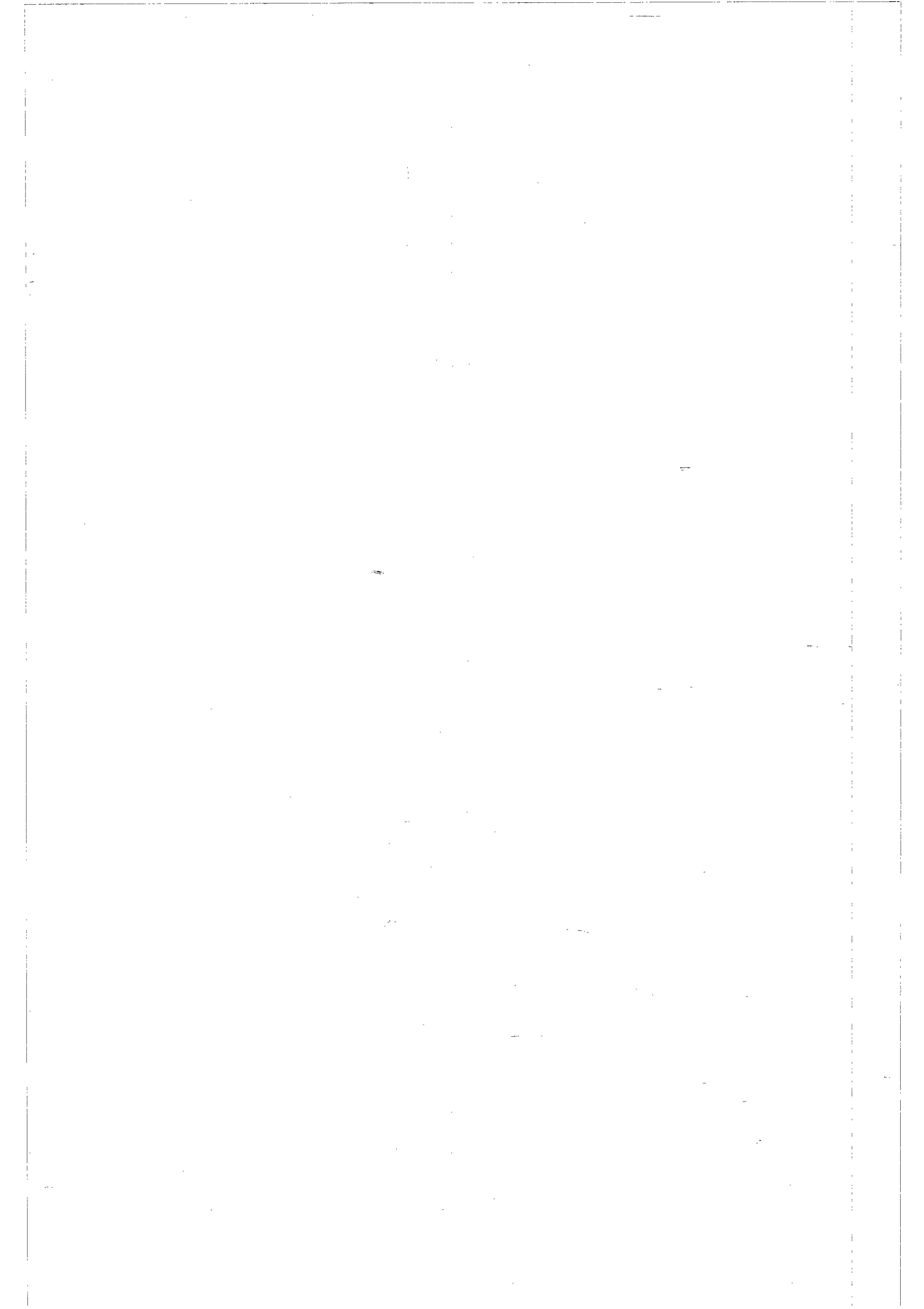
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**Establishing the bioequivalence of
RIFAMPICIN in fixed dose formulations
containing Isoniazid with or without
Pyrazinamide and/or Ethambutol compared to
the single drug reference preparations
administered in loose combination**

Model Protocol

**World Health Organization
Communicable Diseases Cluster**

1999





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IMPORTANT

This protocol is intended to serve as a guideline for the determination of bioavailability of only the rifampicin component in a fixed dose combination (FDC) anti-tuberculosis preparation. It is done by a restriction of the number of assay-points up to 8 hours only, which is different to the number of points which would be used if companion drugs in the preparation (such as pyrazinamide or ethambutol) were to be studied also (0-48 hours). This protocol would, however, also be applicable for estimating isoniazid bioavailability. In all other respects, the procedures are identical to those utilising the usual extended series of time-points. The restriction of time-points does not affect the accuracy of the rifampicin bioavailability estimate (see reference McIlleron et al., p12). It does, however, represent considerable savings in time and cost.

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GLOSSARY

IRB	Institutional Review Board
FDC	Fixed dose combination
GCP	Good clinical practice
C_{max}	Peak drug concentration in plasma
AUC_{0-8}	Area under the plasma drug concentration-time curve from 0 hours to 8 hours
ALT	Alanine transaminase
AST	Aspartate transaminase
ALP	Alkaline phosphatase
Hb	Haemoglobin
Hct	Haematocrit
RBC	Red blood cell count
WCC	White blood cell count
Plt	Platelets
ESR	Erythrocyte sedimentation rate
HIV	Human immunodeficiency virus
R	Rifampicin
H	Isoniazinamide
E	Ethambutol
Z	Pyrazhinamide

CONTACT DETAILS

Investigating centre

Name :

Address :

Telephone :

Fax :

e-mail :

Study site

Name :

Address :

Telephone :

Fax :

e-mail :

Sponsor

Name :

Address :

Telephone :

Fax :

e-mail :

INVESTIGATOR SIGNATURE PAGE

The undersigned hereby confirm that the protocol had been read and understood, and agree to abide by the procedures as stipulated

Responsibility	Name and qualification	Address	Signature and date
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Principal Investigator

Study Doctor /
Clinical Supervisor

Analysis of drug
levels

Pharmacometrician/
Statistician

Project Coordinator

Sponsor

LIST OF STUDY MEDICATIONS

Test product – Fixed dose combination

<Insert as appropriate “Fixed Dose Combination: Rifampicin+Isoniazid+Pyrazinamide+Ethambutol”>

Trade name: *<insert name and batch number>*
Dosage form: *<insert “tablet”, “capsule”, etc>*
Dose: *<no. of tablets/capsules x (xxxmg R + xxxmg H + xxxmg Z + xxxmg E)> (delete as applicable)*
Route: *Oral*
Treatment duration: *Single dose*

Reference products – Separate drugs

Rifampicin

Trade name: *<insert name and batch number>*
Dosage form: *<insert “tablet”, “capsule”, etc>*
Dose: *<4 x 150mg (total 600mg) or 3 x 150mg (total 450mg), to give an equivalent dose to that of the test product>*
Route: *Oral*
Treatment duration: *Single dose*

Isoniazid

Trade name: *<insert name and batch number>*
Dosage form: *<tablet>*
Dose: *<100mg tablets given in a dose equivalent to that of the test product>*
Route: *Oral*
Treatment duration: *single dose*

Pyrazinamide

Trade name: *<insert name and batch number>*
Dosage form: *<tablet>*
Dose: *<500mg tablets given in a dose equivalent to that of the test product>*
Route: *Oral*
Treatment duration: *single dose*

Ethambutol

Trade name: *<insert name and batch number>*
Dosage form: *<Tablet>*
Dose: *<400mg or 100mg tablets given in a dose equivalent to that of the test product>*
Route: *Oral*
Treatment duration: *single dose*

INTRODUCTION

Rationale and purpose of the study

In the treatment of tuberculosis, drugs formulated in fixed dose combination might hold several advantages over administration of the individual drugs separately.^{1,2} These include the following:

- prescribing is simpler
- physicians' prescribing errors are minimised
- patients are less likely to be confused about numbers of tablets and capsules to be taken in self administered dosage schedules
- drug doses can be more precisely adjusted to the patient's weight
- the number of pills to be swallowed is reduced.

The main advantage however, is a public health one. Since the drugs are taken in combination, the possibility of patients taking only a single drug is prevented and hence the risk of failure during treatment as a result of the selection of drug resistant strains is greatly reduced.³ This is based on the assured ingestion of at least rifampicin and isoniazid together – the important 'resistance preventing agents' in the tuberculosis treatment regimen.

However, concern has been expressed about the apparent inadequate bioavailability of rifampicin in some fixed dose combination (FDC) preparations.^{4,5} Consequently, international authorities recommend that the bioavailability of formulations should be compared with that of preparations of reputable efficacy. Only those shown to be bioequivalent should be released into the market⁶

The bioavailability of rifampicin in a fixed dose combination formulation (FDC) will be compared to that of reference preparations administered in free form. The study design will be an open, randomised, single dose, cross-over study in 22 healthy volunteers. Rifampicin and desacetylirifampicin concentrations will be determined in the blood at 0, 1, 2, 4, 6 and 8 hours after each drug administration using a validated high performance liquid chromatography (HPLC) method.

The combined formulations to be tested against established products contain rifampicin and isoniazid with or without pyrazinamide and/or ethambutol. The maximum dose administered for each active component will not exceed the recommended maximum as specified by the WHO for twice weekly intermittent treatment of tuberculosis,¹ namely rifampicin 600mg, isoniazid 600mg, pyrazinamide 2g and ethambutol 45mg/kg.

Pharmacokinetic parameters of maximum plasma concentration (C_{max}), time to achieve C_{max} (T_{max}) and area under the curve (AUC_{0-8}) for the test and reference products will be computed using parametric and non-parametric methods.

Bioequivalence will be declared if the 90% confidence interval for the test/reference ratio of AUC_{0-8} and C_{max} lie completely in the range 80% to 125% and if these parameters for the test product do not vary by more than 20% in either direction from the reference mean values.

Objective

To determine the relative bioavailability of the rifampicin component of a fixed dose combination formulation <insert name of test formulation> compared to equivalent doses of the reference formulations <insert name of reference formulations> administered in free (loose) combination.

METHODS

The procedures detailed below follow the guidelines of the World Health Organisation on registration requirements to establish interchangeability⁷ and on good clinical practice.⁸ (Also see list of Annexes).

Study sites

The clinical study will be performed at <insert name of Clinical Trial Site>. All laboratory drug assays will be performed in the laboratories of <insert name of Laboratory>.

Study design

A randomised crossover study design, utilising at least 22 healthy volunteers, between 18 and 55 years of age and 50 and 75 kg in weight will be used. Drugs will be administered as a single bolus with 200 ml of tap water, in therapeutic doses on an empty stomach after an overnight fast. Prior to each drug administration, there will be a one week washout period during which time no other medications or alcohol should have been taken by the volunteers. After one week, volunteers will receive the alternative study medications in exactly the same dosages as before.

A restricted 0 to 8 hour sampling scheme for the demonstration of bioequivalence for rifampicin will be followed. Such an approach is supported by the earlier work of McIlleron et al.⁹

Randomisation

Any volunteer screened for possible inclusion into the study will be allocated a unique "Screening Number". The 22 study subjects who are successfully recruited into the study will be ranked according to this "Screening Number" and then allocated a "Study Number" between 1 and 22. Eleven random numbers between 1 and 22 will be generated by the study statistician before screening of the volunteers begin, using a random number generator. Subjects with study numbers corresponding to these 11 generated random numbers will be assigned to receive the Test preparation in Period 1 of the study while the remaining subjects will receive the Reference medications.

Sample size

The sample size of 22, allowing for two dropouts during the course of the study, was calculated using the recommendations contained in Diletti et al.¹⁰ In the case of the multiplicative model (log-normal distribution of pharmacokinetic parameters), the power and hence the sample size to achieve a certain power depends on the residual variance (σ^2) after logarithmic transformation of the parameter of interest. A coefficient of variation (CV) for the multiplicative model was estimated using the residual mean square error from the analysis of variance (ANOVA) after logarithmic transformation and after separating the variance component due to other terms in the ANOVA.

$$CV = \sqrt{\exp(\sigma^2) - 1}$$

Assuming a CV of 21% (calculated using rifampicin AUC_{0-t} data on file), a sample size of 20 would have 80% power to correctly conclude bioequivalence when the mean $AUC_{test}/AUC_{reference} = 100\%$ within the range 80 to 125%. This was calculated at a significance level of 0.05 i.e. a 5% probability of erroneously accepting bioequivalence.

Recruitment of study subjects

Study subjects will be volunteers recruited by means of open advertisements. Persons who participated in previous studies (more than 3 months before) may also be contacted directly and informed of the opportunity to volunteer.

Volunteers will not be recruited and the study will not be conducted until regulatory authority approval, including ethics committee approval, had been granted for the use of the specific medicines as detailed in this protocol.

Inclusion criteria

Eligible volunteers will:

- be healthy
- be aged between 18 and 55 years
- weigh between 50kg and 75 kg
- have no significantly abnormal findings on medical history, physical examination or laboratory testing of blood and urine samples
- have read and signed the volunteer information and informed consent documents

Exclusion criteria

Volunteers will be excluded if they:

- have been previously treated for tuberculosis, or is suspected of suffering from tuberculosis
- previously suffered from liver disease, renal disease, gastro-intestinal disorder or ophthalmologic disorder, unless confirmed by the Study Doctor to be clinically irrelevant
- have a history of hypersensitivity to the study medication, or a history of serious allergic reaction to any drug, significant allergic disease, allergic reactions, or active allergies
- have suffered serious physical or mental illness within the past year
- have taken any medication in the week preceding first administration of the study drug, or any medicines known to affect the absorption, distribution, metabolism and/or excretion of the study medications during the preceding month
- have a history of alcohol or drug addiction
- have smoked during the 3 months preceding the study
- consume excessive amounts of alcohol (more than the equivalent of 0.5 liter of wine per day)
- have taken an investigational or recreational drug in the 3 months preceding the study
- have donated blood during the 2 months preceding the trial
- are pregnant or breast feeding
- are of child bearing potential unless they are using an acceptable non-hormonal form of contraception
- are unlikely to comply with the protocol e.g. uncooperative attitude, inability to return for follow-up visits, poor venous access.

Study subject withdrawal

Subjects may withdraw at their own request, or may also be withdrawn if, in the investigator's opinion, continued participation is not in the subject's interest or may jeopardize his/her health. The volunteer must be withdrawn from further administration of the study medication should they develop a serious adverse event that may be related to drug administration. Subjects who elect to withdraw or are withdrawn will not be replaced if they do so after the first drug administration.

Peri-study restrictions

No drugs or medications, including over the-counter preparations may have been consumed in the week preceding the study, or during the study. Should ingestion of any drug during the study be deemed necessary, the investigator should be consulted and the drug should be recorded as concomitant medication in the case record form (Annex 5). No alcohol may have been taken for 48 hours before and 8 hours after drug administration. No strenuous exercise is permitted during the day preceding drug administration.

Informed written consent

Informed written consent (Annexes 1 and 2) will be obtained from each volunteer before admission to the study. Participation must be voluntary and volunteers will be informed of possible side effects and be advised that they are free to withdraw from the study at any stage. Where appropriate a translation of the patient information sheet and consent form into the volunteer's first language will be provided.

HIV-testing

The HIV status of all volunteers will be documented. However, otherwise healthy HIV+ volunteers will not be excluded from the study. In keeping with WHO and other policy guidelines, all subjects will receive pre- and post-test counseling with respect to the HIV test. (Annexes 1 and 2)

The steps to be followed are as follows:

- All volunteers agreeing to participate in the study will be told that their blood will be tested for HIV infection and their consent should be obtained to do the test.
- All volunteers will receive pre-test counseling from trained counsellors and will be asked if they would like to know their result. It should be further explained to them that the results would be kept strictly confidential from all except the trial statistician and, where appropriate, the counsellor.
- Those wishing to know the result will receive post-test counselling.
- A person will be identified locally who, if necessary, will be able to link the laboratory result and the volunteer. This person will be told of any patient asking to know the result of the test. He/she will place the result in a sealed envelope and give it to the counsellor.
- All volunteers must sign a form consenting to have the test performed.

Adverse events

Adverse events will be defined and reported as per Annex 3. Toxicity to anti-tuberculosis drugs is usually associated with prolonged therapy. Although adverse effects such as gastro-intestinal intolerance, pruritis and slight flushing (rifampicin, pyrazinamide) may occur following a single dose of these drugs, serious adverse events such as hepatitis and anaphylactic reactions are uncommon. However, volunteers will be monitored clinically for any adverse events.

A serious adverse event occurring during the first phase of the study will exclude the volunteer from the subsequent crossover of the study. If any volunteer developed a serious adverse event during the study, he/she will be followed to resolution. In the context of this study, a serious adverse event is defined as an event which

- is medically important or immediately life-threatening
- requires hospitalisation or medical intervention to prevent permanent impairment or damage

Selection of reference preparations

Reference preparations need to be selected on the basis of their known quality. Since no global agreement exists as to what constitutes the reference product for rifampicin, it is advisable to select the product which was first approved in the market, or which is widely used in several countries and regions in the world. It would normally be regarded as a "leading" pharmaceutical product. The same applies to the selection of the reference preparations for the other drugs contained in the FDC.

Supply, labelling and packaging of drugs

Supply, packaging and labelling of the drugs will be the responsibility of the investigator and/or sponsor as arranged by prior agreement.

Packaging and labelling of the drugs will be in accordance with the randomisation list drawn up by the study statistician and identified by the study, period and subject number.

Drug storage, dispensing and disposal

Drugs will be stored in a temperature regulated, limited-access area. An inventory will be maintained of all drugs received and administered. Drugs remaining on completion of the study will be returned to the sponsor, stored by the investigator, or destroyed if so agreed. Batch numbers of all study medications will be recorded.

Food intake

Study participants must fast for at least eight hours preceding drug administration. Three hours following drug administration, a light standardised breakfast will be served. A standardised lunch will be served five hours after drug administration and thereafter fluid and light refreshments will be allowed *ad libitum*.

Treatment compliance

The investigators or designated study personnel will directly supervise administration and observe ingestion of the study medication.

Study schedule and data recording (Annex 4 and Annex 5)

VISIT 1: Pre-study screening

The screening visit will take place during the 4 week period prior to the 1st drug administration. Approximately 20ml of blood and a small urine sample will be collected. Evaluations include:

- medical history
- physical examination
- haematology: full blood count (includes Hb, Hct, RBC, WCC, Plt) and differential count
- ESR
- HIV
- blood chemistry: sodium, potassium, creatinine, total protein, total bilirubin, alkaline phosphatase, AST, ALT
- urinalysis (pH, protein, glucose, blood and semi-quantitative screening test for possible substance abuse)
- pregnancy test in women

VISIT 2 and VISIT 4: First and second treatment periods

Study subjects will be admitted to the studycentre on the night before the administration of study medication the next morning. Early the next morning, a cannula for the drawing of blood samples will be inserted into a suitable arm vein of each subject. The well being of each participant will be inquired into and blood pressure, temperature and heart rates recorded. The study drugs will be administered at approximately 08h00. The single dose will be administered with 200ml of water.

Venous blood specimens will be collected into lithium-heparin coated glass tubes for high performance liquid chromatography (HPLC) assay of rifampicin and desacetyl rifampicin, as well as any concurrent medication (e.g. isoniazid, pyrazinamide and ethambutol), if necessary.

The exact times of drug administration and blood sampling will be recorded. Blood specimens will immediately be stored on ice until separation of the plasma. Two aliquots of plasma will be stored in solid CO₂ or in a -80°C freezer. One of the aliquots will be packaged in solid CO₂ and transferred to the analytical laboratory for analysis. Duplicate samples will be held in storage for 12 months at -80°C following completion of the study.

In total, a maximum of 60 ml of blood is required for the analysis of serum concentrations of the study drugs at six different time points.

Sampling times and volume of respective samples

Sample number	Time since ingestion of study medication	Volume required (ml)
1	0-60 min prior to drug ingestion	10 ml
2	1 hour	10 ml
3	2 hours	10 ml
4	4 hours	10 ml
5	6 hours	10 ml
6	8 hours	10 ml

VISIT 3 and VISIT 5: Safety check and final visit

VISIT 3: Six days after the first drug administration (visit 2) the study subjects will return to the Study Centre for a brief 'check-up' visit. Their well being will be inquired into and 5ml of blood will be taken for evaluation of AST, ALT, Alkaline phosphatase and total bilirubin before the 2nd drug administration.

VISIT 5: Six days after the 2nd treatment period (visit 4) study subjects will return for a final safety investigation; their well being will again be inquired into and blood tests will be taken to detect possible adverse events. About 15ml of blood will be collected for a full blood count, and chemistry evaluation (sodium, potassium, creatinine, total bilirubin, alkaline phosphatase, AST and ALT).

Ethical considerations

The local Research Ethics Committee or Institutional Review Board must approve the protocol. Where appropriate, the relevant drug regulatory bodies must approve the importation and use of any medicine that does not carry registration in the country in which the study is to be performed.

The study will be conducted in accordance with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (Annex 6) and the WHO guidelines on Good Clinical Practice (Annex 7).

The investigators and study staff will observe confidentiality of records. The identity of volunteers will be recorded by subject number only on the Case Record and Data Collection Form after initial screening procedures, linked by the same number to an identity code which will be stored with the randomisation code. All documents and records will be retained by the investigator for a minimum of 5 years after study closure.

Liability and insurance

Volunteers will be covered under an appropriate insurance policy should compensation be necessary. Employees (permanent and ad hoc) will also be covered under this policy for professional liability. In addition, clinical investigators performing any invasive procedures will have professional liability insurance.

ANALYTICAL METHODS

Haematology and chemical pathology

All haematology and chemical pathology determinations should be determined at a laboratory that follows the general principles of good laboratory practice (GLP). In particular, these laboratories adhere to international guidelines for

- the control of specimen processing and result distribution
- documentation of standard operating procedures
- maintenance of equipment
- adherence to accepted laboratory safety procedures
- rapid turn-around times
- monitoring and verification of results generated

Drug assay

The assay of rifampicin and desacetyl rifampicin in plasma will be conducted at an approved laboratory using a validated high performance liquid chromatographic (HPLC) assay technique such as that described by Zent and Smith¹¹ or Panchagnula et al.¹²

Analytical procedures should be fully validated and reported as recommended by the 1990 Conference on Analytical Methods Validation.¹³

STATISTICAL AND KINETIC ANALYSIS

The data will be subjected to non-compartmental analysis. Concentration-time curves will be plotted for each series of drug assays. From these plots, C_{max} will be taken as the highest

drug concentration measured, i.e. without interpolation. The area under the plasma concentration-time curve until 8 hours (AUC_{0-8}) for rifampicin, is to be determined by the (linear/logarithmic) trapezoidal rule.

These parameters will be subjected to analysis of variance (ANOVA) after log transformation of the data and using formulation (i.e. treatment or drug), subject (nested within sequence), sequence (i.e. group or order) and period (or phase) as the treatment effects. 90% confidence intervals will be computed for the ratio of test/reference using the non-parametric methods proposed by Hauschke.¹⁴ In addition, the parametric method (based on the ANOVA) as described by Schuirman¹⁵ should be reported.

Bioequivalence will be declared if the 90% confidence interval for the test/reference ratio of the AUC lies completely in the range 80%-125%. In addition, for the parametric analysis the null hypotheses for both the two one sided t-tests¹⁶ should be rejected at the $p < 0.05$ level before bioequivalence can be declared. A detailed description of the parametric methodology is available.¹⁷ Statistical analysis may be conducted using available software packages such as WinNonlin (Statistical Scientific Consulting Inc) or SAS (Proc GLM) or equivalent.

REPORTING OF RESULTS

Results are to be presented clearly and decisively. It remains the responsibility of the investigating team to reveal all information in an unbiased, consistent and complete manner. In this regard, the specific direction given in the WHO guidelines on registration requirements⁷ (p 132) are to be strictly adhered to (Annex 7).

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Information for study subjects

The bioavailability and bioequivalence of rifampicin , isoniazid, and pyrazinamide as a single dose in the fixed dose combination (FDC) formulation <add name>, also containing Ethambutol, <add as appropriate>, compared to equivalent doses of single drug reference preparations of the active components contained in the FDC

Background and study objectives: The administration of drugs in a form known as fixed dose combinations (FDCs) has certain advantages for drug distribution and administration in the treatment of tuberculosis. However, it is necessary to prove that the drugs contained in the FDC are bioavailable, which means that blood concentrations in humans are reached which will be sufficient to kill tuberculosis organisms in the body. It also needs to be shown that the drugs contained in the FDC reach blood concentrations which are equivalent to those achieved by drugs known to be of good efficacy, safety and quality.

The aim of this study, therefore, is to evaluate the bioavailability of the FDC <add name> compared to that of equivalent doses of single drug reference products, and to determine whether the test preparations bioequivalent.

Study design and methods: The study will consist of 2 treatment periods of 8 hours each. At each treatment period you will take either the FDC or the reference tablets. On each occasion you will take a total dose of xxx mg of rifampicin, xxx mg of isoniazid and <add as appropriate>. The drug administ

You will not be included in the study if the following is recorded:

- Any illness or conditions considered by the medical doctor and/or described in the study protocol as a reason for excluding you from the study (e.g. high blood pressure, cancer).
- History of hypersensitivity to any drug(s).
- Active allergic disease or a history of significant allergic disease.
- History of drug or alcohol addiction.
- Consumption of large quantities of coffee, tea, alcohol and wine.
- Blood donation of more than 500ml during the previous 6 months.
- Positive test for HIV or hepatitis B.
- Are a smoker or have smoked at all in the 3 months prior to the study.
- Use of any drugs or medication (including an oral contraceptive) within 2 weeks of the study, or within a month of the study in the case of certain medications.
- Are pregnant or at risk of becoming pregnant.

Description of the procedures on treatment days: You are required to meet at *<provide exact information>* at 20h00 on the evening preceding each dosing day. You will be admitted to *<provide name of ward,/room etc.>* before receiving a light supper. You will not eat or drink anything overnight from 22h00 and you will continue to fast until 10h00 the following day when a light, standardised breakfast will be served. Similarly, a light standardised lunch will be served at 13h00. Further refreshments will also be available after lunch.

On the morning of the dosing day a venous cannula will be inserted into a suitable arm vein. Through this cannula blood samples will be collected for the 8 hours after medication.

Before receiving the first dose, you will have the following procedures: Measurement of blood pressure, heart rate and temperature.

You will receive the study medications with water sitting in an upright position. You will remain in the sitting position for another 30 minutes and thereafter semi-recumbent until 2 hours after taking the medication.

Blood samples will be collected six times for drug concentration determinations as follows: Before medication, 1, 2, 4, 6, and 8 hours after drug administration.

During the second treatment period, the above mentioned procedures will be repeated.

Six days after the last drug administration, you will be required to report to *<provide details>* at 08h00 for further blood tests. These are "safety tests" to detect the unlikely event of damage to your liver, kidneys or blood after exposure to the study drugs.

Not more than 160 ml of blood will be drawn in total during the entire study period for the drug assays and laboratory tests.

Subject's obligation: The following requirements are to be strictly adhered to:

You are obliged to **consume only and completely the meals provided** You are only allowed to eat the standardised meals and refreshments provided. This is an absolute requirement in order to limit the risk of individual variation in the absorption and metabolism of the study drugs.

You are **not allowed to take any non trial medication**, including over-the-counter remedies or food supplements (vitamins, herbal compounds, etc) throughout the study and in the week before the study without consulting the investigator in advance.

No strenuous physical activity may be performed from 48 hours before and until 8 hours after each administration.

No alcohol or caffeine may be consumed from 48 hours before and until 8 hours after each administration.

Withdrawal from the study: You have the right to withdraw from the study at any time. You must, however, agree to obey the instructions of the investigator concerning matters pertaining to your health after drug administration. The clinical investigator also has the right to withdraw you from the study for clinical reasons or if you violate the study protocol. Protocol violation is defined as wilful disobedience of instructions pertaining to the study procedures communicated verbally or in writing.

Remuneration: Compensation for time-loss and inconvenience suffered as a result of participation in the study will be made on completion of the study. If you do not complete the study *for bona fide* reasons or other clinical considerations, you will be compensated according to the amount of time lost and inconvenience suffered i.e. on a pro rata basis. Protocol violation may result in forfeiture of remuneration.

Adverse events: The doses of the tuberculosis treatment which you will ingest during each treatment period is the same or lower than those usually administered to tuberculosis patients on a daily basis for a period of between 2 and 8 months. Repeated administration of the medication which you will be taking, has been associated with the following adverse events: loss of appetite, nausea, vomiting, abdominal discomfort, rashes, joint pains and headache at a rate of between 1/10 to 1/100. The following effects may also occur, although uncommonly: hepatitis (liver damage), peripheral neuritis, "flu-like syndrome", hypersensitivity, blood dyscrasias (damage to the blood cells), nephrotoxicity (kidney damage), neurotoxicity and optic neuritis. Rifampicin may produce an orange-red discolouration of body fluids; *contact lenses should not be worn until 24 hours after each drug administration.*

Please report any unusual symptoms or deterioration in your health to the investigators immediately

Please note: Participation in this study is entirely voluntary; you are not obliged to take part. If you decide to take part you will need to sign to say that you have given your consent to participate. If you agree to participate, you may withdraw from the study at any time, without prejudice to you for doing so. The personal information obtained about you during the course of this study will remain confidential and in reporting the results of the study, you will be referred to only by a code number.

In accordance with legal requirement, during the course of this clinical trial, you will be covered by an insurance policy.

You will be given a copy of this information sheet and consent form, and may ask the following contact persons for additional information, at any time during the study:

Name	Telephone number at Home	Telephone number at Work

Volunteer consent for participation in the study

The bioavailability and bioequivalence of rifampicin , isoniazid, and pyrazinamide as a single dose in the fixed dose combination (FDC) formulation <add name>, also containing Ethambutol, <add as appropriate>, compared to equivalent doses of single drug reference preparations of the active components contained in the FDC

1. I agree to take part in the trial of the bioavailability of a fixed dose combination tablet containing rifampicin, isoniazid and <add as required>, to be carried out in <add name of institution>.
2. I confirm that the Supervising Doctor, _____ has given me a full explanation of the nature, purpose and duration of the study and of what I shall be expected to do and has advised me about the ill-effects, including discomfort or inconvenience, to my health or well-being that he believes might result from participation. I have also read and understood an information document relating to the study.
3. I have been informed that an insurance policy has been taken out for this study.
4. I have been given the opportunity to ask any questions concerning the study and I have to my satisfaction understood the supervising doctor's explanation and advice.
5. I have informed the supervising doctor of all my previous or present illnesses, together with any medication/drugs/remedies/food supplements, of whatever nature, I have taken in the last month, or am taking, or am planning to take, whether prescribed or not, and of any consultation that I have had with my doctor in the last months, whether or not it resulted in medication or drug therapy.
6. I have informed the supervising doctor of any participation by me in other volunteer studies in the past year.
7. I confirm that I do not fulfil any of the exclusion criteria for this study as described in the volunteer information document.
8. I agree to comply in good faith with all instructions given to me by the supervising doctor and undertake to notify him/her at once if I suffer any unexpected and unusual symptoms or any deterioration whatsoever in my health or well-being however caused.
9. I am aware that this study has been subjected to ethics review by a legitimate Ethics Committee.
10. I agree to undergo blood tests as described in the subject information document, including a test for the AIDS virus.
11. I further understand that the following procedures will be carried out as part of the study:
 - a) Administration of the study drugs on 2 occasions.
 - b) The withdrawal of blood specimens during the study periods as described in the subject information document.
12. I understand that I am free to withdraw my consent to participate in the study at any time without the need to justify my decision, but I confirm that while participating in the study I will not knowingly do anything that I might reasonably assume could affect the results of it. I further understand that any information that becomes available during the course of the study that may affect my willingness to take part will be disclosed to me as soon as practicable.
13. On the basis that my name in connection with this study will not be disclosed to any person other than the Sponsor or Regulatory Authority, I do not claim to be entitled to restrict in any way the use to which the results of the study may be put. In particular, I agree to disclosure of any report of those results to Regulatory Authorities for medicines.

Adverse drug effects

All toxic reactions whether minor or major, whether requiring interruption of treatment or not, should be reported to the Clinical Investigator/Study Doctor as soon as they occur, on the appropriate form contained in the Case Record Form (Annex 5)

Minor Toxic Reactions

- *Isoniazid* : Side-effects are negligible

Rifampicin : Urine, saliva, tears, sweat may be coloured red; no action is necessary.

Pyrazinamide : Loss of appetite and nausea may occur and be of no importance. These symptoms may, however, be forerunners to hepatitis (see below). A flushing reaction (erythema and warmth: usually starting in the face and spreading to neck, arms and trunk depending on severity. Usually starts within minutes and subsides over a few hours, relatively common - 1 to 2 per study of 20 volunteers. No action required.

- Arthralgia and swelling of one or more joints (gouty syndrome) may occur in patients who are receiving pyrazinamide and ethambutol - due to increased serum uric acid levels. Treatment with aspirin may be successful.

Major Toxic Reactions

- **Hypersensitivity reactions**

These are characterised by the sudden onset of fever often accompanied by headache and vomiting as well as the appearance of an itchy erythematous rash. When the fever and rash have subsided, proceed to confirm hypersensitivity and identify the causative drug or drugs to which the patient is hypersensitive.

- **Other cutaneous reactions**

Isoniazid : A pellagrous reaction may very rarely occur. It should respond to nicotinic acid 50 mg three times daily or a vitamin B compound preparation.

Rifampicin : Thrombocytopenic purpura may rarely occur due to a fall in the blood platelet count, within three hours of a dose, leading to purpura and bruising. The drug should be stopped and never given again. It is most important to warn the patient of the possibility of this reaction.

- **Hepatitis**

Hepatitis occasionally occurs in patients receiving isoniazid, rifampicin or pyrazinamide. In all cases where there is any manifestation of liver toxicity, all treatment should be stopped, and supportive therapy be given while waiting for the liver function tests to return to normal.

- **Neurotoxicity**

Ethambutol : Loss of visual acuity due to optic neuritis is dose-related in long-term treatment, and reversible if stopped promptly. In single-dose exposures at normal dose, this adverse effect has not been reported. Headaches, dizziness, mental confusion, hallucinations and peripheral neuritis have all been reported infrequently in long-term treatment with the drug.

Isoniazid : Peripheral neuritis and mental confusion may occur. Pyridoxine 50-300 mg daily or a vitamin B compound containing pyridoxine should be tried until resolution.

- **The "Flu" Syndrome**

Rifampicin : This is associated almost exclusively with the intermittent administration of rifampicin in long term therapy. It is characterised by episodes of fever, chills, headaches, dizziness and bone. The symptoms start one to two hours after each dose of rifampicin and last for up to eight hours.

Study schedule

Time	Activity
Month prior to study	<p><i>Pre-study screening</i></p> <ul style="list-style-type: none"> • Medical history, physical examination, pregnancy test (if appropriate) • 20ml blood sample taken for haematology (full blood count including Hb, Hct, RBC, WCC, Plt, and differential), ESR, HIV-test, blood chemistry (sodium, potassium, creatinine, total protein, total bilirubin, alkaline phosphatase, AST, ALT) • small urine sample for urinalysis (pH, protein, glucose, blood and semi-quantitative screening test for cannabinoids)
Day 1	<p>20:00 Admission to study centre 22:00 Fasting begins</p>
Day 2	<p>07:00 Well-being established BP, temperature, heart rate measured Cannula inserted 1st 10 ml blood sample taken 08:00 Study medication administered with 200ml water 09:00 2nd 10 ml blood sample taken 10:00 3rd 10 ml blood sample taken 11:00 Breakfast 12:00 4th 10 ml blood sample taken 13:00 Lunch 14:00 5th 10 ml blood sample taken 16:00 6th 10 ml blood sample taken</p>
Day 8	<p><i>Safety screening</i></p> <ul style="list-style-type: none"> • Well-being established • 5ml of blood taken for evaluation of AST, ALT, Alkaline phosphatase and total bilirubin <p>20:00 Admission to study centre 22:00 Fasting begins</p>
Day 9	<p>07:00 Well-being established BP, temperature, heart rate measured Cannula inserted 1st 10 ml blood sample taken 08:00 Cross-over medication administered with 200ml water 09:00 2nd 10 ml blood sample taken 10:00 3rd 10 ml blood sample taken 11:00 Breakfast 12:00 4th 10 ml blood sample taken 13:00 Lunch 14:00 5th 10 ml blood sample taken 16:00 6th 10 ml blood sample taken</p>
Day 15	<p><i>Safety screening</i></p> <ul style="list-style-type: none"> • Well-being established • 15ml blood sample taken for full blood count, and chemistry evaluation (sodium, potassium, creatinine, total bilirubin, alkaline phosphatase, AST and ALT).

Study Code _____

Subject number: _____

ANNEX V

CASE RECORD FORM

**Bioequivalence of RIFAMPICIN in fixed dose formulations containing
ISONIAZID with or without PYRAZINAMIDE and/or
ETHAMBUTOL compared to the single drug reference preparations
administered in loose combination**

Study Code _____

Subject number: _____

MEDICAL AND SURGICAL HISTORY

Medical or surgical history within the past year no yes

If yes describe below:

	date of onset (mm/yy)	date of end (mm/yy)	ongoing
_____	___/___/___	___/___/___	<input type="checkbox"/>
_____	___/___/___	___/___/___	<input type="checkbox"/>
_____	___/___/___	___/___/___	<input type="checkbox"/>
_____	___/___/___	___/___/___	<input type="checkbox"/>
_____	___/___/___	___/___/___	<input type="checkbox"/>
_____	___/___/___	___/___/___	<input type="checkbox"/>
_____	___/___/___	___/___/___	<input type="checkbox"/>
_____	___/___/___	___/___/___	<input type="checkbox"/>

exclude if any serious mental or physical illness in the past year

TREATMENT HISTORY

Has the subject taken any prescribed or over-the-counter (OTC) drugs / medications within the month prior to the 1st drug administration?

no yes

If yes, list below:

Drug	route:	from (dd/mm/yy)	to (dd/mm/yy)	ongoing
_____	_____	___/___/___	___/___/___	<input type="checkbox"/>
_____	_____	___/___/___	___/___/___	<input type="checkbox"/>
_____	_____	___/___/___	___/___/___	<input type="checkbox"/>
_____	_____	___/___/___	___/___/___	<input type="checkbox"/>
_____	_____	___/___/___	___/___/___	<input type="checkbox"/>
_____	_____	___/___/___	___/___/___	<input type="checkbox"/>
_____	_____	___/___/___	___/___/___	<input type="checkbox"/>

exclude if prescribed medication in the 1 week prior to 1st drug administration, known hepatic or renal elimination altering agents in the 4 weeks prior to 1st drug administration or OTC drugs in the week prior to 1st drug administration. Paracetamol is allowed in moderation

Investigator Name and Signature _____

Study Code _____

Subject number: _____

VITAL SIGNS

date: (dd/mm/yy) ___/___/___

heart rate	(beats/minute)	___	___	___
blood pressure	systolic (mmHg)	___	___	___
	diastolic (mmHg)	___	___	___
temperature	(°C)	___	___	' ___

EXAMINATION

date: (dd/mm/yy) ___/___/___

	normal / abnormal / not done			specify any abnormalities
cardiovascular:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
chest and lungs:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
abdomen:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
nervous system:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
musculo-skeletal:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
skin and mucosae:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
eyes and ears:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____
other:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____

Investigator Name and Signature _____

Study Code _____

Subject number: _____

HAEMATOLOGY

sample date: (dd/mm/yy) ___/___/___

FBC

mark if outside ref range

haemoglobin	____, __	g/dl	<input type="checkbox"/>
red cell count	____, __	x10 ^{e12} /l	<input type="checkbox"/>
haematocrit	<u>0</u> , ____	ratio	<input type="checkbox"/>
white cell count	____, __	x10 ^{e9} /l	<input type="checkbox"/>
platelets	____	x10 ^{e9} /l	<input type="checkbox"/>

DIFFERENTIAL

mark if outside ref range

neutrophils	____, ____	x10 ^{e9} /l	<input type="checkbox"/>
lymphocytes	____, ____	x10 ^{e9} /l	<input type="checkbox"/>
monocytes	__, ____	x10 ^{e9} /l	<input type="checkbox"/>
eosinophils	__, ____	x10 ^{e9} /l	<input type="checkbox"/>
basophils	__, ____	x10 ^{e9} /l	<input type="checkbox"/>
others	__, ____	x10 ^{e9} /l	<input type="checkbox"/>
ESR	____	mm	<input type="checkbox"/>

notable abnormalities: _____

Enter results on this page or attach laboratory report.

URINALYSIS

sample date: (dd/mm/yy) ___/___/___

pH ____

	absent	+	++	+++	++++	trace
glucose	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
protein/ albumin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Investigator Name and Signature _____

Study Code _____

Subject number: _____

blood

BIOCHEMISTRY

sample date: (dd/mm/yy) ____/____/____

			mark if outside ref range
sodium	_____	mmol/l	<input type="checkbox"/>
potassium	____, ____	mmol/l	<input type="checkbox"/>
creatinine	_____	µmol/l	<input type="checkbox"/>
glucose	____, ____	mmol/l	<input type="checkbox"/>
total protein	_____	g/l	<input type="checkbox"/>
total bilirubin	_____	µmol/l	<input type="checkbox"/>
alkaline phosphatase	_____	units/l	<input type="checkbox"/>
AST	_____	units/l	<input type="checkbox"/>
ALT	_____	units/l	<input type="checkbox"/>

Enter results on this page or attach laboratory report.

URINE DRUG SCREEN

sample date: (dd/mm/yy) ____/____/____

	negative	trace	low positive	positive
cannabinoids	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are any of the laboratory screening tests significantly abnormal?

no yes

If yes, does the result indicate that the subject should be excluded from the study?

no yes

If no, motivate: _____

Investigator Name and Signature _____

Study Code _____

Subject number: _____

INCLUSION CRITERIA (all answers should be 'yes' for inclusion)

	no	yes
Healthy volunteer between 18 and 55 years	<input type="checkbox"/>	<input type="checkbox"/>
Normal findings in medical history and physical examination (unless abnormality considered clinically irrelevant by the investigator)	<input type="checkbox"/>	<input type="checkbox"/>
Normal laboratory values (unless abnormality considered clinically irrelevant by the investigator)	<input type="checkbox"/>	<input type="checkbox"/>
Normal vital signs	<input type="checkbox"/>	<input type="checkbox"/>
Non-smoker for at least three months before 1st drug administration	<input type="checkbox"/>	<input type="checkbox"/>
Consent to having an HIV test	<input type="checkbox"/>	<input type="checkbox"/>
Written informed consent obtained		date: (dd/mm/yy) ____/____/____

EXCLUSION CRITERIA (all answers should be 'no' for inclusion)

	no	yes
History of hypersensitivity to any rifamycin antibiotics, isoniazid, pyrazinamide, or ethambutol	<input type="checkbox"/>	<input type="checkbox"/>
History of drug hypersensitivity	<input type="checkbox"/>	<input type="checkbox"/>
History or presence of tuberculosis	<input type="checkbox"/>	<input type="checkbox"/>
Active allergic disease or a history of significant allergic disease	<input type="checkbox"/>	<input type="checkbox"/>
Renal, hepatic or gastrointestinal disease known to interfere with drug absorption, distribution, metabolism or elimination	<input type="checkbox"/>	<input type="checkbox"/>
Serious mental or physical illness within the past year	<input type="checkbox"/>	<input type="checkbox"/>
History of drug abuse or addiction	<input type="checkbox"/>	<input type="checkbox"/>
Consumption of excessive amounts of alcohol	<input type="checkbox"/>	<input type="checkbox"/>
Blood donation in the previous 2 months	<input type="checkbox"/>	<input type="checkbox"/>
Subject unlikely to comply with protocol (e.g. uncooperative attitude, inability to return for follow-up visits)	<input type="checkbox"/>	<input type="checkbox"/>
Participation in another drug study within 3 months of 1st drug administration	<input type="checkbox"/>	<input type="checkbox"/>
Ingestion of any known hepatic or renal clearance altering agents within 30 days of the 1st drug administration	<input type="checkbox"/>	<input type="checkbox"/>
Treatment with any prescribed medication within the week prior to 1st drug administration	<input type="checkbox"/>	<input type="checkbox"/>
Are pregnant, breastfeeding or sexually active without use of	<input type="checkbox"/>	<input type="checkbox"/>

Investigator Name and Signature _____

Study Code _____

Subject number: _____

acceptable non-hormonal form of contraception

FINAL SELECTION

Date (dd/mm/yy) ___ / ___ / ___

Is the subject suitable for enrollment into the study?

no

yes

If no, state the reason: _____

If yes, submit for randomisation as per protocol, and record this number at the top of each page of this Case Record Form

Investigator Name and Signature _____

Study Code _____

Subject number: _____

VISIT 2 : FIRST DRUG ADMINISTRATION

Date: (dd/mm/yy) ____ / ____ / ____

VITAL SIGNS & HEALTH QUESTIONNAIRE

Date & time of last intake of food/drink _____ / _____

Details of any medication ingested in previous 7 days _____

Details of any illness in previous 7 days _____

weight	(kg)	_____
heart rate	(beats/minute)	_____
systolic blood pressure	(mm Hg)	_____
diastolic blood pressure	(mm Hg)	_____
temperature	(°C)	_____

DRUG ADMINISTRATION

(hr : min)

Time subject ingested study medication _____ : _____

Number of capsules/tablets swallowed:

(a) Rifampicin ____ Isoniazid ____ Pyrazinamide ____ Ethambutol ____

(b) Combined formulation ____

I confirm that the subject has taken the study medication according to the category as marked above.

Investigator Name and Signature _____

Study Code _____

Subject number: _____

VISIT 2 (cont)

SAMPLING TIMES

Time of drug administration

(hh : mm) ____ : ____

Plasma sampling time Hours since dose	Actual Time	Comments
0 (pre dose)	____ : ____	
1.0	____ : ____	
2.0	____ : ____	
4.0	____ : ____	
6.0	____ : ____	
8.0	____ : ____	

At completion of the session

Has any adverse event been observed during this session ? No Yes

If yes, complete adverse event form on Page 17

Investigator Name and Signature _____

Study Code _____

Subject number: _____

VISIT 3 : FIRST SAFETY CHECK

BIOCHEMISTRY

Date: (dd/mm/yy) ___ / ___ / ___

mark if outside reference range

total bilirubin ___ μ mol/l

alkaline phosphate ___ u/l

AST ___ u/l

ALT ___ u/l

Does any of the results indicate that the subject should be withdrawn from the study?

No

Yes

Comments :

Investigator Name and Signature _____

Study Code _____

Subject number: _____

VISIT 4 : SECOND DRUG ADMINISTRATION

Date: (dd/mm/yy) ____ / ____ / ____

VITAL SIGNS & HEALTH QUESTIONNAIRE

Date & time of last intake of food/drink _____ / _____

Details of any medication ingested in previous 7 days _____

Details of any illness in previous 7 days _____

weight	(kg)	_____
heart rate	(beats/minute)	_____
systolic blood pressure	(mm Hg)	_____
diastolic blood pressure	(mm Hg)	_____
temperature	(°C)	____, ____

DRUG ADMINISTRATION

(hr : min)

Time subject ingested study medication _____ : _____

Number of capsules/tablets swallowed:

(a) Rifampicin ____ Isoniazid ____ Pyrazinamide ____ Ethambutol ____

(b) Combined formulation ____

I confirm that the subject has taken the study medication according to the category as marked above (category should reflect the opposite as on page 10).

Investigator Name and Signature _____

Study Code _____

Subject number: _____

VISIT 4 (cont)

SAMPLING TIMES

Time of drug administration

(hh : mm) _____ : _____

Plasma sampling time Hours since dose	Actual Time	Comments
0 (pre dose)	____ : ____	
1.0	____ : ____	
2.0	____ : ____	
4.0	____ : ____	
6.0	____ : ____	
8.0	____ : ____	

At completion of the session

Has any adverse event been observed during this session ? No Yes

If yes, complete adverse event form on Page 17

Investigator Name and Signature _____

Study Code _____

Subject number: _____

VISIT 5 : FINAL VISIT

BIOCHEMISTRY

sample date: (dd/mm/yy) ____/____/____

			mark if outside ref range
sodium	_____	mmol/l	<input type="checkbox"/>
potassium	__, __	mmol/l	<input type="checkbox"/>
creatinine	_____	µmol/l	<input type="checkbox"/>
glucose	____, ____	mmol/l	<input type="checkbox"/>
total protein	_____	g/l	<input type="checkbox"/>
total bilirubin	_____	µmol/l	<input type="checkbox"/>
alkaline phosphatase	_____	units/l	<input type="checkbox"/>
AST	_____	units/l	<input type="checkbox"/>
ALT	_____	units/l	<input type="checkbox"/>

Enter the results on this page or attach laboratory report

HAEMATOLOGY

sample date: (dd/mm/yy) ____/____/____

			mark if outside ref range
haemoglobin	____, ____	g/dl	<input type="checkbox"/>
red cell count	____, ____	x10 ^{e12} /l	<input type="checkbox"/>
haematocrit	<u>0</u> , ____	ratio	<input type="checkbox"/>
white cell count	____, ____	x10 ^{e9} /l	<input type="checkbox"/>
platelets	_____	x10 ^{e9} /l	<input type="checkbox"/>

Investigator Name and Signature _____

Study Code _____

Subject number: _____

STUDY CONCLUSION

Study completed as per protocol: Yes No

If no, reason for premature discontinuation :

- adverse event
- lost to follow up
- other : _____

Describe any protocol deviation:

I have reviewed the case record form for this subject.

*I confirm that based on information supplied to me, and to the best of my knowledge,
these forms are complete and accurate.*

___/___/___
Date (dd/mm/yy)

(Study Doctor/Clinical Supervisor)

___/___/___
Date (dd/mm/yy)

(Principal Investigator)

World Medical Association Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964

and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989; and the
48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

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

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

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

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

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

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

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

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

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

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

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

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

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE

(Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

(Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

Supporting literature

- Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products (WHO Technical Report Series No. 850, 1995)
- Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (WHO Technical Report Series No. 863, 1996)

