International Consortium for Trials of Chemothrapeutic Agents in Tuberculosis
(INTERTB)

AN INTERNATIONAL MULTI CENTRE CONTROLLED CLINICAL TRIAL TO EVALUATE HIGH DOSE RIFAPENTINE AND A QUINOLONE IN THE TREATMENT OF PULMONARY TUBERCULOSIS

RIFAQUIN

Version number 1.8
15 April 2011

ISRCTN 44153044

Authorised by:

Name: Dr Amina Jindani, MD, FRCP  Role: Chief Investigator
Signature: [Signature]
Date: 15 April 2011

Name: Prof Andrew Nunn, BSc, MSc  Role: Lead Statistician
Signature: [Signature]
Date: 15 April 2011
General information
This document describes the RIFAQUIN trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial. Clinical problems relating to this trial should be referred to the Chief Investigator.

Compliance
The trial will be conducted in compliance with the protocol, Principals of GCP as laid down in ICH GCP Guidelines (E6), and other regulatory requirements applying in the countries in which the trial will be conducted.

Sponsor
St. George’s Hospital Medical School trading as St. George’s, University of London
Centre for Infection
Department of Cellular and Molecular Medicine
St. George’s, University of London
Jenner Wing, Cranmer Terrace
London SW17 0RE
United Kingdom

Main Contacts:

Chief Investigator
Dr. Amina Jindani
Centre for Infection
Department of Cellular and Molecular Medicine
St. George’s, University of London
Jenner Wing, Cranmer Terrace
London SW17 0RE,
United Kingdom

Assistant Chief Investigator
Professor Tom Harrison
Centre for Infection
Department of Cellular and Molecular Medicine
St. George’s, University of London
Jenner Wing, Cranmer Terrace
London SW17 0RE
United Kingdom
Consultant Microbiologist & Investigator
Professor Denny Mitchison
Centre for Infection
Department of Cellular and Molecular Medicine
St. George’s, University of London
Jenner Wing, Cranmer Terrace
London SW17 0RE
United Kingdom

Consultant Microbiology Technologist
David Coleman
Centre for Infection
Department of Cellular and Molecular Medicine
St. George’s, University of London
Jenner Wing, Cranmer Terrace
London SW17 0RE
United Kingdom

Trial Statistician & Investigator
Professor Andrew Nunn
MRC Clinical Trials Unit
222 Euston Road
London NW1 2DA
United Kingdom

Trial Manager and Monitor
Michelle Tetlow
MRC Clinical Trials Unit
222 Euston Road
London NW1 2DA
United Kingdom

Principal Investigators
Dr. Mark Hatherill, Cape Town, South Africa
Dr. Salome Charalambous, Johannesburg, South Africa
Dr. Stanley Mungofa, Harare, Zimbabwe
Dr. Simukai T Zizhou, Marondera, Zimbabwe
Dr. Janneke van Dijk, Macha, Zambia
Dr. James Shepherd, Gaborone, Botswana
Clinical laboratories, medical and technical departments, institutions
Name, address of laboratories, departments or institutions involved in the trial

1. Department of Cellular & Molecular Medicine, St George’s, University of London, Jenner Wing, Cranmer Terrace, London, SW17 0RE, United Kingdom.
2. MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA, United Kingdom.
3. SATVI, Institute of Infectious Disease & Molecular Medicine, University of Cape Town, Room 2.01, Wernher Beit South, Anzio Road, Observatory, Cape Town, 7925, South Africa.
4. Division of Clinical Pharmacology, Health Sciences Faculty, Private Bag, Rondebosch 7701 South Africa.
5. Aurum Institute for Health Research, 29 Queens Road, Parktown, Johannesburg South Africa.
6. Biomedical Research and Training Institute, Nicoz House, 29 Samora Machel Ave, P.O.Box CY 1753, Causeway, Harare, Zimbabwe
7. Harare City Health Department, Harare City, Box 596, Harare, Zimbabwe.
8. Provincial Medical Directorate Mashonaland East, PO Box 10, Marondera, Zimbabwe.
9. Medical/Malaria Institute at Macha, Macha Mission Hospital, P.O. Box 630166, Choma, Zambia
10. BOTUSA, P. O. Box 90, Gaborone, Botswana.
CONTENTS

1. SUMMARY ........................................................................................................... 8
   1.1 Lay summary .................................................................................................. 8
   1.2 Abstract and summary of trial design ............................................................... 8
   1.3 Outcome measures ......................................................................................... 8
   1.4 Ancillary assessments ...................................................................................... 9
   1.5 Flow diagram .................................................................................................. 9

2. Background .......................................................................................................... 10
   2.1 Introduction .................................................................................................... 10
   2.2 Population ....................................................................................................... 10
   2.3 Rationale and objectives ................................................................................ 10
   2.4 Relevant studies/trials ................................................................................... 11
   2.5 Risks and benefits ........................................................................................ 13
   2.6 Selection of centres ...................................................................................... 14

3. Selection of Patients .......................................................................................... 15
   3.1 Patient inclusion criteria ............................................................................... 15
   3.2 Patient exclusion criteria ............................................................................. 15
   3.3 Late screening exclusions ............................................................................ 16
   3.4 Number and source of patients ..................................................................... 16
   3.5 Screening procedures and pre-randomisation investigations ....................... 16

4. Randomisation & Enrolment procedure ............................................................. 17

5. Treatment of Patients ....................................................................................... 18
   5.1 Introduction ................................................................................................... 18
   5.2 Drug supply and storage ............................................................................. 18
   5.3 Treatment schedules ................................................................................... 19
   5.4 Treatment procedures ............................................................................... 20
   5.5 Failures and relapses ................................................................................... 20
   5.6 Accountability and unused drugs/devices ..................................................... 21
   5.7 Measures of adherence .............................................................................. 21
   5.8 Non-trial treatment .................................................................................... 22
   5.9 Dispensing .................................................................................................. 22

6. Assessments and Procedures ............................................................................ 22
   6.1 Follow-up schedule .................................................................................... 22
   6.2 Summary of investigations during treatment and follow-up ....................... 24
   6.3 Procedures for assessing efficacy ............................................................... 25
   6.4 Procedures for assessing safety .................................................................. 25
   6.5 Absconding from treatment ....................................................................... 25
   6.6 Loss to follow-up after completion of treatment .......................................... 26
   6.7 Trial closure ............................................................................................... 26
   6.8 Reference bacteriology ............................................................................ 26
   6.9 Population PK study .................................................................................. 26

7. Withdrawal of Patients .................................................................................... 27
   7.1 Stopping trial treatment ............................................................................. 27

8. Statistical Considerations ................................................................................ 27
   8.1 Method of randomisation ........................................................................... 27
   8.2 Outcome measures ..................................................................................... 27
   8.3 Sample size ................................................................................................ 28
   8.4 Interim monitoring and analyses ................................................................. 29
   8.5 Preliminary analysis plan .......................................................................... 29
   8.6 Analysis of adverse events ........................................................................ 30
9. Trial Monitoring
9.1 Extent and nature of monitoring ................................................................. 30
9.2 Site monitoring ............................................................................................ 30
9.3 Direct access to data .................................................................................... 32
9.4 Confidentiality ............................................................................................ 32

10. Safety reporting
10.1 Safety Reporting ....................................................................................... 32
10.2 Severity/grading of adverse events ............................................................ 34
10.3 Relationship to trial treatment ................................................................... 34
10.4 Follow-up after adverse events ................................................................. 34

11. Ethical Considerations and Approval
11.1 Ethical considerations ............................................................................... 35
11.2 Ethical approval ......................................................................................... 35

12. Regulatory Approval

13. Indemnity

14. Finance

15. Trial Committees
15.1 Trial Management Group (TMG)................................................................. 36
15.2 Trial Steering Committee (TSC) ................................................................. 36
15.3 Independent Data Monitoring Committee (IDMC) .................................... 36

16. Publication

17. Protocol Amendments

18. References

19. Appendices
Appendix 1: Patient Information sheet ............................................................. 50
Appendix 2: Patient Information Sheet (Population PK assessments) ............. 54
Appendix 3: Consent forms ............................................................................ 56
Appendix 4: Management of expected adverse events ................................... 60
Appendix 5: Algorithm for HIV testing .......................................................... 62
Appendix 6: ART for HIV/ tuberculosis co-infection27 .................................. 63
Appendix 7: Recommendations for initiating anti-retroviral therapy in adults and adolescents with documented HIV infection27 .............. 63
Appendix 8: WHO staging system for HIV infection and disease in adults and adolescents28 .......................................................... 64
Appendix 9: PK-Interaction assessments ......................................................... 65
Appendix 10: Flow chart for assessing and notifying adverse events ............. 81
Appendix 11: Patient Treatment Cards ............................................................ 82
Abbreviations and Glossary

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>ART/ARV</td>
<td>Anti-Retroviral Therapy/Anti-Retroviral</td>
</tr>
<tr>
<td>CF</td>
<td>Consent Form</td>
</tr>
<tr>
<td>CI</td>
<td>Chief Investigator</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CTU</td>
<td>Clinical Trials Unit</td>
</tr>
<tr>
<td>DTM</td>
<td>Domiciliary Treatment Monitor</td>
</tr>
<tr>
<td>ERC</td>
<td>Endpoint Review Committee</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator’s Brochure</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>IDMC</td>
<td>Independent Data Monitoring Committee</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
</tr>
<tr>
<td>NTP</td>
<td>National Tuberculosis Programme</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PIS</td>
<td>Patient Information Sheet</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedures</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TMG</td>
<td>Trial Management Group</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
</tbody>
</table>
1. **SUMMARY**

1.1 Lay summary

The current treatment of tuberculosis involves taking drugs daily for 6 or 8 months. Although the drugs are free to patients in low income countries this still involves a substantial cost, in terms of time and administration, to both the patient and the treatment services. If the length of treatment could be shortened to 4 months, or treatment administration simplified by, for example, being given once or twice weekly rather than daily, this would be of great benefit to the patients and the treatment services. Reduced doses of the drugs could also reduce side effects from the drugs.

In this trial, we are assessing whether rifapentine (a rifamycin) and moxifloxacin (a quinolone), when given together, can achieve these objectives. In previous trials, when rifapentine was given at the standard dose of 600mg once weekly, relapse rates were unacceptable and some HIV positive patients who relapsed had bacilli resistant to rifamycins. We are testing whether doubling the dose of rifapentine can reduce the overall relapse rates and eliminate rifamycin resistance in those HIV positive patients who may relapse.

Laboratory experiments suggest that replacing isoniazid with moxifloxacin could strengthen the treatment. We are also assessing whether, by substituting moxifloxacin for isoniazid, it is possible to simplify, and even reduce the duration of, the continuation phase of treatment.

The possibility of increased side effects from a high dose of rifapentine and of moxifloxacin will be monitored closely.

1.2 Abstract and summary of trial design

**Type of design**

An open-label 3-arm trial to compare a standard control regimen with two alternative treatment regimens for the treatment of tuberculosis (TB).

**Disease/patients studied**

Patients diagnosed with TB by having 2 sputum smear specimens positive for tubercle bacilli on direct smear microscopy.

**Trial interventions - research and control**

Two regimens will be compared with a standard control regimen.

**Control Regimen:** 2 months of daily ethambutol, isoniazid, rifampicin, and pyrazinamide followed by 4 months of daily isoniazid and rifampicin (2EHRZ/4HR).

**Study Regimen 1:** 2 months of daily ethambutol, moxifloxacin, rifampicin, and pyrazinamide followed by 2 months of twice weekly moxifloxacin and rifapentine (2EMRZ/2P2M2).

**Study Regimen 2:** 2 months of daily ethambutol, moxifloxacin, rifampicin, and pyrazinamide followed by 4 months of once weekly moxifloxacin and rifapentine (2EMRZ/4P1M1).

1.3 Outcome measures

**Primary outcome measure**

1. Combined rate of failure at the end of treatment and relapse by 18 months
2. Presence of rifamycin monoresistance (RMR) in relapse cultures of HIV infected patients
3. Occurrence of grade 3 or 4 adverse events at any time during chemotherapy

**Secondary outcome measure**
• Sputum culture results at two months after the initiation of chemotherapy
• Rate of completion of chemotherapy according to the protocol
• Number of observed doses of chemotherapy ingested
• Any adverse events

**Duration**

Patients will be followed up for 18 months from the commencement of chemotherapy. Follow-up visits will occur monthly until 12 months then at 15 and 18 months. However, follow-up will be stopped 12 months after the last patient has been randomised into the study; thus patients randomised in the final 6 months will have reduced follow-up.

**Data recording**

Data will be recorded on paper case report forms (CRF)s and kept at the local centre.

**1.4 Ancillary assessments**

In a sample of patients in Cape Town, blood levels will be tested to detect any interaction between rifapentine and moxifloxacin (see Appendix 9, PK-interaction assessments). In addition, the first 400 patients enrolled in the two experimental arms in Cape Town, Harare and Johannesburg will have blood samples taken at one visit during the 4th month of chemotherapy for moxifloxacin and rifapentine levels for population PK studies and to allow association of drug levels with clinical outcome to be evaluated. **Please see section 6.8.**

**1.5 Flow diagram**

**Trial entry, randomisation, treatment and analysis**

```
Eligible Patients
  Randomise
  Control Regimen
    (2EHRZ/4HR)  (6 months)
  Study Regimen 1
    (2EMRZ/2P2 M2)  (4 months)
  Study Regimen 2
    (2EMRZ/4P1M1)  (6 months)

Patient follow-up:
  Monthly to 12 months after randomisation
  15 months and 18 months
  The last few patients randomised will be followed up to 12 months *

Analysis of Outcome Measures
```

* Follow-up will be stopped 12 months after the last patient has been randomised into the study
2. BACKGROUND

2.1 Introduction

Tuberculosis and HIV are two of the three major diseases in the developing world; the incidence of new cases of tuberculosis has increased dramatically in recent years due, in large part, to co-infection with HIV. The annual incidence of pulmonary tuberculosis is currently estimated to be 9 million, with 2 million deaths.

Effective short-course regimens of chemotherapy for the treatment of pulmonary tuberculosis have been evaluated in numerous controlled trials worldwide. When adequately administered, they are capable of cure rates of 95% or more in patients with drug sensitive organisms.

That these cure rates are not always achieved in the routine treatment services may, in part, be that treatment durations of 6 or 8 months are still too long and that daily drug taking is not always observed by the patients. If the continuation phase could be administered once weekly, or even twice weekly, instead of daily, this would have several important advantages. It would reduce the number of treatment doses that patients have to take, might reduce toxicity as well as the cost of treatment and may also improve compliance. If the length of treatment could also be shortened without loss of efficacy, this would also improve adherence to treatment and further reduce costs.

2.2 Population

The study population will be TB patients, at the centres participating in the study, who fulfil the inclusion/exclusion criteria outlined in section 3.1 and 3.2.

Two regimens will be compared with a standard control regimen. See section 5 for full details.

2.3 Rationale and objectives

The principal aims of the trial are:-

1) To assess whether a treatment regimen containing moxifloxacin (400 mg) substituted for isoniazid in the intensive phase, followed by a once weekly dose of 1200mg of rifapentine and 400 mg of moxifloxacin, in a 4 month continuation phase, will have a relapse rate not inferior to a standard control regimen based on rifampicin and isoniazid.

2) To assess whether a treatment regimen containing moxifloxacin (400 mg) substituted for isoniazid in the intensive phase, followed by a once weekly dose of 1200mg of rifapentine and 400 mg of moxifloxacin, in a 4 month continuation phase, will prevent the occurrence of rifamycin mono-resistance in relapsing HIV positive patients.

3) To assess whether a treatment regimen containing moxifloxacin (400 mg) substituted for isoniazid in the intensive phase, followed by twice weekly doses of 900 mg rifapentine and 400 mg of moxifloxacin, in a 2 month continuation phase, will have a relapse rate not inferior to a standard control regimen based on rifampicin and isoniazid.

4) To assess whether a treatment regimen containing moxifloxacin (400 mg) substituted for isoniazid in the intensive phase, followed by twice weekly doses of 900 mg rifapentine and 400 mg of moxifloxacin, in a 2 month continuation phase, will prevent the occurrence of rifamycin mono-resistance relapsing in HIV positive patients.

5) To evaluate whether rifapentine and moxifloxacin concentrations are associated with treatment outcome.
2.4 Relevant studies/trials

The long half-life of rifapentine (about 12-13 hours) and its efficacy in once-weekly treatment of experimental murine tuberculosis raised the hope that it could be given once weekly with isoniazid in the continuation phase of the treatment of pulmonary tuberculosis. The three trials of intermittent rifapentine, at standard doses, conducted so far have been reviewed by Hirsch and Johnson. Each trial compared a continuation phase of rifapentine/isoniazid once weekly with intermittent rifampicin and isoniazid after two months of treatment with four drugs. The trial conducted in Hong Kong reported 12% (18/151) failure/relapse rates in patients' allocated rifapentine/isoniazid once weekly compared to 5% (7/152) in patients receiving isoniazid and rifampicin three times a week. In a trial conducted in South Africa and North America relapse rates of 12% (29/248) were reported in the once weekly rifapentine/isoniazid group compared to 7% (15/226) in the patients who received isoniazid and rifampicin twice weekly. Most recently a trial in the USA reported a combined failure/relapse rate of 9% (46/502) in HIV negative patients receiving rifapentine/isoniazid once weekly compared to 6% (28/502) for those receiving rifampicin and isoniazid twice weekly. Thus all three trials demonstrated that the once weekly rifapentine/isoniazid regimen, at standard dosage, was inferior to the intermittent rifampicin and isoniazid regimen.

Of particular concern was the report of the emergence of rifamycin mono-resistance (RMR) in 4 out of 5 HIV positive patients who relapsed in the most recent of these trials. All of the 4 patients then responded satisfactorily to their further treatment for the relapse of their tuberculosis (personal communication, A Vernon). Relapse was associated with severe immunosuppression. In contrast, RMR has never been encountered in HIV-negative patients treated with once weekly rifapentine who relapsed and is rare in HIV positive patients treated with twice weekly rifampicin. These problems were thought to be due to the high plasma binding (97%) of rifapentine and the availability of only the unbound fraction within tuberculous lesions. This would have led to a small pulse size and to the regrowth of bacilli during the interval between doses when active drug was no longer present. Regrowth would be more likely to occur in HIV-positive patients with lowered cellular immunity. RMR could, therefore, be prevented by an increase in the dose size, as has been argued by a study of the early bactericidal activity of rifapentine at various dose sizes.

There is contention about the role of the companion drug, isoniazid, in preventing the emergence of RMR during once weekly rifapentine/isoniazid treatment. In the study conducted in Hong Kong, failure/relapse occurred at similar rates in patients with initially isoniazid-resistant strains to those with sensitive organisms, and was not associated with a different rate of acetylation of isoniazid. These findings strongly suggest that isoniazid did not contribute to the failure/relapse rate. However, in CDC Study 22, where patients were also treated with once weekly rifapentine/isoniazid, an association was found between low isoniazid plasma concentrations and the occurrence of relapse suggesting that isoniazid might have been ineffective in preventing RMR. While there is no satisfactory reason to explain the discrepancy between the findings in these two trials, there is at least a suggestion that a better companion drug might be helpful in preventing RMR.

Moxifloxacin is a strong candidate for use as an alternative to isoniazid as companion drug to rifapentine, particularly as it has a similarly long half-life of about 14 hrs. Moxifloxacin also has greater bactericidal activity against dormant bacilli than isoniazid in vitro and has the longest half-life of those fluoroquinolones particularly active against M. tuberculosis.

An additional reason for supposing that the combination of rifapentine with moxifloxacin would be more effective than the combination with isoniazid arises from the studies in experimental murine tuberculosis with moxifloxacin in combination with other drugs. In the first of these studies, 6 month assessments were made of regimens in which moxifloxacin was either added to a regimen of isoniazid, rifampicin and pyrazinamide or substituted in turn for isoniazid, rifampicin or pyrazinamide. The results, when it was substituted for isoniazid (2MRZ/4MR), were greatly superior to those with the control regimen (2HRZ/4HR). These results could not be explained as being due to differences in absorption or metabolism of the drugs in the combination. They were thought to be the result of a drug-drug interaction between isoniazid and rifampicin. Thus, the combination of
moxifloxacin and a rifamycin would be expected to be more effective in sterilising lesions than an isoniazid/rifamycin combination.

Further studies in mouse tuberculosis have shown that the moxifloxacin/rifapentine combination is exceptionally effective in rapidly sterilising lesions. A combination of once weekly rifapentine 15 mg/kg (corresponding to a dose size of 900 mg rifapentine) and isoniazid was more effective than twice weekly rifampicin/isoniazid 18. The authors conclude that the efficacy of the once weekly isoniazid/rifapentine continuation phase can be increased by substituting moxifloxacin for isoniazid and by increasing the dose size of rifapentine to 15 mg/kg. Another mouse study19 (Fig 2) with twice weekly rifapentine indicates remarkable sterilising activity particularly as the size of the rifapentine dose is increased from 10 mg/kg (equivalent to 600 mg dose in patients of 60 kg) to 15 mg/kg and to 20 mg/kg. When 20 mg/kg rifapentine (P) (equivalent to 1200 mg dose in patients of 60 kg) was given with moxifloxacin and pyrazinamide (last column on the right in Fig 2), no bacilli were recovered after only 2 months – a truly remarkable result. These results suggest that twice weekly rifapentine at a dose size of 15 mg/kg should be capable of shortening the treatment period to 4 months in total. One possible conclusion is that the sterilising activity of rifapentine is dependent on the total amount of drug given during the week. The patient would receive twice the dose when it is administered twice weekly rather than once weekly.

A study on the potential toxicity of increased size doses of rifapentine has been carried out within a CDC study20. Treatment was discontinued in 6%, 4% and 6% in the 600, 900 and 1200 mg treatment arms respectively. Only one discontinuation, in the 1200mg arm, was due to an adverse event possibly associated with the study therapy. This was, however, a small study, carried out on a total of 150 patients. As there remains some doubt about the safety of the 1200 mg dose it is important that larger studies are carried out to compare the number of toxic events for different regimens.

A large interaction between moxifloxacin and rifapentine is unlikely since moxifloxacin is not metabolized by the liver P450 system21. A recent study22 has demonstrated a reduction of 27% in moxifloxacin AUC with concomitant rifampicin administration. The authors conclude that additional studies are required to determine whether this difference is clinically relevant and to exclude a period effect of study. Genetic variation in the MDR1 gene may modify moxifloxacin pharmacokinetic values consistent with altered bioavailability.

In designing the study, a choice had to be made between once weekly rifapentine which is convenient to supervise but with a higher risk of allowing RMR in HIV-positive patients and twice weekly rifapentine, which requires twice as much supervision, but delivers a greater total amount of rifapentine in the week.

During twice weekly administration, there is almost no period during the week with an absence of effective rifapentine plasma concentrations, so that bacillary re-growth would be most unlikely and therefore RMR is much less likely to occur.

The choice between ease of supervision and potential efficacy and lack of RMR can only be assessed by comparing once weekly and twice weekly administration. To date there have been two clinical studies of moxifloxacin (both unpublished) in which the fluoroquinolone replaced ethambutol.

When compared with the standard four drug regimen of isoniazid, rifampicin, pyrazinamide and ethambutol more rapid sputum conversion occurred in the OFLOTUB Phase II SSCC study23 and culture negativity rates were significantly higher at 4 and 6 weeks in CDC Study 2724. In the light of this data, the EBA study of 1200 mg rifapentine11 and the data from the murine studies we believe that a study of a higher dose of rifapentine, as well as the substitution of moxifloxacin for isoniazid, is both relevant and timely.
2.5 Risks and benefits

The major problem with chemotherapy for tuberculosis is that successful regimens are too long. As a result, adherence to treatment and, consequently, outcomes are frequently poor. The development of shorter regimens would provide a major benefit for public health by ensuring a higher completion rate, and reducing the risk of emergence of multiple drug resistance. For individuals participating in this trial there is a possibility that either the once weekly continuation phase regimen or the
shortened twice weekly phase regimen may prove as good as, or superior to, the standard regimen. Both regimens may be successful in eliminating rifamycin mono-resistance in relapses that may occur in HIV-infected patients.

On the other hand it is possible that either or both of these regimens could prove inferior either in efficacy or toxicity. If the twice-weekly regimen is not capable of achieving shortening to 4 months and increased numbers of relapses occur it is likely, on the basis of previous short course chemotherapy studies, that in patients not infected with HIV they will remain fully susceptible to the drugs with which they have been treated. Emergence of rifamycin mono-resistance in HIV-infected patients seems unlikely on this regimen since sufficient unbound rifapentine plasma concentrations would be present throughout the continuation phase.

An increase in the relapse rate after the once-weekly regimen could also occur but once again in HIV-uninfected patients relapse strains are very likely to be fully susceptible.

Should rifamycin mono-resistance arise in either of the test regimens in HIV-infected patients, retreatment with an isoniazid-based regimen will still be possible.

The Independent Data Monitoring Committee (IDMC) will review safety and efficacy data regularly. If rifamycin mono-resistance is confirmed to have occurred in two patients in either of the test arms, enrolment into that arm of the study will be stopped pending further investigations.

There is a possibility that the moxifloxacin containing regimens might prove more toxic than the standard arm. This is unlikely as the toxicity profile for moxifloxacin is well known. There is sufficient toxicity data available to indicate that moxifloxacin containing regimens are safe. Moxifloxacin is now being used in the treatment of patients with MDR tuberculosis or who are not able to tolerate the standard therapy. In this trial, patients with medical conditions likely to be exacerbated by moxifloxacin will be excluded. Patients in the trial will be closely monitored for adverse events. All patients who enroll in the study will benefit indirectly as it is well established that the outcome for patients enrolled in clinical trials is almost always better than patients in routine care.

The benefits of both the reduction of the total duration of drug ingestion as well as the simplification of its administration would result in the reduction of the burden of administration to the treatment services, the reduction in the amount of drugs ingested by the patients, as well as a possible reduction of toxicity.

2.6 Selection of centres

Participating centres must fulfil the following criteria:

1. They are in a country with an established National Tuberculosis Programme (NTP).
2. They have access to a laboratory capable of microscopy, culture and susceptibility testing with a system of quality assurance.
3. An uninterrupted supply of drugs and diagnostic materials, free of charge, for all patients.
4. A treatment service where directly observed treatment, whenever rifampicin is given, is routine.
5. An established recording and reporting system, following the IUATLD/WHO guidelines, providing all the information necessary for a cohort analysis.
6. Adequately trained personnel capable of supervising treatment and monitoring progress.
7. Adequately trained personnel for counselling in testing for HIV infection.
8. Where necessary an agreement from the Ministry of Health for participation in clinical trials.
9. The centres must be located in Africa.
10. The centres must have a high prevalence of HIV/TB co-infection.

In addition the centre must have the following staff available locally to run the trial.
A Medical Officer – who would oversee the general conduct of the study. This person will be designated as the Principal Investigator of the Study in that centre.

Treatment Supervisor(s) - who will ensure that all patients will receive their treatment as directed, and attend for follow-up regularly. They will also be responsible for completing the study forms correctly and for despatching the forms to the Principal Investigator for signature.

A Home Visitor - who will be responsible for verifying the patients’ addresses and for tracing patients who fail to attend as directed.

The staff members concerned in the management of the study patients will form a Management Committee and meet at regular intervals to discuss the progress of the study. A member of the laboratory staff will also be present. A brief report of the discussions will be sent to the Chief Investigator.

3. SELECTION OF PATIENTS

3.1 Patient inclusion criteria

1. Newly diagnosed pulmonary tuberculosis.
2. Two sputum specimens positive for tubercle bacilli on direct smear microscopy.
3. Either no previous anti-tuberculosis chemotherapy, or less than 2 weeks of previous chemotherapy at enrolment.
4. Aged 18 years and over.
5. A firm home address that is readily accessible for visiting and be intending to remain there or within the recruitment area for the entire treatment and follow up period.
6. Willing to agree to participate in the study and to give a sample of blood for HIV testing (and in Botswana have their HIV status disclosed to them).
7. Pre-menopausal women must be using a barrier form of contraception or be surgically sterilised or have an IUCD in place for the duration of the treatment phase.

3.2 Patient exclusion criteria

A patient will not be eligible for entry to the study if he/she:

1. Has any condition (except HIV infection) that may prove fatal during the study period.
2. Has TB meningitis.
3. Has pre-existing non-tuberculous disease likely to prejudice the response to, or assessment of, treatment e.g. insulin-dependent diabetes, liver or kidney disease, blood disorders, peripheral neuritis.
4. Is female and known to be pregnant, or breast feeding.
5. Is suffering from a condition likely to lead to uncooperative behaviour such as psychiatric illness or alcoholism.
6. Has contraindications to any medications in the study regimens.
7. Has a history of prolonged QTc syndrome or current or planned therapy with quinidine, procainamide, amiodarone, sotalol, disopyramide, ziprasidone, or terfenadine during the intensive phase of TB therapy.
8. Haemoglobin <7g/l.
9. Either AST or ALT > 5 times the upper range.
10. Creatinine clearance of < 30mls/min.
11. Has a history of seizures.
12. If HIV positive with a CD4 count of less than 150/mm³
13. Weight < 35kg.
14. Already receiving anti-retroviral therapy (ART)

Patients with concurrent illness in a mild form requiring routine treatment are eligible.

3.3 Late screening exclusions

Patients with initial resistance to isoniazid, rifampicin or moxifloxacin are not eligible and will not be included in the analysis. However, in most cases, it will not be possible to identify these patients until after randomisation. When the pre-treatment susceptibility test results become available and a patient is found to be resistant to any one of these drugs, they will be withdrawn from the trial and will be referred to the NTP for treatment with the WHO recommended Category II treatment. If, however, a patient has had an adverse event the patient should not be withdrawn until it has been resolved. The appropriate sections of the ‘withdrawal and loss to follow-up form 12’ should be completed and the Trial Manager notified.

Patients with only negative, contaminated or missing culture result from sputum samples taken pre-treatment will be withdrawn from the trial as soon as the results are available and referred to the NTP for further management. Such patients will be withdrawn from treatment and follow-up and will not be included in any analysis. If, however, a patient has had an adverse event the patient should not be withdrawn until it has been resolved. The appropriate sections of the withdrawal and loss to follow-up form 12 should be completed and the Trial Manager notified.

3.4 Number and source of patients

For selection of centres and staffing levels refer to section 2.6

A total of 1100 patients will be enrolled from six centres in sub-Saharan Africa.

3.5 Screening procedures and pre-randomisation investigations

Patients known to be direct smear microscopy positive on two sputum specimens will be invited to be screened for inclusion in the trial. These two smear results may come from a local laboratory or one may come from a local laboratory and one from the centre's laboratory. In the case where only one result is obtained from a local laboratory consent for screening must be taken before the patient gives a sputum sample for smear microscopy. Patients will be given a Patient Information Sheet (PIS) about the trial and will be told that screening includes collecting blood and urine samples. Blood analysis will include testing for HIV by an agreed algorithm. Patients will be encouraged to be informed of the result but this will not be mandatory (except for patients who are recruited at the Botswana site). HIV seropositive individuals, who wish it, will be referred to the local HIV management services.

Patients will be told that agreeing to be screened does not mean that they have to join the trial; participation in the trial will require attendance at scheduled study visits both during and after completion of their chemotherapy. Any information entered into the database for the trial, or sent to the laboratory will be identified by a number and the patient's initials but not by name. Patients will be told that they will be free to withdraw from the study at any time and if they do so this will not jeopardise their current or future care.

If the staff are satisfied that the patient understands the above information about the screening procedures, and is willing to continue, they will be asked to indicate their consent to be screened either by signature or by thumbprint (if the participant is illiterate) on the screening consent form. Illiterate participants will be asked to have a witness present (friend, family or another member of staff independent of the study team) to witness the discussion, thumbprint consent and confirm that there has been no coercion. Participants will be given a copy of the signed/thumbprinted consent form and an information sheet to take away.

Once a participant has signed an informed screening consent form, their details will be recorded in a Screening Register. Patients will be enrolled into the study based on the criteria of eligibility outlined
in sections 3.1 and 3.2. For those found to be ineligible in the course of screening, the reason for non-inclusion should be recorded on the Screening Register. For the purposes of the study data, it is most important that this register is maintained with scrupulous attention.

At the screening stage, the following forms will need to be completed.

i) Patient’s home details:
When a patient has consented to screening it is the duty of the Home Visitor to ensure that follow-up will be possible. The Treatment Supervisor should interview the patient and make the appropriate entries in all sections of the home details form. The addresses given on the home details form should be verified at the earliest opportunity (ideally within 1 week of enrolment) by the Home Visitor.

At enrolment, each patient will nominate their Domiciliary Treatment Monitor (DTM) who will supervise them and ensure that the treatment given to be taken at home is swallowed by the patient. The Principal Investigator or an appropriately delegated member of the trial team should interview this person, ideally before any trial drug is given to the participant to take home, and ensure that they understand their responsibility.

ii) Pre-treatment investigations:
As indicated in section 3.5 one sputum sample for smear microscopy may be taken to qualify a patient for screening if two results are not available from a local laboratory.

A further two pre-treatment specimens of sputum should be collected for examination in the laboratory using microscopy, culture and susceptibility testing as shown below:

At screening the patient should be given a sputum container and asked to return at the time agreed for the enrolment visit. At enrolment, the patient should bring the container with sputum collected that morning and the second sample will be a spot sample obtained at the visit.

The following laboratory tests will also be carried out at screening

- Haemoglobin.
- Either AST or ALT
- Serum creatinine.
- HIV test (see Appendix 4).
- CD4 count in patients found to have a positive HIV result.
- Urine dipstick test for glucose.
- Pregnancy test (women of child-bearing age, who deny being pregnant should have a pregnancy test. If this is negative, they may be enrolled in the study but must be counselled to avoid getting pregnant during the treatment period). If a woman becomes pregnant during treatment, this should be reported on the appropriate assessment form.

4. RANDOMISATION & ENROLMENT PROCEDURE

Patients found to be eligible when the results of screening tests become available will be invited to enter the trial. They will be reminded that enrolment will require attendance at scheduled study visits both during and after completion of their chemotherapy. Any information entered into the database for the trial or sent to the laboratory will be identified by a number and the patient’s initials but not by name. They will be free to withdraw from the study at any time and if they do so this will not jeopardise their future care. Again, once the staff are satisfied that the patient understands the procedures, they will be required to sign a second consent form consenting to participate in the trial.

A randomisation schedule will be created by an independent statistician using randomised blocks of variable size.
Sealed opaque envelopes containing the treatment allocation slips will be held by the pharmacist. When a patient is found to be eligible their details will be entered on the enrolment log by the designated member of the clinic team against the next available study number. These patient details and the study number will be entered on to the patient’s prescription. This will be taken to the pharmacy and the patient details entered onto the pharmacy register by the pharmacist against the next study number which will act as a check that the correct (next available) study number had been used. The pharmacist will then take the envelope corresponding to the study number and reveal the treatment allocation which will be written on the allocation slip. This will then be attached to the prescription and kept in the patient’s Trial folder or other appropriate place and the designated member of the clinic team made aware of the treatment allocation.

Within two weeks of enrolment each patient should have a postero-anterior chest radiograph taken unless one has been performed in the month previous to enrolment that can be used for trial purposes. All radiographs should be stored electronically for eventual transmission to the Sponsor at the end of the trial. Each radiograph should be identified by study number only.

5. TREATMENT OF PATIENTS

5.1 Introduction
Patients will be randomised to either the control regimen or to one of the two test regimens:

**Control regimen**
2 months of daily ethambutol, isoniazid, rifampicin, and pyrazinamide followed by 4 months of daily isoniazid and rifampicin (2EHRZ/4HR)

**Study regimen 1**
2 months of daily ethambutol, moxifloxacin, rifampicin, and pyrazinamide followed by 2 months of twice weekly moxifloxacin and rifapentine (2EMRZ/2P2M2).

**Study regimen 2**
2 months of daily ethambutol, moxifloxacin, rifampicin, and pyrazinamide followed by 4 months of once weekly moxifloxacin and rifapentine (2EMRZ/4P1M1).

Because the absorption of rifapentine has been shown to be increased after food, patients will be given a light meal of 2 hard boiled eggs and bread just before their rifapentine containing treatment.

Patients requiring anti-retroviral treatment (ART) after initiation of trial regimen will be treated according to the local policy (see Appendix 5). If ART is required during anti-TB treatment, drugs known to interact with the rifamycins (rifampicin or rifapentine) should be excluded from the ART.

The occurrence of RMR will be closely monitored. If, in either of the test regimens 2 or more patients relapse with RMR strains, enrolment to that regimen will be discontinued pending further investigations.

5.2 Drug supply and storage

Arrangements to acquire and supply the drug will be made through INTERTB, but the drug supply will be coordinated by MRC CTU.

The drugs will be supplied in the following dosages:
Rifampicin (150 mg) tablet; rifapentine (150 mg) tablet; isoniazid (300 mg) tablet; ethambutol (400 mg and 100 mg) tablet; pyrazinamide (500 mg) tablet; moxifloxacin (400 mg) tablet; pyridoxine (25 mg) tablet.
Once the centre has received approval for participation from their appropriate regulatory body, arrangements will be made for the dispatch of the drugs to a designated person. Each centre will be responsible for the clearance of the drugs from their Customs Department.

Patients requiring second or third line drugs will be treated, according to WHO guidelines, with drugs from local supplies. If the drugs are not available in the country, the Chief Investigator should be informed.

All trial drugs must be stored at less than 25°C as stipulated in the safety product information. Minor temperature excursions are permitted but the trial manager must be informed should excursions occur at any site. Study centres must have written arrangements in place should any of the temperature controlling equipment malfunction.

5.3 Treatment schedules

Treatment Cards
Every centre will be supplied with a batch of treatment cards (Appendix 11). When a patient fulfilling the criteria for enrolment has signed the enrolment consent form, and the allocated regimen is known, the Treatment Supervisor will select the appropriate Treatment Card and enter the patient’s study number on the card. The patient’s regimen and date of start of treatment will also be entered against his/her name in the Enrolment Register. The patient may then begin the treatment.

Details of Drug Dosages
All drugs will be given in single dose formulations. No combination formulations will be used.

Initial intensive phase daily treatment
The doses of drugs to be given to each patient are shown below and are based on the weight of the patient at the time of starting treatment.

Table 1 Study regimens 1 and 2 - daily for 2 months

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>Number of tablets (total dose) for different weights (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35-39</td>
</tr>
<tr>
<td>ethambutol(400mg)</td>
<td>1 (400mg)</td>
</tr>
<tr>
<td>ethambutol(100mg)</td>
<td>2 (200mg)</td>
</tr>
<tr>
<td>moxifloxacin(400mg)</td>
<td>1 (400mg)</td>
</tr>
<tr>
<td>rifampicin(150mg)</td>
<td>3 (450mg)</td>
</tr>
<tr>
<td>pyrazinamide(500mg)</td>
<td>2 (1000mg)</td>
</tr>
<tr>
<td>ethambutol(400mg)</td>
<td>1 (400mg)</td>
</tr>
<tr>
<td>ethambutol(100mg)</td>
<td>2 (200mg)</td>
</tr>
<tr>
<td>isoniazid(300mg)</td>
<td>1 (300mg)</td>
</tr>
<tr>
<td>rifampicin(150mg)</td>
<td>3 (450mg)</td>
</tr>
<tr>
<td>pyrazinamide(500mg)</td>
<td>2 (1000mg)</td>
</tr>
<tr>
<td>pyridoxine (25mg)</td>
<td>1 (25mg)</td>
</tr>
<tr>
<td>pyridoxine (25mg)</td>
<td>1 (25mg)</td>
</tr>
</tbody>
</table>

Table 2 Control regimen - daily for 2 months

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>Number of tablets for different weights (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35-39</td>
</tr>
<tr>
<td>ethambutol(400mg)</td>
<td>1 (400mg)</td>
</tr>
<tr>
<td>ethambutol(100mg)</td>
<td>2 (200mg)</td>
</tr>
<tr>
<td>isoniazid(300mg)</td>
<td>1 (300mg)</td>
</tr>
<tr>
<td>rifampicin(150mg)</td>
<td>3 (450mg)</td>
</tr>
<tr>
<td>pyrazinamide(500mg)</td>
<td>2 (1000mg)</td>
</tr>
<tr>
<td>pyridoxine (25mg)</td>
<td>1 (25mg)</td>
</tr>
<tr>
<td>pyridoxine (25mg)</td>
<td>1 (25mg)</td>
</tr>
</tbody>
</table>

Continuation (maintenance) phase treatment

Study regimen 1: rifapentine and moxifloxacin - twice weekly for 2 months
Patients allocated to this arm will receive 900 mg of rifapentine (6 tablets) and 400 mg (1 tablet) of moxifloxacin twice a week for 2 months.
Each dose will be preceded by a meal of 2 hard boiled eggs and bread.

Study regimen 2: rifapentine and moxifloxacin - once weekly for 4 months
Patients allocated to this arm will receive 1200 mg of rifapentine (8 tablets) and 400 mg (1 tablet) of moxifloxacin once a week for 4 months.
Each dose will be preceded by a meal of 2 hard boiled eggs and bread.

**Control regimen: rifampicin, isoniazid and pyridoxine daily for 4 months**
Doses are based on the weight of the patient at enrolment.

**Table 3 Control regimen - Daily for 4 months**

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>35-39</th>
<th>40-54</th>
<th>55-70</th>
<th>&gt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>rifampicin (150mg)</td>
<td>3 (450mg)</td>
<td>3 (450mg)</td>
<td>4 (600mg)</td>
<td>4 (600mg)</td>
</tr>
<tr>
<td>isoniazid (300mg)</td>
<td>1 (300mg)</td>
<td>1 (300mg)</td>
<td>1 (300mg)</td>
<td>1 (300mg)</td>
</tr>
<tr>
<td>pyridoxine (25mg)</td>
<td>1 (25mg)</td>
<td>1 (25mg)</td>
<td>1 (25mg)</td>
<td>1 (25mg)</td>
</tr>
</tbody>
</table>

**5.4 Treatment procedures**

Throughout the period of treatment every dose should be given under direct observation (DOT) by the Treatment Supervisor or the Domiciliary Treatment Monitor (DTM), who must check that the drugs have been swallowed, and record the amount taken on the Treatment Card.

Full details of the drug regimen, including drug dosages, for each patient and of the procedure to be followed are also given on each Treatment Card.

**Initial intensive phase**
Patients may be admitted to hospital, or be required to attend the treatment facility daily, or weekly for the initial intensive phase (first eight weeks) of chemotherapy so that the drug ingestion can be directly observed (DOT) and the appropriate entries made in the Treatment Card. For those days the facility is expected to be closed (Saturdays, Sundays and National holidays and patients attending the treatment facility weekly) the ambulatory patients may be given intensive phase doses to take under the supervision of the designated DTM. However, the intensive phase must include at least 40 daily DOT doses (8 weeks x 5 DOT doses per week), and should not exceed 56 total doses (DOT plus self-administered doses combined).

**Continuation phase**
In those patients allocated to receive either of the two study regimens, all the continuation phase doses must be given as DOT by the Treatment Supervisor, so that each patient receives a minimum of 16 and a maximum of 18 DOT doses (either once weekly for 18 weeks or twice weekly for 9 weeks).

The days on which intermittent treatment is given may be selected by the centre and/or the patient, but there must be a separation of at least 48 hours between the doses on the twice weekly regimen and 3 days on the once weekly regimen. Every dose must be given under the full supervision of a member of the medical staff and seen to be swallowed.

Patients allocated to the control regimen, will be given a supply (according to the amount usually given at that centre) to take home and drug ingestion will be supervised by the DTM.

The Treatment Cards should be returned to the clinic at each visit.

**5.5 Failures and relapses**

In all cases, the further management of the patient who might require retreatment should be discussed with the Chief Investigator before retreatment is restarted.

1. **Failures:** If the sputum is culture positive for MTB at the end of month 3 or 4 in the four month regimen (2EMRZ/2P2M2) or month 5 or 6 in the six month regimens (2EMRZ/4P,M1 and 2EHRZ/4HR),
2 further sputum specimens should be collected immediately for smear, culture and susceptibility testing, one for testing locally and the second to send to London if necessary. Treatment should not be modified until the results of these examinations are available. If a culture positive for MTB is obtained from either of these confirmatory specimens, the patient should be considered to have failed.

2. Relapses: If the sputum is culture positive for MTB after the end of treatment, two further sputum specimens should be collected immediately for smear, culture and susceptibility testing, one for testing locally and the second to send to London if necessary. Treatment should not be modified until the results of these examinations are available. If a culture positive for MTB is obtained from either of these confirmatory specimens, the patient should be considered to have relapsed.

If at any visit there is reason to believe, either from reported symptoms, clinical condition or a positive smear, that the patient is not responding to treatment or has relapsed, additional sputum samples should be collected for smear and culture examination.

In the case of failures and relapses, follow-up should continue until the patient has reached the end of scheduled follow-up.

**It is most important that, in all cases considered to require retreatment, the further management of the patient should be discussed with the Chief Investigator before retreatment is started.**

Note: If the sputum is smear positive at the end of month 2, there should be no extension of the intensive phase and the patient should be given the continuation phase chemotherapy as allocated.

Results of susceptibility tests of the pre-treatment sputum specimens should be available by the end of the initial intensive phase of treatment. If resistance is found to isoniazid, rifampicin or moxifloxacin, patients should be referred to the NTP for treatment according to the WHO treatment guidelines.

### 5.6 Accountability and unused drugs/devices

Drug stocks will be regularly monitored and the remaining stocks checked against the amounts dispensed. At the end of the study, all remaining investigational drugs will be destroyed.

### 5.7 Measures of adherence

Adherence to treatment is a measure of the number of DOT doses of the allocated drugs the patient has taken.

DOT doses for the intensive phase of all arms of the trial and for the continuation phase of the control arm will include both doses supervised at the clinic and by the DTM at home. For the continuation phase of the two test arms, DOT doses will only be administered at the clinic, or if the patient does not attend, at home during a home visit by the treatment supervisor or home visitor.

The number of DOT doses missed may be made up provided this takes place within a certain period of time. This will also depend on whether treatment was missed during the initial intensive phase or the continuation phase.

**The following procedure is recommended:**

1. **Treatment missed during the initial (first eight weeks) intensive phase.**
   Patients must receive a minimum of 40 and a maximum of 56 daily DOT doses in the intensive phase of treatment. Patients may, in exceptional circumstances, also receive self-administered doses, but
the total of DOT + self-administered doses should not exceed 56 doses. If patients miss some doses, they have a total of 70 days from the date of start of chemotherapy to complete their required number of daily doses. The same limits apply whether the therapy is given as an inpatient or as an outpatient.

2. Treatment missed during the continuation phase
Continuation phase therapy is a minimum of 90 daily DOT doses and a maximum of 126 daily DOT doses during the subsequent 18 weeks in the control regimen, or a minimum of 16 and a maximum of 18 doses, at a rate of once or twice a week, during the subsequent 18 or 9 weeks of therapy for patients on the two study arms. If patients miss some doses, they have a total of 13 weeks (if allocated to the 4 month regimen) or 22 weeks (if allocated to a 6 month regimen), from the date of start of continuation phase, to complete the required doses. There should always be at least 48 hours between any two doses in the twice weekly regimen, and 3 days in the once weekly regimen.

In the case where a patients treatment needs to be prolonged due to missed doses this should be according to the ‘Instructions for prolongation of treatment’ that can be found in the centre’s working practice documents.

Patients who have not adhered to the above schedule will have further treatment at the discretion of the local Principal Investigator who may choose to continue with the allocated regimen. These patients will be classified as treatment failures in the ITT analysis. Centres must continue to follow the protocol for investigations and reports for these patients until the end of their period in the study (i.e. until the end of the follow-up period).

5.8 Non-trial treatment

Medications permitted
Drugs not known to have any interaction with the trial drugs will be permitted.

Medications not permitted/precautions
if a patient is eligible for ART, i.e. their CD4 count is below the threshold for recommended treatment in their country, then they should be treated with ARVs that are compatible with their TB treatment.

Current or planned therapy with quinidine, procainamide, amiodarone, sotalol, disopyramide, ziprasidone, or terfenadine during the intensive phase of TB therapy will not be permitted in the trial.

Data on concomitant medication
All non-trial treatment taken by the patient will be recorded at enrolment and in the event of an SAE occurring.

5.9 Dispensing

The drugs will be stored in the pharmacy. The treatment supervisors will collect the amounts needed for that day from the pharmacy. Detailed records of drugs dispensed and received will be maintained by both the pharmacist and the treatment staff.

For days when the treatment facility is expected to be closed (weekends and public holidays), drugs will be given to the patient to take at home and supervised by the DTM.

6. ASSESSMENTS AND PROCEDURES

6.1 Follow-up schedule

Each patient enrolled should be seen by the Principal Investigator or Trial Physician at each monthly visit during the treatment phase.
When the required amount of chemotherapy (see section 5.7 entitled ‘Measures of Compliance and Adherence’) has been successfully completed, the patient should be seen by the Principal Investigator, or recruiting physician, and be instructed to return at intervals shown below up to the end of follow-up.

Follow-up will be stopped 12 months after the last patient in the trial has been randomised. Patients with scheduled follow-up visits after this date will be called back for a final follow-up visit before this date. Those randomised within the last 6 months of the recruitment period will have reduced follow-up ranging from 12 to 18 months from randomisation.

At each of the visits a sputum specimen will be collected for smear and culture examination, the appropriate CRF completed, the top copy sent for data entry, and the duplicate retained in the patient’s Trial Folder (see section 6.2 below).

Entries made in the CRF must be either verifiable against source documents, or have been directly entered into the CRF, in which case the entry in the CRF will be considered as the source data. The study file and all source data should be retained until notification is given by the sponsor for destruction.
### 6.2 Summary of investigations during treatment and follow-up

#### 6 month regimen

<table>
<thead>
<tr>
<th>Month/visit</th>
<th>Consent</th>
<th>Locator form</th>
<th>Clinical form</th>
<th>Chest xray</th>
<th>Blood tests: Haemaglobin, AST/ALT, creatinine, and HIV</th>
<th>Urine tests: Glucose and pregnancy (HCG)</th>
<th>Treatment phase report</th>
<th>Follow-up phase report</th>
<th>Sputum smear/culture</th>
<th>Sensitivity test (if culture +ve)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-screening</strong> *</td>
<td>✓*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screen (0s)</td>
<td>✓∗∗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrolment (0b)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

* A pre-screening sputum sample should only be taken if two smear results are not available from a local laboratory. This sample should only be taken after the consent for screening has been done.

** If the consent for screening was done at pre-screening then it does not need to be administered again at screening.

*** If the site deems it necessary, i.e. there is a high rate of initial resistance seen at that site for patients already enrolled, then the HAIN test for isoniazid and rifampicin resistance may be carried out on a pre-screening smear positive sputum sample.

### 4 month regimen

<table>
<thead>
<tr>
<th>Month/visit</th>
<th>Consent</th>
<th>Locator form</th>
<th>Clinical form</th>
<th>Chest xray</th>
<th>Blood tests: Haemaglobin, AST/ALT, creatinine, and HIV</th>
<th>Urine tests: Glucose and pregnancy (HCG)</th>
<th>Treatment phase report</th>
<th>Follow-up phase report</th>
<th>Sputum smear/culture</th>
<th>Sensitivity test (if culture +ve)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-screening</strong> *</td>
<td>✓*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screen (0s)</td>
<td>✓∗∗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrolment (0b)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

* A pre-screening sputum sample should only be taken if two smear results are not available from a local laboratory. This sample should only be taken after the consent for screening has been done.

** If the consent for screening was done at pre-screening then it does not need to be administered again at screening.

If the site deems it necessary, i.e. there is a high rate of initial resistance seen at that site for patients already enrolled, then the HAIN test for isoniazid and rifampicin resistance may be carried out on a pre-screening smear positive sputum sample.

*** If the site deems it necessary, i.e. there is a high rate of initial resistance seen at that site for patients already enrolled, then the HAIN test for isoniazid and rifampicin resistance may be carried out on a pre-screening smear positive sputum sample.

### Notes

*Population PK blood samples: first 400 patients in the two experimental arms (200 in each arm) in Cape Town, Harare and Johannesburg only.

---

RIFAQUIN Protocol Version 1.8, 15 April 2011

Page 24 of 97

St Georges, University of London - RIFAQUIN
If a patient’s monthly visit date falls on a day that is inconvenient, there is a window of 3 days either side of the date in which the visit can be scheduled and 7 days either side of the date for 3 monthly visits.

At any time a patient may come for an unscheduled visit and should be asked to produce a sputum sample for smear and culture. A treatment phase report or follow-up phase report should be completed depending on when the patient comes in for the unscheduled visit.

### 6.3 Procedures for assessing efficacy

The primary outcome efficacy measures are 1) the combined failure/relapse rate, 2) the proportion of relapse cultures with RMR in HIV infected patients and 3) grade 3 or 4 adverse events.

Outcome at the end of treatment will be based on culture results at 5 and 6 months for the 6 month duration regimens, and 3 and 4 months for the 4 month duration regimen. Patients with negative cultures at both assessments will be classified as having a favourable response, those with positive cultures at both months will be considered to have an unfavourable response. Those with a positive culture for MTB in the last month of treatment without confirmation in the preceding month will be classified as having an unfavourable response if the culture taken a month after stopping treatment is positive for MTB.

Relapse after stopping chemotherapy will be defined on the basis of culture results in the period 7 to 18 months for the 6 month regimen and 5 to 18 months for the 4 month regimen. Relapse will be defined as two positive cultures on two separate occasions on either medium in any 3 month period. Investigators will be strongly discouraged from restarting chemotherapy on the basis of a single positive culture (or smear). Should, however, treatment be restarted, such patients will be classified as relapses.

In the event of any uncertainty about the classification of the outcome at the end of treatment or in the follow-up period an independent endpoint review committee will assess individual outcomes blinded to the months of the culture results to be assessed.

### 6.4 Procedures for assessing safety

Throughout this study patients will be closely monitored for signs and symptoms of drug toxicity. All toxicities leading to the study therapy being temporarily or permanently discontinued and all Grade 3 or 4 toxicity effects will require thorough investigation with relevant clinical and laboratory tests, as clinically indicated. These should be repeated as needed until final resolution or stabilization of the toxicity. All symptoms and laboratory findings will be graded according to severity using the modified Division of AIDS toxicity criteria filed in the Trial Master File. Laboratory events will be reported only if clinically significant. If the patient has a medical diagnosis at enrolment whose signs or symptoms worsen during the study to a Grade 3 or 4, this is a notifiable adverse event that must be reported.

Serious Adverse Events (SAEs) and other notifiable adverse events (NAEs) will be reported, as they occur, to the CI and the MRC Clinical Trials Unit, as well as other bodies required to be notified in each country.

For details of safety reporting, expected adverse events and flow chart for assessing and notifying adverse events see section 10, Appendix 4 and Appendix 10.

### 6.5 Absconding from treatment

A patient will be deemed to have absconded if he/she does not attend the treatment centre to take the treatment as prescribed for a period of one week.
The Treatment Supervisor should ask the Home Visitor to visit the addresses given on the home details form (Form A) and make every effort to persuade the patient to attend the treatment centre as directed and complete the allocated regimen.

If the patient is not found at home, every effort should be made to find him/her by interviewing relatives and neighbours, and by visiting the alternative addresses given on the home details form.

If the patient has not resumed trial treatment within seven days of absconding, i.e. if the patient has missed at least two weeks of therapy, the ‘treatment stopped’ section of the ‘Withdrawal and loss to follow-up Form 12’ should be completed. This procedure should be repeated every time a patient has not attended for treatment for a period of one week.

For the subsequent management of patients who abscond one or more times, see section 5.7 Measures of adherence.

6.6 Loss to follow-up after completion of treatment

Patients who fail to attend for a follow-up visit despite at least three attempts to contact them will be considered to be lost to follow-up and the ‘loss to follow-up’ section of Form 12 should be completed. If a patient considered a loss to follow-up subsequently attends the study clinic, follow-up should continue according to the protocol.

Every effort should be made at the final scheduled follow-up visit to contact those who have been lost to follow-up.

6.7 Trial closure

The trial will be considered closed when the last randomised patient has completed 12 months in the study and all follow-up and laboratory reports have been received. Early termination could occur if there is an unacceptable level of adverse events including development of rifampicin resistance, or in the event of an unacceptably high failure/relapse rate occurring in both test arms.

6.8 Reference bacteriology

Since the emergence of rifamycin mono-resistance is a primary end point, and the presence of initial resistance to any of the trial drugs is a reason for exclusion, the ability of participating laboratories to obtain reliable susceptibility test results is crucial to the trial. This will be done by systematic selection of sputum samples and cultures for parallel testing to isoniazid, streptomycin, rifampicin, pyrazinamide and moxifloxacin, by Mr David Coleman, Division of Medical Microbiology, Department of Cellular and Molecular Medicine, St George’s, University of London, Cranmer Terrace, London SW17 0RE. Transport of infected material will be arranged with World Courier.

One pre-treatment culture (2 if there is enough space in the freezer) will be stored at -20°C until the end of trial or until the patient relapses/fails treatment. These will then be paired with the specimen/culture of the unfavourable outcome and sent to London for RFLP of M.TB in order to distinguish reinfection from true relapse.

All specimens will be destroyed at the end of the trial.

6.9 Population PK study

400 participants enrolled in the two experimental arms of the study in Cape Town, Johannesburg and Harare will be sampled during a dose interval in the 4th month of treatment. Participants should be notified of the date they are required to be present for the sampling procedure and be told that the sampling will be for a period of approximately 6 hours on Day 1 and approximately 1 hour on Day 2 or 3. The procedures will involve drawing, recording, handling and storage of PK samples and data collection. The name of the phlebotomist and the times of sampling should be recorded. Samples
must be stored at -80 °C until transfer in dry ice (to ensure an unbroken cold chain) to the Division of Clinical Pharmacology, University of Cape Town, K45 Old Main Building, Groote Schuur Hospital, Observatory, Cape Town.

Patients will be re-consented separately for the Population PK study at either 3 or 4 months post enrolment

7. WITHDRAWAL OF PATIENTS

In consenting to the trial, patients are consenting to trial treatment, trial follow-up and data collection. If a patient wishes to stop their trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes. If the patient explicitly states their wish not to contribute further data to the study the appropriate sections of the withdrawal and loss to follow-up Form 12 should be completed and the Chief Investigator informed in writing by the local Principle Investigator. A patient who withdraws consent for trial treatment, trial follow-up and data collection in this way is defined as a trial withdrawal as is the case with those patients outlined in section 3.3.

7.1 Stopping trial treatment

Patients may have the trial intervention stopped for severe and intolerable adverse events, inability to comply with the trial protocol, inability to attend regularly for treatment or assessment, pregnancy (if they are on either of the study regimens), or if a patient chooses to stop trial treatment. If the patient’s trial intervention is stopped for any reason their treatment will be changed to the standard NTP regimen. These patients should not be withdrawn from follow-up which should be continued unless the patient explicitly withdraws consent for follow-up (as above). However follow-up can be less frequent. Ideally it should be every 3-4 months and every effort should be made to ensure the 18 month visit is completed for all patients. These patients are not defined as withdrawals and follow-up should be continued as part of the study. The appropriate section of the withdrawal and loss to follow-up Form 12 still needs to be completed and the Trial Manager notified.

At each visit, women of child bearing age will be asked if they are pregnant and a pregnancy test carried out. Patients who become pregnant during treatment on Study Regimen 1 or Study Regimen 2 will stop their allocated treatment and commence treatment according to the following:

**If in intensive phase:** withdraw moxifloxacin and re-start treatment with a conventional 6 months regimen including isoniazid and rifampicin.  
**If in continuation phase:** withdraw moxifloxacin and continue treatment with isoniazid and rifampicin to ensure a total of at least 6 months treatment.

Women who become pregnant at any time up to 3 months after completing their allocated regimen will be followed up for the outcome of their pregnancy. A pregnancy outcome form should be completed in all instances.

8. STATISTICAL CONSIDERATIONS

8.1 Method of randomisation

A randomisation schedule will be created using randomised blocks of variable size. Details of treatment allocation are shown in Section 4.

8.2 Outcome measures
Primary outcomes
1. The proportion of patients classified as failure/relapse by 18 months after the start of treatment expressed as the difference between the proportion in the intervention regimens and the control regimen.
2. Number of relapses with rifamycin mono-resistance (RMR) occurring in HIV-infected patients,
3. Grade 3 or 4 adverse events.

Secondary outcomes
1. Per protocol analysis of the first primary outcome.
2. Time to failure/relapse assessed using Kaplan Meier and Cox regression survival analysis methods
3. The proportions of patients achieving culture negativity at 8 weeks
4. Adverse events graded according to the modified DAIDS criteria.
5. Rate of completion of chemotherapy according to the protocol.
6. Number of observed doses of chemotherapy ingested

8.3 Sample size

The trial is a non-inferiority design and the original sample size calculations were based on the following assumptions:

1. The failure/relapse rate in the control regimen will be 4%, this is consistent with finding in many randomised trials, most recently an international study conducted in African and Asian centres under less strictly controlled conditions.
2. A non-inferiority margin of 4% in failure/relapse rate between the control and either of the intervention regimens is acceptable.
3. A one sided significance level of 0.05 is appropriate, since this is a non-inferiority trial, not an equivalence study.
4. Patients will be randomised in equal proportions to the three regimens.
5. Up to 24% of randomised patients may be unassessable on account of loss to follow-up, including death from non-tuberculous causes, or initial drug resistance.
6. The power of the study to determine non-inferiority will be 80%

Subsequent to determining the sample size for RIFAQUIN, a revision of the sample size assumptions in the REMoxTB trial (which were closely aligned to those in RIFAQUIN) took place. An FDA requirement was that the chosen level of δ, the margin of non-inferiority, should be justified on both statistical and clinical grounds. The justification for a δ of 6% which has been adopted in the REMoxTB trial is also appropriate for RIFAQUIN and will be included in the statistical analysis plan. A similar revision has taken place in the trial conducted by the OFLOTUB consortium. A number of outcomes that were originally classified as unassessable have been reclassified as unfavourable. These include all-cause mortality during treatment, changes of treatment for any reason and failure to complete treatment with no further follow-up visits.

The RIFAQUIN power calculations have been revised as follows:

a) The non-inferiority margin, δ, in the failure/relapse rate is 6%.
b) Patients failing to complete treatment, either on account of death from any cause or default from treatment will be classified as unfavourable; it is assumed that the rate of unfavourable outcome will be 10%.
c) 15% of randomised patients will be unassessable (some patients previously classified as unassessable will now be classified as unfavourable).

Assumptions concerning power and the significance level remain the same.

A total of 310 evaluable participants per arm will be needed to demonstrate non-inferiority, corresponding to 365 participants per arm needing to be enrolled. The revised sample size is therefore 1100.
If two thirds of the patients are HIV-infected and the bacteriologically confirmed relapse rate in the rifapentine containing regimens is 4%, a total of 310 evaluable patients per arm would provide approximately 8 relapses per arm among HIV-infected patients in the two study regimens receiving rifapentine to assess the sensitivity of the relapse strains.

If there are no cases of RMR among 8 relapses, the one sided upper 90% confidence level for the proportion with resistance would be 25%, the corresponding upper 80% confidence level would be 18%. If both rifapentine arms can be combined and there are 16 relapses the corresponding one sided upper 90% and 80% confidence levels are 13% and 10% respectively. A relapse rate higher than 4% would result in lower upper confidence limits.

### 8.4 Interim monitoring and analyses

There will be no formal interim analysis but the Independent Data Monitoring Committee (IDMC) will review analyses of failures at the end of treatment, combined failure and relapse rates, 2 month culture conversion rates, and notifiable adverse events every 4-6 months. RMR, occurring in HIV-infected patients who have relapsed, will be reported to the IDMC in real time. On the basis of their findings the IDMC will make recommendations to the Trial Steering Committee (TSC) about the continuation of the study.

The IDMC will advise the Chair of the TSC if, in its view, the randomised comparisons in the trial have provided both:

(a) proof beyond reasonable doubt that one or other of the regimens are clearly indicated or clearly contraindicated in terms of efficacy which outweighs any serious adverse effects of treatment or vice versa. (Appropriate criteria of proof beyond reasonable doubt cannot be specified but a difference of at least three standard deviations in an interim analysis would be needed to justify stopping one of the regimens or closing the study prematurely for lack of efficacy).

and

(b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the results of any other studies.

If these criteria are used, the exact number of interim analyses is of little importance so no fixed schedule is proposed.

In the event of RMR relapses occurring, a decision is likely to be made to terminate the study or one test arm early. The IDMC will be informed of each case of RMR as soon as it is confirmed.

### 8.5 Preliminary analysis plan

After data cleaning, analysis will proceed according to a pre-designed analysis plan. The primary analysis will be analysed on both a per protocol and a modified intention-to-treat population (MITT). All patients randomised who are assessable, excluding those with evidence of no tuberculosis disease on culture at baseline or initial drug resistance (see section 3.3), will be included in the MITT population.

The following additional participants will be excluded from the per protocol analysis:
- Those who did not receive adequate chemotherapy. See section 5.7 for the definition of inadequate chemotherapy.

After the unadjusted primary analysis has been performed, an adjusted analysis will be performed including covariates (such as age, gender, and baseline severity of disease as assessed by radiography and microbiology, and smoking status) which may influence outcome.
A subgroup analysis by HIV status will be performed. A full analysis plan will be developed before the final analysis is conducted.

8.6 Analysis of adverse events

The primary endpoint for adverse events is the occurrence of a Grade 3 or 4 adverse event. In addition, all patients will be classified according to whether they have had an adverse event necessitating:

- An interruption of the allocated regimen of more than 7 days.
- Stopping or changing one or more drug for that adverse event.

9. TRIAL MONITORING

The purposes of trial monitoring are to verify that:

- The rights and well-being of human subjects are protected.
- The reported trial data is accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with principles as laid down in ICH GCP Guidelines (E6), and with the applicable regulatory requirements.

9.1 Extent and nature of monitoring

The sites will be visited at regular intervals in order to monitor the conduct of the trial. These visits will be made by the Trial Manager and other members of staff at the MRC CTU. Visits will also be made by the Chief Investigator, Assistant Chief Investigator and the Trial Statistician. The frequency of monitoring visits will be determined according to site specific requirements and pre-defined triggers as determined by the MRC CTU risk assessment and as detailed in the Monitoring Plan.

9.2 Site monitoring

At monitoring visits the data entered in the CRFs will be checked against available source data according to the procedures described in the trial monitoring plan filed in the Trial Master File. Data stored will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. If any such problems are identified any data which are changed should be crossed through with a single line and initialled. Particular attention will usually be given to some or all of the following:

(a) Verifying, for the investigational products:
   
   (i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

   (ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

   (iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).

   (iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

   (v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.
(b) Verifying that the local investigator follows the approved protocol and all approved amendment(s), if any.

(c) Verifying that written informed consent was obtained before each subject's participation in the trial.

(d) Ensuring that the Principal Investigator has received the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

(e) Ensuring that the local investigator and the investigator's trial staff are adequately informed about the trial.

(f) Verifying that the local investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the local investigator/institution, and have not delegated these functions to unauthorised individuals.

(g) Verifying that the local investigator is enrolling only eligible subjects.

(h) Reporting the subject recruitment rate.

(i) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

(j) Verifying that the local investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

(k) Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. In particular:

   (i) The data required by the protocol is reported accurately on the CRFs and is consistent with the source documents.

   (ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.

   (iii) Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.

   (iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.

   (v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

(l) Informing the local investigator of any CRF entry error, omission, or illegibility. Any corrections, additions, or deletions made, are dated, explained (if necessary), and initialled by the local investigator or by a member of the investigator's trial staff who is authorised to initial CRF changes for the investigator. This authorisation should be documented.

(m) Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

(n) Determining whether the local investigator is maintaining the essential documents

(o) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the local investigator and taking appropriate action designed to prevent recurrence of the detected deviations.
9.3 Direct access to data

The investigator will permit trial-related monitoring, audits, ethics committee review and regulatory inspections by providing direct access to source data/documents.

9.4 Confidentiality

All patient information will be kept in locked cabinets and will be available only to the treatment staff.

The patient’s name and address will not be disclosed to the trial sponsor.

The patient’s data/specimens will be identified by study number and/or initials only. Individual patients will not be identified in the resulting publications and presentations from the trial. The trial will comply with the principles of the Data Protection Act of the country of the participating centre.

10. SAFETY REPORTING

10.1 Safety Reporting

Terms and definitions for adverse events

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Notifiable Adverse Event</em></td>
<td>Any of the following occurrences:</td>
</tr>
<tr>
<td>NAE</td>
<td>• Pregnancy</td>
</tr>
<tr>
<td></td>
<td>• Grade 3 toxicity or event</td>
</tr>
<tr>
<td></td>
<td>• Worsening of pre-existing condition to grade 3</td>
</tr>
<tr>
<td></td>
<td>• Study drug discontinued</td>
</tr>
<tr>
<td></td>
<td>• Identification of rifamycin mono-resistance (RMR)</td>
</tr>
<tr>
<td><em>Adverse Event</em></td>
<td>Any untoward medical occurrence in a subject to whom a medicinal product</td>
</tr>
<tr>
<td>AE</td>
<td>has been administered including occurrences which are not necessarily</td>
</tr>
<tr>
<td></td>
<td>caused by or related to that product.</td>
</tr>
<tr>
<td><em>Adverse Reaction</em></td>
<td>Any untoward and unintended response in a subject to an investigative</td>
</tr>
<tr>
<td>AR</td>
<td>medicinal product, which is related to any dose administered to that</td>
</tr>
<tr>
<td></td>
<td>subject.</td>
</tr>
<tr>
<td><em>Serious Adverse Event</em></td>
<td>Respectively, any adverse event or adverse reaction that:</td>
</tr>
<tr>
<td>SAE</td>
<td>• Results in death</td>
</tr>
<tr>
<td></td>
<td>• Is life-threatening*</td>
</tr>
<tr>
<td></td>
<td>• Requires hospitalisation or prolongation of existing hospitalisation**</td>
</tr>
<tr>
<td></td>
<td>• Results in persistent or significant disability or incapacity</td>
</tr>
<tr>
<td></td>
<td>• Consists of a congenital anomaly or birth defect</td>
</tr>
<tr>
<td></td>
<td>• Other important medical event(s)***</td>
</tr>
<tr>
<td><em>Serious Adverse Reaction</em></td>
<td>A serious adverse reaction the nature and severity of which is not</td>
</tr>
<tr>
<td>SAR</td>
<td>consistent with the information about the medicinal product in question</td>
</tr>
<tr>
<td></td>
<td>set out in:</td>
</tr>
<tr>
<td></td>
<td>• The Summary of Product Characteristics (SPC) for that product (for</td>
</tr>
<tr>
<td></td>
<td>products with a marketing authorisation)</td>
</tr>
<tr>
<td></td>
<td>• The Investigator's Brochure (IB) relating to the trial in question (for</td>
</tr>
<tr>
<td></td>
<td>any other investigational product)</td>
</tr>
</tbody>
</table>

* The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
Other events that may not result in death, are not life threatening, or do not require hospitalisation may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above (excluding new cancers or result of overdose).

**Institution Responsibilities**

All SAEs/NAEs occurring whilst the patient is in the treatment phase or within 30 days of finishing it, must be reported immediately by the Principal Investigator or delegated person at the site by e-mail to the RIFAQUIN group at MRC CTU on an SAE/NAE Form 8. The only exceptions to this are death and rifamycin monoresistance, which should be reported at any stage during the patient’s treatment or follow-up. A member of the RIFAQUIN group will then inform the Chief Investigator or the assistant Chief Investigator by email. All other adverse events should be reported in the patient’s medical notes and adverse reactions in the regular progress/follow-up reports via Form 7.

**Procedures**

1. The SAE/NAE Form 8 should be completed by the responsible investigator (medical officer named on the signature list and delegation of responsibilities log who is responsible for the patient’s care). The investigator should assess the SAE/NAE for the likelihood that it is a response to an investigational medicine. In the absence of the responsible investigator the form should be completed and signed by a member of the site trial team and emailed to the MRC CTU immediately. The responsible investigator should check the SAE/NAE Form 8, make changes as appropriate, sign and then email to the MRC CTU as soon as possible. The initial report shall be followed by detailed, written reports via a follow-up SAE/NAE Form 8.

2. The SAE form should be sent by email (within 24 hours or next working day) to the RIFAQUIN group at MRC CTU.

   **RIFAQUIN group email:** enquiriesRifaquin@ctu.mrc.ac.uk

   The CTU will notify the Chief Investigator, Assistant Chief Investigator or designated Clinical Reviewer.

3. Follow-up of SAEs/NAEs: In the case of an SAE (or relevant NAE) the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary. Follow-up information is noted on another SAE/NAE Form 8 by ticking the box marked ‘follow-up’ and emailing to the MRC CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The patient must be identified by study number, date of birth and initials only. The patient’s name should not be used on any correspondence.

The Chief Investigator, Assistant Chief Investigator or designated Clinical Reviewer, will evaluate all SAEs/NAEs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported as necessary. The causality assessment given by the PI at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report. All evaluated SAE/NAEs will be faxed back within agreed timescales to the PI at the site from where it originated.

All SAEs, SARs, NAEs, and SUSARs will be reported within an agreed timescale by the PI or delegated person to the necessary regulatory and ethics authorities for that site as laid out in the approvals and/or corresponding regulations and RIFAQUIN site specific working practice documents.

**All adverse events – Guidelines for reporting**

These lists are not exhaustive, and only include examples of what constitutes an event and what does not.

RIFAQUIN Protocol Version 1.8, 15 April 2011
### Adverse events include

| a) an exacerbation of a pre-existing illness |
| b) an increase in frequency or intensity of a pre-existing episodic event/condition |
| c) a condition (even though it may have been present prior to the start of the trial) detected after trial drug administration |
| d) continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment |

### Adverse events do not include

| a) medical or surgical procedures- the condition which leads to the procedure is the adverse event |
| b) pre-existing disease or conditions present before treatment that do not worsen |
| c) situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery |
| d) overdose of medication without signs or symptoms |
| e) the disease being treated or associated symptoms/signs unless more severe than expected for the patient’s condition |

### 10.2 Severity/grading of adverse events

This will be according to the modified DAIDS Classification filed in the Trial Master File.

### 10.3 Relationship to trial treatment

When reporting on serious adverse events, the trial investigator will state whether they believe that the event is causally associated with any of the trial treatments and the strength of the causal relationship. They will also state whether the adverse event was expected and what, if any, action was taken.

### 10.4 Follow-up after adverse events

Patients may be either admitted to hospital or seen at intervals to monitor the progress, recovery and investigations of the adverse events.

If treatment is interrupted, attempts should be made to identify the drug concerned. After complete recovery, treatment may be gradually re-introduced until the allocated regimen has been re-instituted.

In the event that treatment needs to be modified or changed, the Principal Investigator should inform the Chief Investigator and agree on the new treatment.

Women who become pregnant will continue to receive scheduled follow-up, not receive additional X-rays unless clinically indicated, and be classified as being on a non-study regimen. The outcome of pregnancies occurring in the treatment phase (of the study regimens and up to three months post treatment) will be reported on a Pregnancy Outcome Form (Form 13) and the Serious Adverse Event and Notifiable Adverse Event Form (Form 8) – see section 7.1.

**For details of safety reporting, expected adverse events and flow chart for assessing and notifying adverse events see section 10.1, Appendix 4 and Appendix 10.**
11. ETHICAL CONSIDERATIONS AND APPROVAL

11.1 Ethical considerations

The patients will, before being enrolled into the study, have the conditions of the study, as set out in the Patient Information Sheet (Appendix 1) explained to them. The information contained in the PIS will be translated into the local dialect. Literate patients will be asked to read the PIS and the illiterate patients will have the contents explained to them by the Principal Investigator or a senior treatment supervisor. The patient will have the opportunity to discuss the PIS with the medical officer/treatment supervisor. Once this person is satisfied that the patient has understood the PIS and the consent form, the patient will be asked to sign the screening consent form. The top copy should be filed in the patient’s study folder and the duplicate, together with a copy of the PIS, given to the patient.

This process will be repeated after the pre-treatment investigations show that the patient fulfils the eligibility criteria and at each amendment to the protocol.

The right of the patient to refuse to participate in the trial without giving reasons will be respected.

After the patient has entered the trial, the clinician will remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the patient will remain free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing his/her further treatment.

11.2 Ethical approval

Version 1.3 was submitted to SGUL ethics committee. This and subsequent versions were submitted to all ethics committees of those countries participating in the study.

The protocol will also be submitted to the Medical Ethics Committee of each participating clinical site and/or country and enrolment to the study will start only after receiving the written agreement of the relevant body(ies).

The trial should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki from the World Medical Association.
http://www.wma.net/e/ethicsunit/helsinki.htm

12. REGULATORY APPROVAL

Principal Investigators will be expected to obtain, in writing, approval to participate from their Regulatory Authority.

13. INDEMNITY

The sponsor of the trial is St. George’s, University of London. Patients will be indemnified, for non-negligent harm only through a separate policy taken out by the trial sponsor.

All personnel involved in the trial will be expected to be indemnified by their employing authority.
14. FINANCE

This trial is funded by the European and Developing Countries Clinical Trials Partnership (EDCTP).

Each participating centre will be supported according to the submissions of their budgetary requirements.

Reimbursements will be made according to a Contract/Memorandum of Understanding (MOU) signed between the sponsor and the participating centres.

15. TRIAL COMMITTEES

15.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the MRC Clinical Trials Unit. The TMG will be responsible for the day-to-day running and management of the trial and will meet at regular intervals.

15.2 Trial Steering Committee (TSC)

The Trial Steering Committee (TSC) will be constituted. The Chairman will be independent of the running of the trial.

Its terms of reference will be:

1. to monitor and supervise the progress of the trial towards its interim and overall objectives;
2. to review at regular intervals relevant information from other sources (e.g. other related trials);
3. to consider the recommendations of the Independent Data Monitoring Committee;

The role of the TSC is to provide overall supervision for the trial and provide advice through its Independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.

15.3 Independent Data Monitoring Committee (IDMC)

There will be an Independent Data Monitoring Committee whose terms of reference will be as follows:

1. To review safety data regularly, in particular all serious adverse events possibly attributable to the trial drugs, such as local reactions or unexpected deaths.
2. To monitor the conduct of the trial with respect to the ethical aspects of the trial.
3. To assess the results of the formal analyses with the possibility of advising the Trial Steering Committee (TSC) that the trial should be modified or discontinued.

16. PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must not publish data concerning their patients that are directly relevant to questions posed by the study until the Trial Management Group has published its report.
The Trial Management Group will form the basis of the Writing Committee and will advise on the nature of publications.

The names of all the investigators will be included in any publication either in the authorship or listed in the article. Any authorship policy will be agreed by all the investigators before any publication.

The members of the TSC and IDMC will be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

Publications will include any public presentation of the data emerging from the trial. In order to manage the strategy, a publications committee will be set up which will include the Chief Investigator, the Principal Investigators and others, such as the Trial Statistician, involved in the trial. Additional individuals may be involved as necessary with the agreement of the group. This publications group will agree and circulate the publication strategy. The use of the data for the purposes of publication must first be approved by the group. It is anticipated that this group will meet at intervals as necessary and will communicate by e-mail and teleconferences as necessary. Written publications will be through international peer reviewed journals. Updates on the progress of the trial will be presented at the annual EDCTP Meeting of Investigators. The results of interim analyses, if significant, will be presented at the EDCTP Investigators Meeting and at other international scientific conferences. If they concern policy decisions, dissemination will be through the press, national governments at meetings and international organisations at conferences.

17. PROTOCOL AMENDMENTS

Version 1.2
Version 1.3

1. Page 16, section 3.1, point 7 ‘Pre-menopausal women must be using a barrier form of contraception or be surgically sterilised or have an IUCD in place’ added.

2. Page 19, section 5.3, ‘enter the patient’s name’ removed and ‘and enter the patient’s study number on the card’ added.

3. Page 24, ‘Summary of Investigations during Treatment and Follow-Up’ tables, sensitivity test heading changed to include ‘if culture +ve’

4. Page 26, section 6.7, details of samples to be sent to London removed and replaced with ‘Pre-treatment cultures are retained until the end of trial or the patient relapses/fails treatment, these are then paired with the specimen/culture of the unfavourable outcome and sent to London for RFLP of M.TB in order determine reinfection from true relapse and then destroyed at the end of the trial’.

5. Page 27, section 7.1, ‘If the Patient is withdrawn from the trial intervention for any reason their treatment will be changed to the standard regimen’ added.

6. Page 36, Section 16 modified to include the paragraph ‘A publication will include any public presentation of the data emerging from the trial. In order to manage the strategy, a publications committee will be set up which will include the Chief Investigator, the principal investigators and others, such as the trial statistician, involved in the trial. Additional individuals may be involved as necessary with the agreement of the group. This publications group will agree and circulate the publication strategy. The use of the data for the purposes of publication must first be approved by the group. It is anticipated that this group will meet at intervals as necessary and will communicate by e-mail and teleconferences as necessary. Written publications will be through international peer reviewed journals. Updates on the progress of the trial will be presented at the annual EDCTP Meeting of Investigators. The results of interim analyses, if significant, will be presented at the EDCTP Investigators Meeting and at other international scientific conferences. If they concern policy decisions, the population may be informed through the press, national governments at meetings and international organisations at conferences’

7. Page 43, point 1, ‘However, the rifapentine has only been used at the dose of 600mg. In this trial we will be testing higher doses of 900mg and 1200mg’ added.

8. Page 43, point 2, sentence 1, ‘TB’ replaced with ‘Tuberculosis’
9. **Page 43**, point 2, 'This is an infection which is caused by a germ which can affect any part of the body. It is curable if you take your treatment as directed' added.

10. **Page 43**, point 4, 'Some of your sputum and bacteria cultured from your sputum may be sent to London for further tests. However all of these samples will be destroyed at the end of the trial' added.

11. **Page 43**, point 4, 'will also do an HIV test' changed to 'You must also agree to have an HIV test'.

12. **Page 43**, point 4, 'This is a blood test to detect if you have been infected with the human immune deficiency virus which is most commonly transmitted by sexual intercourse with an infected person' added.

13. **Page 43**, section 4, 'We will not tell anyone else about your result without your permission.' removed.

14. **Page 43**, point 4, 'There will be 3 different treatments using either the test drugs or a standard treatment. Patients will be randomly assigned to one of the 3 treatments and the results compared to see if one is better than the others. You may be treated with either the test tablets or the standard treatment. We will give you the TB medicines for 17 or 26 weeks' replaced with 'You will receive one of three treatments. It will be decided by chance (like flipping a coin) which treatment you will receive. The possible treatments are standard TB treatment for six months; study treatment for four months with twice-weekly treatment during the last two months; or study treatment for six months with once-weekly treatment during the last two months. Patients in the two study treatment groups will receive the test medicines (moxifloxacin throughout and rifapentine after the first two months) instead of standard medicines (rifampicin and isoniazid). If you are chosen to receive the test drugs you will be given a meal of hard boiled eggs and bread just before taking your medicine. You will not have to pay for this.'

15. **Page 43**, section 4, 'If you are a pre-menopausal women you must use a barrier form of contraception or be surgically sterilised or have an IUCD in place during the course of the trial' added.

16. **Page 43**, section 5, 'or 8 months' added

17. **Page 44**, section 5, 'The total time you will be in the trial is 18 months.' added

18. **Page 44**, section 5, 'Each sample of blood taken will be less than 5mls.' added

19. **Page 44**, section 6, 'of 900mg or 1200mg. These are higher than the standard dose of 600mg' added.

20. **Page 44**, section 8, 'Before you enter the trial you should tell the doctor if you are taking any other medicines including birth control pills or injections.' added

21. **Page 44**, section 10 'There will be no direct benefit to you from taking part however' added

22. **Page 45**, section 14, 'appropriately.' added

23. **Page 45**, section 16, 'We will provide compensation for any injury caused by taking part in this study in accordance with the guidelines of the insurance company.' replaced with 'Compensation will be paid for reasonable medical expenses incurred as a result of study-related injury or illness, determined according to the guidelines laid down by the Association of the British Pharmaceutical Industry (ABPI Guidelines), and Guidelines for Good Clinical Practice in the Conduct of Clinical Trials in Human Participants in South Africa.'

24. **Page 46**, section 21, 'The sponsor is St Georges, University of London.' added

25. **Page 46**, section 22, 'has received approval' added

26. **Page 46**, 'The top copy of this form should be filed in the patient's study folder. The duplicate should be given to the patient.' replaced with '*One copy of this form to be given to the patient to keep.'

27. **Page 47** Acronym and title of study has been inserted. 'Centre Number (if applicable): xxx
Trial Number: xxx' removed. 'Name of Researcher:' removed. 'Screening No.: [ ]' added.

28. **Page 47** Point 1 '(or had read to me)' added.

29. **Page 47**, Point 6, 7 and 8 '6. I agree to have an HIV test, 7. I agree to be informed of the result of the HIV test, 8. I agree if I am a pre-menopausal women I must be using a barrier form of contraception or be surgically sterilised or have an IUCD in place' added.

30. **Page 47**, Place for researcher name, signature and date replaced with 'name of witness (if patient is illiterate), signature or thumbprint and date'.

---

RIFAQUIN Protocol Version 1.8, 15 April 2011

Page 38 of 97
31. Page 47, ‘(if different from researcher)’ removed from ‘name of person taking consent’.
32. Page 47, ‘3 copies: 1 for patient, 1 for researcher, 1 to be kept with medical notes’ replaced with ‘2 copies: 1 for patient, 1 for the patient’s confidential Trial folder’
33. Page 47, Acronym and title of study has been inserted. ‘Centre Number (if applicable): xxx 
   Trial Number: xxx’ removed. ‘Name of Researcher’ removed. ‘Study No.: [ ]’ added.
34. Page 48, Point 1 ‘(or had read to me)’ added.
35. Page 48, Place for researcher name, signature and date replaced with ‘name of witness (if patient is illiterate), signature or thumbprint and date’.
36. Page 48, ‘(if different from researcher)’ removed from ‘name of person taking consent’.
37. Page 48, ‘3 copies: 1 for patient, 1 for researcher, 1 to be kept with medical notes’ replaced with ‘2 copies: 1 for patient, 1 for the patient’s confidential Trial folder’

Version 1.4

1. Page 8, section 1.3, ‘grade 3 or 4’ added and ‘serious’ removed
2. Page 9, section 1.4 ‘Please see section 6.8’
3. Page 10, section 2.2 ‘below’ removed and ‘in section 3.1 and 3.2’ added
4. Page 11, reference to ‘fig 2’ changed to ‘fig 1’
6. Page 16, section 3.2 ‘(Appendix 5 and 9)’ added
7. Page 16, section 3.3 ‘procedures before start up’ removed and ‘staffing levels’ added
8. Page 17, section 3.4 ‘but neither’ ‘nor the staff looking after them’ and ‘be informed of the result unless the patient wishes it’ removed
9. Page 17, section 3.4 be encouraged to be informed of the result but this will not be mandatory’ added
10. Page 17, section 3.4 second paragraph, ‘current or’ added
11. Page 17, section 3.4 third paragraph ‘and’ removed and ‘and confirm no coercion’ added
12. Page 18, ‘and third specimens’ changed to ‘specimen’, ‘two universal containers’ changed to ‘a universal container’, ‘that visit’ changed to ‘enrolment’, ‘both the containers’ changed to ‘the container’ and ‘and the third spot sputum sample will be obtained at the visit’ added
13. Page 18, section 4 ‘Patients will be randomised, in equal proportions to the 3 regimens, either by telephoning a computer based central randomisation service or through the internet. In the event that neither of these methods is logistically possible,’ removed
14. Page 18, section 4 ‘sealed envelopes’ changed to ‘Sealed opaque envelopes’
15. Page 18, section 4, ‘a person independent of the trial and the local investigator’ changed to ‘the pharmacist’
16. Page 18, section 4 ‘Will contact this person when a patient is eligible for enrolment; the person holding the sealed envelopes will enter the patient’s name in a register against the next available study number, the allocation envelope with that study number opened and the investigator informed of the treatment arm to which the patient has been allocated’ removed
17. Page 18, section 4 ‘When a patient is found to be eligible their details will be entered on the enrolment register by the designated member of the clinic team against the next available study number. These patient details and the study number will be entered on to the patient’s prescription. This will be taken to the pharmacy and the patient details entered onto the pharmacy register against the next study number which will act as a check that the correct (next available) study number had been used. The pharmacist will then take the envelope corresponding to the study number, and reveal the treatment allocation which will be written on the allocation slip. This will then be attached to the prescription and kept in the patient’s Trial folder and the designated member of the clinic team made aware of the treatment allocation.’ added
18. Page 19, Study regimen 2, ‘a hard boiled egg’ changed to ‘2 hard boiled eggs’
19. Page 19, Study regimen 2, ‘Patients with initial isoniazid resistance’ changed to ‘Patients with initial isoniazid, moxifloxacin or rifampicin resistance’ and ‘to any of the drugs in the trial’ and ‘with’ removed

RIFAQUIN Protocol Version 1.8, 15 April 2011
20. Page 19, section 5.2 'London, in bulk to each centre as follows:' removed
21. Page 19, section 5.2 'The pharmacist in charge of re-packing and distribution of the drugs will be Shanesh Rambaran, Unit for Clinical and Biomedical TB Research, Medical Research Council, 491 Ridge Road, Overport, 4067, Durban, South Africa' added
22. Page 19, section 5.2 '10-50' changed to '25'
23. Page 19, section 5.2 'and 100mg' added
24. Page 19, section 5.2 'despatch' corrected to 'dispatch'
25. Page 19, section 5.2 'For patients requiring second or third line drugs, the local Principal Investigator will make an application to the Green Light Committee to obtain these drugs at reduced rates.' Changed to 'Patients requiring second or third line drugs will be treated with drugs from local supplies where necessary.'
26. Page 19, section 5.3 '(Appendix 8)' and 'enrolment' added
27. Page 20, section 5.3 'Screening register' changed to 'Enrolment register'
28. Page 20, table 2a and 2b changed to show ethambutol 100mg and 400mg tablet dosages.
29. Page 20, '1 tablet' changed to '1 tablet'
30. Page 20, 'Doses are based on the weight of the patient upon completion of the initial intensive phase' changed to 'Doses are based on the weight of the patient at enrolment'.
31. Page 20, section 5.3, title 'Table 2c Control regimen – Daily for 4 months' added.
32. Page 20, section 5.3 '10-50' changed to '25'
33. Page 22, section 5.5, 'or moxifloxacin' added
34. Page 22, section 5.5, 'as in Table 2c' changed to 'as in Table 2e'.
35. Page 22, section 5.5, 'isoniazid resistance' and 'rifampicin or moxifloxacin resistance' added
36. Page 22, section 5.5, 'For patients who relapse with rifampicin mono-resistance (RMR)' changed to 'For acquired rifampicin mono-resistance (RMR)'
37. Page 23, section 5.7 'of and (Section 6.8) grade 3 or 4 adverse events.' added
38. Page 24, section 6.1, '5) grade 3 or 4 adverse events.' added
39. Page 24, section 6.2, '0s' added next to screening and '0b' added next to enrolment on both tables
40. Page 24, section 6.2, '1' added under smear/culture for screening and '3' changed to '2' under smear/culture for enrolment on both tables.
Page 27, section 6.7, second paragraph 'until' added and 'determine' changed to 'to
distinguish’

Page 27 section 6.7, second paragraph 'Pre-treatment cultures are retained’ removed
and 'One pre-treatment culture (2 if there is enough space in the freezer) will be stored at
-20°C’ added

Page 27 section 6.7, second paragraph 'These are then paired’ changed to These will
then be paired’ and 'and then destroyed at the end of the trial’ removed.

Page 27, section 6.8 Population PK study '400 participants enrolled in the two
experimental arms of the study in Cape Town, Jo'burg and Harare will be sampled during a
dose interval in the 4th month of treatment. Participants should be notified of the date they
are required to be present for the sampling procedure and be told that the sampling will be
for a period of approximately 6 hours on Day 1 and approximately 1 hour on Day 2 or 3.
The procedures will involve drawing, recording, handling and storage of PK samples and
data collection. The name of the phlebotomist and the times of sampling should be
recorded. Samples must be stored at -80 °C until transfer in dry ice (to ensure an
unbroken cold chain) to the Division of Clinical Pharmacology, University of Cape Town,
K45 Old Main Building, Groote Schuur Hospital, Observatory, Cape Town’ added.

Page 27 section 7 'by the PI’ added

Page 27, section 7.1, ‘also’ removed, ‘the’ changed to ‘a’ and ‘Patient’ changed to
‘patient’

Page 27, section 7.1, ‘At each visit, women of child bearing age will be asked if they are
pregnant. If pregnancy is confirmed in women randomised to receive the test arms
containing moxifloxacin, the moxifloxacin will be stopped and they will be transferred to
the standard treatment as in the control arm. Follow up will continue until the 18 month
period as well as to the end of the pregnancy’ added.

Page 28, section 8.2 'Serious adverse events’ changed to ‘Grade 3 or 4 adverse events’

Page 30, section 8.6 'an SAE or’ removed

Page 30, section 9 ‘ICH’ added

Page 30, section 9.1 ‘Chief Investigator and the Assistant Chief Investigator’ changed to
'Trial Manager and other members of the MRC-CTU’

Page 30, section 9.1 ‘Regular visits’ changed to ‘Visits’

Page 30, section 9.1 ‘Chief Investigator, Assistant Chief Investigator and the’ added and
‘and a trial monitor’ removed

Page 30, section 9.1 ‘determined’ and ‘site specific risk assessments and pre-defined
triggers’ added and ‘need’ removed

Page 31, section 9.2 ‘unauthorized’ changed to ‘unauthorised’ and ‘authorization’
changed to ‘authorisation’

Page 32 section 9.4 ‘trial number’ changed to ‘study number’

Page 33, ‘or delegated person’ added

Page 33, ‘that’ removed

Page 33, procedures number 3 ‘trial number’ changed to ‘study number’

Page 33, ‘Medically qualified staff at the MRC-CTU and’ deleted

Page 34 ‘that’ added.

Page 34, section 10.4, ‘Women who become pregnant will continue to receive scheduled
follow-up, not receive additional X-rays unless clinically indicated, and be classified as
being on a non-study regimen. The outcome of pregnancies occurring in the treatment
phase will be reported on a Pregnancy Outcome Form (Form 13) and the Serious Adverse
Event and Notifiable Adverse Event Form (Form 8).’ added.

Page 36, section 15.2, ‘=’ deleted

Page 37, section 16, ‘A publication’ changed to ‘Publications’

Page 37, ‘the population may be informed’ changed to ‘dissemination will be’

Page 45, section 4 ‘Tuberculosis’ changed to ‘tuberculosis’

Page 45, section 4 ‘human immune deficiency virus’ changed to ‘human
immunodeficiency virus’

Page 45 section 4 ‘of the test’ inserted

Page 45, section 4 ‘but we would encourage you to do so, so that further treatment can
be administered if necessary’ added
81. **Page 45, section 4,** 'two months' changed to 'four months' and 'women' changed to 'woman'.

82. **Page 46** A sentence in section 5 was modified so it now reads: *Half of the patients will have a 24 hour measurement and the other half will have a 48 hour measurement.*

83. **Page 46,** part 5 'If a woman who is participating in the study becomes pregnant she must inform her doctor immediately. She will be withdrawn from the study treatment and given standard TB therapy (which is known to be safe in pregnancy) but will be seen in the study clinic until she delivers’ added.

84. **Page 46,** part 8 'combined tablet’ changed to test treatment’

85. **Page 49** last sentence on consent form changed from ‘Trial folder’ to ‘records’

86. **Page 50** last sentence on consent form changed from ‘Trial folder’ to ‘records’

87. **Page 51** last sentence on consent form changed from ‘Trial folder’ to ‘records’

88. **Page 51,** title changed from 'CONSENT FORM FOR THE COLLECTION AND TRANSMISSION TO LONDON OF SPUTUM AND CULTURES’ to 'C. CONSENT FORM FOR THE COLLECTION, STORAGE AND TRANSMISSION OF BLOOD, SPUTUM AND CULTURES'.

89. **Page 51,** point 1 changed from ‘I accept that some of my sputum will be sent to London for analysis’ to ‘I accept that some of my sputum (and culture) and plasma may be sent abroad to specialist laboratories for analysis.’

90. **Page 51,** Point 2 changed from ‘I accept that some of the cultures from my sputum may be stored.’ to ‘I accept that some of the cultures from my sputum may be stored for the length of the trial.’

91. **Page 51,** point 3 changed from ‘I understand that some of these materials will be analysed only for this trial’ to ‘I understand that these materials will be analysed only for this trial’.

92. **Page 53,** 'it is a notifiable event’ added.

93. **Page 53,** 'or follow up’ removed.

94. **Page 53,** 'should’ changed to ‘Should’.

95. **Page 53** appendix 3 section D, reference to 'form 2 or form 5’ changed to 'form 7 and form 8’

96. **Page 53,** 'The outcome of the pregnancy should be recorded on form 13’ added.

97. **Page 54,** Appendix 4, section 2 ‘All patients should be encouraged to receive their HIV results.’ Added.

98. **Page 54,** Appendix 4, section 2, ‘It should be further explained to them that the results will be kept strictly confidential from all except the trial statistician and where appropriate the counsellor. If the patient agrees,’ removed and the next sentence changed to read ‘The treating doctor will be informed of the result’.

99. **Page 55,** table A added.

100. **Page 56,** Annex E added.

101. **Page 57,** ‘assessments’ changed to 'assessments’

102. **Page 57,** 'randomized' changed to ‘randomised’

103. **Page 59,** ‘antituberculosis’ changed to ‘anti-tuberculosis’

104. **Page 59,** ‘non-randomized’ changed to ‘non-randomised’

105. **Page 60,** section 1.6, ‘assessments’ changed to 'assessment', ‘(PK CRF)s’ changed to '(PK CRFs), and ‘and’ deleted

106. **Page 60,** section 2, ‘in vitro’ changed to 'in vitro’

107. **Page 60,** section 2, 'it’s’ changed to ‘its’

108. **Page 61,** section 3, ‘trails’ changed to ‘trials’

109. **Page 63,** ‘and’ deleted

110. **Page 63,** ‘a hard boiled egg’ changed to '2 hard boiled eggs’

111. **Page 66,** section 10 ‘duplicate’ changed to 'triplicate’

112. **Page 68,** annex 1, ‘which’ deleted and ‘you’ added

113. **Page 69,** ‘amount in your body of the anti-TB medicine moxifloxacin is affected’ changed to 'amount of the anti-TB medicine moxifloxacin in your body is affected’

114. **Page 69,** ‘a boiled egg’ changed to '2 boiled eggs’

115. **Page 70,** ‘center’ changed to 'centre’

116. **Page 71,** ‘research’ changed to 'research’

117. **Page 74,** appendix 8 added, ‘Patient Treatment Cards’. 

RIFAQUIN Protocol Version 1.8, 15 April 2011
Version 1.5

1. **Page 7**, Definition of UAR removed from ‘abbreviations and glossary’ and ‘SPC – Summary of Product Characteristics’ added
2. **Page 9**, Section 1.4, ‘Appendix 6’ changed to ‘Appendix 7’
3. **Page 10**, Section 2.1, ‘and’ and ‘also’ removed and ‘and may also improve compliance’ added
4. **Page 12**, a reference was added (number 23) and all other references were renumbered according
5. **Page 16**, Section 3.1 ‘during the entire treatment and follow up period and’ changed to ‘or within the recruitment area of the trial for the entire treatment and follow up period’
6. **Page 16**, Section 3.1 ‘for the duration of the treatment phase’ added
7. **Page 17**, Section 3.4, ‘If the volunteer is illiterate and declines to have a witness present, this will be recorded on the informed consent form’ and ‘if they wish’ deleted
8. **Page 17**, Section 3.4 ‘that there has been’ added
9. **Page 17**, Section 3.4, ‘volunteer’ and ‘volunteers’ changed to ‘participant’ and ‘participants’ respectively
10. **Page 17**, Section 3.4, ‘screening’ changed to ‘enrolment’
11. **Page 17**, Section 3.4 ‘participate in the study’ changed to ‘screening’ and ‘consent being given’ changed to ‘enrolment’
12. **Page 17**, Section 3.4 ‘on the home details form’ added
13. **Page 18**, Section 3.4 ‘universal’ changed to ‘sputum’
14. **Page 18**, Section 4, ‘containing the treatment allocation slips’ added
15. **Page 19**, Section 5.2, ‘The pharmacist in charge of re-packing and distribution of the drugs will be Shanesh Rambaran, Unit for Clinical and Biomedical TB Research, Medical Research Council, 491 Ridge Road, Overport, 4067, Durban, South Africa’ removed
16. **Page 19**, Section 5.3, ‘Appendix 8’ changed to ‘Appendix 9’
17. **Page 21**, ‘possible’ replaced with ‘necessary’
18. **Page 22**, ‘possible’ replaced with ‘necessary’
19. **Page 22**, ‘isoniazid resistance’ changed to ‘isoniazid or moxifloxacin resistance’ and ‘rifampicin or moxifloxacin resistance’ changed to ‘rifampicin resistance’
20. **Page 22**, ‘For a supply of the drugs an application may be made to the Green Light Committee’ removed
21. **Page 23**, Section 5.7, ‘For patients on the control regimen, drug swallowing will be supervised by the designated DTM at home’ removed and ‘DOT doses for the intensive phase of all arms of the trial and for the continuation phase of the control arm will include both doses supervised at the clinic and by the DTM at home. For the continuation phase of the two test arms, DOT doses will only be administered at the clinic or at home during a home visit by the treatment supervisor or home visitor’ added
22. **Page 23**, Section 5.7, ‘a minimum of 90 daily DOT doses and a maximum of’ and ‘DOT’ added
23. **Page 23**, Section 5.7, ‘18’ replaced with ‘13 weeks (on the 9 week arm) and (on the 18 week arm)’ added
24. **Page 24**, Section 6.1, ‘form’ changed to CRF and ‘to the Principal Investigator’ changed to ‘for data entry’
25. **Page 24**, Section 6.1, ‘study folder’ changed to Trial Folder
26. **Page 24**, Section 6.2, 1 added in both tables under sensitivity test at screening
27. **Page 25**, Section 6.2, ‘If a patient’s monthly or 3 monthly visit date falls on a day that is inconvenient, there is a window of 3 days either side of the date in which the visit can be scheduled’ added
28. **Page 25**, Section 6.3, ‘outcome committee’ changed to ‘endpoint review committee’ and ‘The first’ deleted
29. **Page 26**, Section 6.4, ‘At the time of enrolment, if the patient already has a medical diagnosis’ changed to ‘If the patient has a medical diagnosis at enrolment’
30. **Page 26**, Section 6.4, ‘an adverse event’ changed to ‘a notifiable adverse event’
31. **Page 26**, Section 6.4, ‘Appendix 3 and Appendix 7’ changed to ‘Appendix 4 and Appendix 8’
32. Page 26, Section 6.5, ‘(Form A)’ added
33. Page 27, section 6.7, ‘presence of initial isoniazid resistance’ changed to ‘presence of initial resistance to any of the trial drugs’
34. Page 27, Section 6.7, ‘streptomycin’ and ‘pyrazinamide’ added
35. Page 27, Section 6.7, ‘for susceptibility to isoniazid, rifampicin, streptomycin, moxifloxacin and pyrazinamide’ deleted
36. Page 27, Section 6.8, ‘Jo’burg’ changed to ‘Johannesburg’
37. Page 27, Section 6.8, ‘Patients will be re-consented separately for the Population PK study at either 3 or 4 months post enrolment’ added
38. Page 32, Section 10, Definition for Unexpected Adverse Reaction (UAR) changed to definition for Suspected Unexpected Serious Adverse Reaction (SUSAR) and definition for Notifiable Adverse Event (NAE) added
39. Page 32, Section 10, ‘serious’ and ‘or’ added and ‘or unexpected adverse reaction’ deleted
40. Page 32, Section 10, ‘/NAE’ added wherever there was previously only ‘SAE’ in this section
41. Page 33, Section 10, ‘at the site’ and ‘in the patient’s medical notes and adverse reactions in the regular progress/follow-up reports via Form 7’ added
42. Page 33, Section 10, ‘SAE form’ changed to ‘SAE/NAE Form 8’ at all occurrences in this section
43. Page 33, Section 10, ‘via a follow-up SAE/NAE Form 8’ added
44. Page 33, Section 10, ‘(or relevant NAE)’ added
45. Page 33, Section 10, 3 bullet points deleted
46. Page 33, Section 10, ‘to regulatory authorities’ replaced with ‘as necessary’
47. Page 33, Section 10, ‘All evaluated SAEs/NAEs will be faxed back to the site PI from where it originated within agreed timescales’ and ‘All SAEs, SARs, NAEs and SUSARs will be reported within an agreed timescale to the necessary regulatory and ethics authorities for this site as laid out in the approvals and/or corresponding regulations and RIFAQUIN site specific working practice documents by the PI or delegated person’ added
48. Page 34, ‘All’ added
49. Page 34, Section 10.4, ‘Appendix 3 and Appendix 7’ changed to ‘Appendix 4 and Appendix 8’
50. Page 34, Section 10.4, ‘See section 7.1’ added
51. Page 36, Section 15.3, ‘interim’ deleted
52. Page 36, Section 15.3, ‘every four to six months’ replaced by ‘regularly’
53. Page 37, Section 16, ‘principal investigator’ changed to ‘Principal Investigator’ and ‘trial statistician’ changed to ‘Trial Statistician’
54. Page 46, reference 24, ‘May 4; [Epub ahead of print]’ changed to ‘174:331-338’
55. Page 47, ‘Why you have I been chosen’ changed to ‘Why you have been chosen’
56. Page 47, ‘For this reason, it is important that your home is accessible to the treatment centre for the next 18 months’ added and ‘The first’ deleted
57. Page 48, ‘If you wish to participate in this part of the trial you will be given additional information and asked to sign an additional consent form at either the 3rd or 4th month of treatment. If you decide you do not want to participate in this part of the trial it will not affect either your enrolment into the RIFAQUIN trial or your continued participation’ added
58. Page 51, Patient information sheet (Population PK assessment) added as Appendix 2. All other Appendices renumbered as appropriate
59. Page 52, ‘*One copy of this form to be given to the patient to keep.’ Added
60. Page 53, Appendix 3, ‘for the duration of the treatment phase’ added
61. Page 53, 54 & 55 ‘or thumbprint’ deleted from space for signature of witness if patient is illiterate
62. Page 53 & 54 ‘and have had these answered satisfactorily’ added to first statement on consent forms
63. Page 54 & 55, ‘Consent Form’ deleted
64. Page 56, D. Consent Form for Population PK Assessment Enrolment added as part of Appendix 3
65. Page 60, ‘TABLE A’ and ‘Annex E’ deleted
66. **Page 65**, ‘volunteers’ and ‘volunteer’ changed to ‘participants’ and ‘participant’ respectively
67. **Page 74**, ‘and consent leaflet’ changed to ‘Sheet
68. **Page 74, Annex 1** ‘this assessments’ changed to ‘these assessments’
69. **Page 76**, ‘*One copy of this form to be given to the patient to keep*’ added
70. **Page 77**, Consent Form for Interaction PK Assessment Enrolment added as Annex 2 and Certificate of Consent (PK- Interaction assessment) removed from Annex 1
71. **Page 79**, Appendix 8 updated
72. **Page 80-95** Treatment cards updated (version 1.4)
73. **Page 17**, second paragraph ‘their’ changed to ‘the patient’s’ and ‘They’ to ‘The patient’s’.
74. **Page 17**, seventh paragraph ‘and, ideally, within 1 week of enrolment,’ changed to ‘(ideally within 1 week of enrolment)’.
75. **Page 18**, first paragraph, ‘then’ deleted.
76. **Page 18**, section 4, first paragraph ‘their’ changed to ‘the patient’s’.
77. **Page 19**, sixth paragraph, ‘resistant rifampicin’ changed to ‘resistant to rifampicin’ and ‘according a’ changed to ‘according to a’.
78. **Page 20**, ‘Table 2a’ changed to ‘Table 1’, ‘Table 2b’ changed to ‘Table 2’, ‘Table 2c’ changed to ‘Table 3’.
79. **Page 23**, section heading ‘Measures of compliance and adherence’ changed to ‘Measures of adherence’.
80. **Page 26**, first paragraph ‘after taking study medication’ added.
81. **Page 30**, section 8.6 ‘stopped’ changed to ‘stopping’ and ‘changed’ changed to ‘changing’
82. **Page 32**, section 10.1, ‘serious’ deleted from SAE definition
83. **Page 33**, second paragraph ‘who’ changed to ‘The trial manager’.
84. **Page 60**, Appendix 6 split into appendix 6, 7 and 8 all other appendices and references changed accordingly.

**Version 1.6**

**Summary of substantial amendments to protocol from version 1.5:**

<table>
<thead>
<tr>
<th>No.</th>
<th>Summary of amendment</th>
<th>Reason for change</th>
<th>Section</th>
<th>Page number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Addition of Prof. Innocent Gangaidzo as PI in Harare and removal as Dr. Elizabeth Corbett as PI in Harare.</td>
<td>Change of PI at the Harare recruiting site in Zimbabwe.</td>
<td>Main contacts</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Addition of Dr. James Shepherd as PI for Gaborone, Botswana and addition of the Botswana site.</td>
<td>Addition of Gaborone, Botswana as a recruiting site.</td>
<td>Main contacts, and list of institutions</td>
<td>3 and 4</td>
</tr>
<tr>
<td>3</td>
<td>Removal of Dra. Zulmira Almeida da Silva as PI in Mozambique and removal of site in Mozambique</td>
<td>Mozambique no longer taking part in the RIFAQUIN trial.</td>
<td>Main contacts, and list of institutions</td>
<td>3 and 4</td>
</tr>
<tr>
<td>4</td>
<td>Inclusion criteria – in Botswana patients must agree to have their HIV status disclosed to them.</td>
<td>Specific requirement in Botswana.</td>
<td>3.1</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>Removal of exclusion criteria ‘Requires anti-retro viral treatment (ART) at diagnosis’</td>
<td>WHO and individual sites national guidance of when to start ARVs are changing. To accommodate this with the current design (where patients who are HIV positive with a CD4 of over 200 being eligible) patients can now start ARVs at the same as their TB treatment within</td>
<td>3.2</td>
<td>15</td>
</tr>
<tr>
<td>No.</td>
<td>Summary of amendment</td>
<td>Reason for change</td>
<td>Section</td>
<td>Page number</td>
</tr>
<tr>
<td>-----</td>
<td>---------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>6</td>
<td>Addition of section 3.3 outlining patients excluded post randomisation for initial resistance to rifampicin, isoniazid or moxifl oxacin or having consistently negative cultures pre-treatment.</td>
<td>Omitted in version 1.5</td>
<td>3.3</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>Clinics now have the option of obtaining one of the pre-screening smear results post consent for screening and from a RIFAQUIN laboratory rather than relying on two from a local reference laboratory.</td>
<td>To prevent patients being enrolled who then go on to have consistently negative smears and cultures pre-treatment. It appears that at some sites the local reference laboratories are giving false positive results for smear samples.</td>
<td>3.5</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>Postero-anterior chest radiograph to be done within two weeks of enrolment rather than at screening.</td>
<td>V1.5 was unclear about whether this was done at screening or enrolment.</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>9</td>
<td>Removal of directions for treatment of those found to be initially resistant to rifampicin, isoniazid or moxifl oxacin</td>
<td>This is now to be according to local policies.</td>
<td>5.1</td>
<td>19</td>
</tr>
<tr>
<td>10</td>
<td>Number of doses for the continuation phase of the study regimens changed to 16-18 doses from 18 doses.</td>
<td>This is in line (relative to number of weeks treatment) to the control regimen.</td>
<td>5.4</td>
<td>21</td>
</tr>
<tr>
<td>11</td>
<td>Each patient enrolled should be seen by the Principal Investigator or Trial Physician at each monthly visit during the treatment phase.</td>
<td>This was not explicitly stated in V1.5.</td>
<td>6.1</td>
<td>23</td>
</tr>
<tr>
<td>12</td>
<td>Removal of sputum sample taken at screening (OS) in both the 4 and 6 month regimens.</td>
<td>Reference bacteriology no longer being done on pre-treatment sputum.</td>
<td>6.2</td>
<td>24</td>
</tr>
<tr>
<td>13</td>
<td>Visit window increased to 7 days either side of the visit for visit months 15 and 18</td>
<td>This is a more reasonable visit window for a 3 month visit.</td>
<td>6.2</td>
<td>25</td>
</tr>
<tr>
<td>14</td>
<td>Addition of requirement to collect a sputum sample at every unscheduled visit.</td>
<td>This was not explicitly stated in V1.5.</td>
<td>6.2</td>
<td>25</td>
</tr>
<tr>
<td>15</td>
<td>The algorithm for classifying patients with an unfavourable status is updated.</td>
<td>The algorithm in version 1.5 was unclear for different culture media.</td>
<td>6.3</td>
<td>25</td>
</tr>
<tr>
<td>16</td>
<td>Loss to follow-up defined as unable to contact patient after three attempts, and one further attempt to be made at month 18.</td>
<td>Clarification of definition compared to V1.5.</td>
<td>6.6</td>
<td>26</td>
</tr>
<tr>
<td>17</td>
<td>Patients whose treatment is stopped for any reason need only be followed up every 3 – 4 months.</td>
<td>To reduce likelihood of loss to follow-up or withdrawals of those who</td>
<td>7.1</td>
<td>27</td>
</tr>
<tr>
<td>No.</td>
<td>Summary of amendment</td>
<td>Reason for change</td>
<td>Section</td>
<td>Page number</td>
</tr>
<tr>
<td>-----</td>
<td>----------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>18</td>
<td>The sample size is changed from 1250 to 1100.</td>
<td>Based on discussions with the FDA with regards to another related TB treatment shortening trial, the value for δ (the margin of non-inferiority) and the endpoint definition was changed leading to a reduction in the sample size.</td>
<td>8.3</td>
<td>29</td>
</tr>
<tr>
<td>19</td>
<td>The definition of the per protocol population in this section giving details on the preliminary analysis plan is updated.</td>
<td>The definition of adequate and inadequate treatment was ambiguous in version 1.5.</td>
<td>8.5</td>
<td>29-30</td>
</tr>
<tr>
<td>20</td>
<td>Removal of 6 monthly on-site monitoring</td>
<td>6 monthly on site visits were unrealistic with only one Trial Manager and 6 sites in 4 countries. Also moving over to using local monitors and more central monitoring.</td>
<td>9.1</td>
<td>30</td>
</tr>
<tr>
<td>21</td>
<td>Following up pregnancies where conception occurs up to three months post treatment.</td>
<td>Inclusion of moxifloxacin wash out period.</td>
<td>10.4</td>
<td>34</td>
</tr>
</tbody>
</table>

### Summary of substantial amendments to patient information sheet (PIS) from version 1.5 (contained in protocol version 1.5) and version 1.6 (stand alone document dated 23/04/2008):

<table>
<thead>
<tr>
<th>No.</th>
<th>Version No. of PIS that change first appears in</th>
<th>Summary of amendment</th>
<th>Reason for change</th>
<th>Page number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Version 1.6 23/04/2009</td>
<td>Alerting the female patients that there is a small risk the trial treatment may harm an unborn child if they become pregnant</td>
<td>Elaborating on reasons for needing to use barrier contraception compared to version 1.5.</td>
<td>51 (protocol),1 (PIS)</td>
</tr>
<tr>
<td>2</td>
<td>Version 1.6 23/04/2009</td>
<td>Explanation to female patients that they may need to re-start treatment if they become pregnant in the treatment phase of the trial.</td>
<td>Information missing from version 1.5.</td>
<td>52 (protocol),2 (PIS)</td>
</tr>
<tr>
<td>3</td>
<td>Version 1.6 23/04/2009</td>
<td>Side effect of Moxifloxacin: 'Moxifloxacin is a drug that has been widely used for treatment of infections other than tuberculosis. Uncommon side effects include nausea, diarrhoea, headache and dizziness. Disturbances of blood sugar,</td>
<td>Updated information from Moxifloxacin IB V12</td>
<td>52 (protocol),2 (PIS)</td>
</tr>
<tr>
<td>No.</td>
<td>Version No. of PIS that change first appears in</td>
<td>Summary of amendment</td>
<td>Reason for change</td>
<td>Page number</td>
</tr>
<tr>
<td>-----</td>
<td>-----------------------------------------------</td>
<td>----------------------</td>
<td>------------------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>liver function or kidney function might also occur in a few cases.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>There are other unlikely but serious side effects that can occur: inflammation of the gut, allergic reaction, loss of smell and mental/mood changes (including behaviour that may result in self-harm). There are also some very unlikely but very serious side effects that can occur: irregular heartbeat, seizures, severe allergic reaction, tendon rupture and kidney failure.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Very rarely there are severe complications from both the standard and the test TB treatment which may be life threatening. These complications are liver inflammation leading to liver failure and a severe skin rash with blistering and peeling.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Version 1.6 07/01/2010</td>
<td>Side effect of Moxifloxacin: ’Taking moxifloxacin may result in an impairment of your ability to drive or operate machinery, therefore you should use caution when carrying out these activities. You should also report if you develop jaundice, your urine is pale in colour or if you develop a skin rash.</td>
<td>Updated information from Moxifloxacin IB V13 2 (PIS)</td>
<td>52 (protocol) ,2 (PIS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If you are taking antacids, anti-retroviral drugs or other preparations containing magnesium or aluminum, sucralfate and agents containing iron or zinc, they should be administered at least 4 hours before or 2 h after ingestion of a moxifloxacin dose. Remember to tell the doctor about any tablets you regularly take so that you can be advised whether or not to stop them.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Version 1.7**

**Summary of substantial amendments to protocol from version 1.6:**

<table>
<thead>
<tr>
<th>No.</th>
<th>Summary of amendment</th>
<th>Reason for change</th>
<th>Section</th>
<th>Page number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Change of exclusion criteria 12 to 'If HIV positive with a CD4 count of less than 150/mm$^3$’ from 'If HIV positive with a CD4 count of less than 200/mm$^3$’</td>
<td>Change in WHO guidelines, more generalisable results and a projected increase in recruitment.</td>
<td>3.2</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>Appendix 6 and 7 changed to new WHO guidelines</td>
<td>New WHO guidelines – see reference 27</td>
<td>Appendix 6 and 7</td>
<td>64</td>
</tr>
</tbody>
</table>

**Summary of substantial amendments to patient information sheet (PIS) from version 1.6 07/01/2010:**

None

**18. REFERENCES**

16. Lubasch A, Keller I, Borner K, Koepepe P and Lode H. Comparative pharmacokinetics of ciprofloxacin, gatifloxacin, grepafloxacin, levofloxacin, trovafloxacin and moxifloxacin after single-dose administration in...
Moxifloxacin- containing regimen greatly reduces time to culture conversion in murine tuberculosis. Am J 
Respir Crit Care Med 2004;169: 421-426.
one-weekly rifapentine and moxifloxacin regimens against Mycobacterium tuberculosis in mice. 
Tuberculosis. American Journal of Respiratory and Critical Care Medicine; July 1, 2006; 174, 1; ProQuest Library: 94
and the Tuberculosis Trials Consortium. A prospective, randomised continuation phase of tuberculosis 
Consortium, Denver, CO, Atlanta, GA, San Antonio, TX. 2006. The Effects of Rifampin and Human 
Multidrug Resistance Gene Polymorphism on Serum Concentrations of Moxifloxacin, Proceedings of the 
B, Mitchison DA and the Gatifloxacin for TB (OFLOTUB study team. A phase II study of the sterilizing activities of 
treatment for pulmonary tuberculosis. Am J Respir Crit Care Med. 2006; 174:331-338
Comparison of Chinese and Western rifapentines and improvement of bioavailability by prior taking of various meals. 

19. APPENDICES

Appendix 1: Patient Information sheet

Part 1.
You are being invited to take part in a research trial. Before you decide to take part in the trial, it is important 
for you to understand why the research is being done and what it will involve. Please take time to read the 
following information carefully. Talk to others about the study if you wish.
1. Part 1 tells you the purpose of this study and what will happen to you if you take part.
2. Part 2 gives you more detailed information about the conduct of the study.
Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether 
or not you wish to take part. Initially we only need your permission to assess whether you are eligible for the 
study. You will have a further opportunity to decide if you wish to take part.

1. What is the purpose of the trial? 
The usual treatment for tuberculosis of the lungs is either six or eight months long. We are doing this research 
study to test two tablets called rifapentine and moxifloxacin. Both have been used for the treatment of 
tuberculosis. By using these tablets, we would like to see if the treatment can be simplified to once or twice 
weekly and/or shortened from 6 months to 4 months. However, the rifapentine has only been used at the dose 
of 600mg. In this trial we will be testing higher doses of 900mg and 1200mg.

2. Why you have been chosen? 
We are inviting you to join this study because you have tuberculosis of the lungs. This is an infection which is 
caused by a germ which can affect any part of the body. It is curable if you take your treatment as directed. 
We will be asking 1100 patients with TB in Zambia, Zimbabwe, Botswana and South Africa to join this study.

3. Do I have to take part? 
No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to 
keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a 
reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care 
you receive.

4. What will happen to me if I take part?

RIFAQUIN Protocol Version 1.8, 15 April 2011

Page 50 of 97
Before letting you join in this study, we will examine you to be sure you are suitable for the study. We will do a chest X-ray, blood tests, a sputum test and a urine test. Some of your sputum and bacteria cultured from your sputum may be sent to London for further tests. However all of these samples will be destroyed at the end of the trial. You must also agree to have an HIV test. This is a blood test to detect if you have been infected with the human immunodeficiency virus which is most commonly transmitted by sexual intercourse with an infected person. You will be given the result of the HIV test from a trained counsellor if you wish. You do not have to get the result of the test if you prefer not to but we would encourage you to do so, so that further treatment can be administered if necessary.

You will receive one of three treatments. It will be decided by chance (like tossing a coin) which treatment you will receive. The possible treatments are standard TB treatment for six months; study treatment for four months with twice-weekly treatment during the last two months; or study treatment for six months with once-weekly treatment during the last four months. Patients in the two new study treatment groups will receive the test medicines (moxifloxacin throughout and rifapentine after the first two months) instead of standard medicines (rifampicin and isoniazid)

If you are chosen to receive rifapentine you will be given a meal of hard boiled eggs and bread just before taking your medicine. You will not have to pay for this.

If you are taking any other medicines, including birth control pills or injections, you should tell the doctor. If you are woman who is still having periods you must use a barrier form of contraception or be surgically sterilised or have an IUCD in place during the course of the trial. This is because the effectiveness of birth control pills and injections can be reduced by one of the study drugs, rifampicin. There is a small chance that the treatment may harm the unborn child so barrier contraception is needed, either alone or in conjunction with birth control pills or injections, to ensure pregnancy during treatment does not occur.

5. What do I have to do?
In the study, you must come to clinic to receive the medicine every day or every week for the first two months. Then you must come to clinic, at intervals required by your doctor, for the next two or four months. After you finish the medicines, you must come for checks every month for 6 or 8 months, and then every three months for the next 6 months. At each visit we will check your sputum for TB. The total time you will be in the trial is 18 months. For this reason, it is important that you live near to the treatment centre for the next 18 months.

400 patients enrolled in the two experimental arms in Cape Town, Harare and Johannesburg only will have blood samples taken at one visit during the 4th month of chemotherapy for moxifloxacin and rifapentine drug levels to be evaluated. Three samples will be collected from each patient: 2, 5, and either 24, or 48 hours after taking the study drug. Half of the patients will have a 24 hour measurement and the other half will have a 48 hour measurement. Each sample of blood taken will be less than 5mls. You may be one of the 400 patients asked to provide these extra samples. If you are one of these 400 patients, to make collection of the last blood sample easier, you may be asked to stay overnight for one night at the time of this visit. If you wish to participate in this part of the trial you will be given additional information and asked to sign an additional consent form at either the 3rd or 4th month of treatment. If you decide you do not want to participate in this part of the trial, it will not affect either your enrolment into the RIFAQUIN trial or your continued participation.

You will be compensated for any travel expenses you incur for visits made in connection with the trial.

If a woman who is participating in the study becomes pregnant she must inform her doctor immediately. She will be withdrawn from the study treatment and given standard TB therapy (which is known to be safe in pregnancy) but will be seen in the study clinic until she delivers. She may be required to restart treatment depending on which treatment she was originally allocated and how long she was on treatment before she discovered she was pregnant.

6. What is the drug that is being tested?
There are two drugs being tested. They are called rifapentine and moxifloxacin. Both are taken by mouth. The rifapentine will be given at doses of 900mg or 1200mg. These are higher than the standard dose of 600mg

7. What are the alternative treatments?
The alternative treatment is the regular treatment given by the National TB Programme.

8. What are the side effects of any treatment received when taking part?
Side effects expected with the two new drugs are expected to be similar to those seen with standard treatment. These include stomach pain, nausea, vomiting diarrhoea, dizziness, pain in the legs and problems
with eyesight. With rifapentine expected, but uncommon, side effects include skin rash, yellow eyes and change in urine colour.

Moxifloxacin is a drug that has been widely used for treatment of infections other than tuberculosis. Uncommon side effects include nausea, diarrhoea, headache and dizziness. Disturbances of blood sugar, liver function or kidney function might also occur in a few cases. Taking moxifloxacin may result in an impairment of your ability to drive or operate machinery, therefore you should use caution when carrying out these activities. You should also report if you develop jaundice, your urine is pale in colour or if you develop a skin rash.

If you are taking antacids, anti-retroviral drugs or other preparations containing magnesium or aluminum, sucralfate and agents containing iron or zinc, they should be administered at least 4 hours before or 2 hours after ingestion of a moxifloxacin dose. Remember to tell your doctor about any tablets you regularly take so that you can be advised whether or not these can be safely taken at the same time as your moxifloxacin.

There are some unlikely but serious side effects that can occur as a result of taking moxifloxacin or rifapentine: inflammation of the gut, allergic reaction, loss of smell, mental/mood changes (including behaviour that may result in self-harm), irregular heartbeat, seizures, severe allergic reaction, tendon rupture and kidney failure.

Very rarely there are severe complications from both the standard and the test TB treatment which may be life threatening, such as liver inflammation leading to liver failure and a severe skin rash with blistering and peeling.

If you have bad side effects and need to go to hospital, we will pay the hospital. Before you enter the trial you should tell the doctor if you are taking any other medicines including birth control pills or injections.

9. What are the other possible disadvantages and risks of taking part?
There is a small risk that you will develop resistance to the drugs. In such a case, we will treat you with different drugs to which you will respond. If a pregnant woman participates or becomes pregnant while in the trial, the treatment could harm the unborn child. The treatment for the pregnant woman may be changed and may have to be re-started which could mean she is on treatment for longer than if she had not taken part in the trial.

10. What are the possible benefits of taking part?
There will be no direct benefit to you from taking part however your progress will be monitored frequently and the information we get might help to improve the treatment of people with TB.

11. What happens when the treatment stops?
After the treatment has been completed, it is expected that your TB will be cured. You will continue to be followed up. If your symptoms return, you should consult the trial doctor immediately.

12. What if there is a problem?
If you have questions, or if you are having any problem from any medicines, you should talk to the study nurse or doctor.

13. Will my taking part in the trial be kept confidential?
Your medical record will be kept safe and only your doctor or nurse can see it. We will not use your name in any study report.

Contact details:
Dr.
Dr.
Nurse

This completes Part 1 of the Information Sheet.
If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2.

14. What if relevant new information becomes available?
Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it and discuss whether you want to or should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue appropriately. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

15. What will happen if I do not carry on in the trial?
You can withdraw from treatment but keep in contact with us to let us know your progress. Information collected may still be used. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish.

16. What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions (Contact number). If you remain unhappy and wish to complain formally, details of complaints procedures can be obtained from the hospital.

Compensation will be paid for reasonable medical expenses incurred as a result of study-related injury or illness, determined according to the guidelines laid down by the Association of the British Pharmaceutical Industry (ABPI Guidelines), and Guidelines for Good Clinical Practice in the Conduct of Clinical Trials in Human Participants in South Africa.

We will pay compensation where the injury probably resulted from:
- A drug being tested or administered as part of the trial protocol
- Any test or procedure you received as part of the trial

Any payment would be without legal commitment. (Please ask if you wish for more information on this)
We would not be bound by these guidelines to pay compensation where
- The injury resulted from a drug or procedure outside the trial protocol
- The protocol was not followed

17. Will my taking part in the trial be kept confidential?
If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from the company sponsoring and/or the company organising the research. They may also be looked at by people from the company or by representatives of regulatory authorities to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site.

18. What will happen to any samples I give?
Any samples that you give will be used only for the evaluation of this trial unless you have given separate written consent allowing them to be used for other tests (e.g. the measurement of drug levels). Your samples may be sent to the Department of Medical Microbiology, St. George’s, University of London for parallel testing for susceptibility to the drugs being given to you. If they are required for any other evaluations, you will be asked for your permission to use any stored samples and will be asked to sign a separate consent form.

19. Will any genetic tests be done?
No, there will be no genetic tests

20. What will happen to the results of the trial?
The results of the trial will be published so that they are available to the medical profession throughout the world. However, no patients will be identified individually.

21. Who is organising the funding of the trial?
The trial is funded by the European and Developing Countries Clinical Trials Partnership (EDCTP). Most of the drugs have been donated by the company that manufactures them. The sponsor is St Georges, University of London.

22. Who has reviewed the trial?
The trial has been reviewed by the Trial Steering Committee and the Ethics Committee of St. George’s, University of London. It has also been reviewed by the Ethics Committee of your country and has received approval.

*One copy of this form to be given to the patient to keep.

**Appendix 2: Patient Information Sheet (Population PK assessments)**

**INTRODUCTION:**

Four hundred (400) patients taking part in the RIFAQUIN study in Worcester, Harare or Johannesburg will be invited to undergo additional blood tests to measure the amount of moxifloxacin and rifapentine in their blood. This information will help researchers to optimize the doses of moxifloxacin and rifapentine for TB patients. In this way the additional measurements will benefit future patients with tuberculosis.

This information follows on from that you received prior to enrolment to the RIFAQUIN trial (Patient Information Sheet version _______ Date______). Contained in that document was information about the Population PK assessment and by giving informed consent for the RIFAQUIN trial you have also consented to take part in the Population PK assessment. However this document and accompanying consent form contain additional information and an opportunity to re-consent for the Population PK assessment if you wish to take part.

Before agreeing to take part, it is important that you read and understand the following explanation of the purpose of the research, and the procedures, benefits, risks, discomforts, and precautions. You should fully understand what is involved before you agree to take part. You should not agree to take part unless you are satisfied about all the procedures involved. If you have any questions, do not hesitate to ask the study doctor.

Your right to continue taking part in the rest of the RIFAQUIN study will not be affected if you decide not to undergo this additional assessment.

It is your right to withdraw from these procedures at any time. Your access to medical treatment will not be affected in any way if you withdraw. Your participation in the rest of the RIFAQUIN study will not be affected if you decide to withdraw.

For the assessments to be useful, it is important that all the information you give the study doctor is truthful and that you follow the study instructions carefully.

If you decide to take part, you will be asked to sign and date this document to confirm that you understand the procedures and agree to take part. You will be given a copy to keep.

**PROCEDURES:**

If you decide to take part, you will undergo 3 additional blood tests on 2 days during the fourth (4th) month of the study treatment:

The study team will arrange a time for the blood sampling. On the appointed day, you need to arrive at the study centre /clinic early in the morning.

It is important NOT to take any medicines before your arrival at the study centre. You will be given your TB treatment and breakfast (of a boiled egg and bread) at the centre /clinic.

Two blood samples (each 4 milliliters/ less than 1 teaspoon) will be taken at approximately 2 and 5 hours after you have taken your study treatment. A third sample (also 4 ml) will be taken the following morning or the morning after that (the study team will arrange a time for you to be at the center /clinic. It may be necessary to stay at the study center/ or clinic for one night. All meals and refreshments will be provided.

**FURTHER INFORMATION:**
The risks of taking part in this addition assessment are minimal. The blood samples will be drawn in the usual way: from a suitable arm vein using a needle. Experienced and qualified study staff will draw the blood to minimize bruising, and bleeding.

There will be no direct medical benefits to you from this procedure. Information that will be obtained from this procedure may be useful scientifically and may benefit future TB patients.

You will be compensated for the inconvenience to you and for transport costs to and from the study center.

All information concerning your person and the data collected will remain confidential and anonymous. Your personal information cannot be used by anyone other those conducting the research, the regulatory authority or research ethics committees.

If you have questions about this research you should discuss them with the study team of your doctor, or the ethics committee (contact details as provided on this form).

The blood samples will only be used for the purpose of measuring drug concentrations. The samples from your blood will be stored for a year after completion of the procedure. The specimens will then be destroyed.

Compensation and/or treatment available to you in the event of trial-related injury is given in the RIFAQUIN Patient Information Sheet version_______ date ________.

**IMPORTANT CONTACT DETAILS:**

If you are concerned about your health or have any questions at any given time during the course of the study, please do not hesitate to contact the study doctor or a study team member.

Study doctor: Name ____________________________
Tel: ____________________________
Cell: ____________________________

If you want any information regarding your rights as a research participant, or have complaints regarding this research study, you may contact Dr Marc Blockman, the Chairperson of the Research Ethics Committee at the University of Cape Town (021 406 6492).

After you have consulted your doctor or the ethics committee and they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:

The Registrar, SA Medicines Control Council Department of Health, Private Bag X 828 PRETORIA 0001

*One copy of this form to be given to the patient to keep*
Appendix 3: Consent forms

A. CONSENT FORM FOR SCREENING
(TO BE PRESENTED ON LOCAL HEADED PAPER)

Screening No.: [Blank]

Date and version: dd/mm/yyyy, Vxx.x

RIFAQUIN - AN INTERNATIONAL MULTICENTRE CONTROLLED CLINICAL TRIAL TO EVALUATE HIGH DOSE RIFAPENTINE AND A QUINOLONE IN THE TREATMENT OF PULMONARY TUBERCULOSIS

Please initial box to agree

1. I confirm that I have read (or had read to me) and understand the information sheet dated ......................... (version ............) for the above study and have had the opportunity to ask questions and have these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

1. I understand that being screened for possible participation in this study does not mean that I have agreed to be enrolled in the study.

2. I agree to sections of any of my medical notes being looked at to assess my eligibility for this study.

5. I agree to being screened for eligibility to take part in the above study.

4. I agree to have an HIV test.

5. I agree to be informed of the result of the HIV test.

6. I agree if I am a pre-menopausal women I must be using a barrier form of contraception or be surgically sterilised or have an IUCD in place for the duration of the treatment phase.

______________________    ________________ _____________________
Name of Patient        Date       Signature or thumbprint
_________________________ ________________ ____________________
Name of witness        Date       Signature
(if patient is illiterate)
_________________________ ________________ ____________________
Name of Person taking consent    Date       Signature

2 copies: 1 for patient, 1 for the patient’s confidential records.
B. CONSENT FORM FOR STUDY ENROLMENT

(TO BE PRESENTED ON LOCAL HEADED PAPER)

Study No.:

Date and version: dd/mm/yyyy, Vxx.x

RIFAQUIN - AN INTERNATIONAL MULTICENTRE CONTROLLED CLINICAL TRIAL TO EVALUATE HIGH DOSE RIFAPENTINE AND A QUINOLONE IN THE TREATMENT OF PULMONARY TUBERCULOSIS

Please initial box to agree

1. I confirm that I have read (or had read to me) and understand the information sheet dated ......................... (version ..........) for the above study and have had the opportunity to ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at by responsible individuals involved in the running of the trial or from regulatory authorities where it is relevant to my taking part in research, and that I will followed up through usual National Tuberculosis Programme Services.

   I give permission for these individuals to have access to my records.

4. I agree to take part in the above study.

   __________________________  __________________________  __________________________
   Name of Patient             Date                        Signature or thumbprint

   __________________________  __________________________  __________________________
   Name of witness             Date                        Signature
   (if patient is illiterate)

   __________________________  __________________________  __________________________
   Name of Person taking consent  Date                        Signature

2 copies: 1 for patient, 1 for the patient’s confidential records.
C. CONSENT FORM FOR THE COLLECTION, STORAGE AND TRANSMISSION OF BLOOD, SPUTUM AND CULTURES

(TO BE PRESENTED ON LOCAL HEADED PAPER)

Study No.: □□□□□□

Date and version: dd/mm/yyyy, Vxx.x

[Local date and version]

**RIFAQUIN** - AN INTERNATIONAL MULTICENTRE CONTROLLED CLINICAL TRIAL TO EVALUATE HIGH DOSE RIFAPENTINE AND A QUINOLONE IN THE TREATMENT OF PULMONARY TUBERCULOSIS

Please initial box to agree

1. I accept that some of my sputum (and culture) and plasma may be sent abroad to specialist laboratories for analysis.

2. I accept that some of the cultures from my sputum may be stored for the length of the trial.

3. I understand that these materials will be analysed only for this trial.

4. I understand that all these materials will be destroyed once the trial has ended.

______________________    ________________ _____________________
Name of Patient       Date           Signature or thumbprint

_________________________ ________________ ____________________
Name of witness       Date           Signature
(if patient is illiterate)

_________________________ ________________ ____________________
Name of Person taking consent       Date           Signature

2 copies: 1 for patient, 1 for the patient’s confidential records.
D. CONSENT FORM FOR POPULATION PK ASSESSMENT ENROLMENT

(TO BE PRESENTED ON LOCAL HEADED PAPER)

Study No.: [Box for Study No.]

Date and version: dd/mm/yyyy, Vxx.x

[Local date and version]

RIFAQUIN - AN INTERNATIONAL MULTICENTRE CONTROLLED CLINICAL TRIAL TO EVALUATE HIGH DOSE RIFAPENTINE AND A QUINOLONE IN THE TREATMENT OF PULMONARY TUBERCULOSIS

POPULATION PK ASSESSMENT

Please initial box to agree

1. I confirm that I have read (or had read to me) and understand the information sheet dated ......................... (version ............) for the above study and have had the opportunity to ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at by responsible individuals involved in the running of the trial or from regulatory authorities where it is relevant to my taking part in research, and that I will followed up through usual National Tuberculosis Programme Services. I give permission for these individuals to have access to my records.

4. I agree to take part in the above study.

__________________________________________________________________________________
Name of Patient Date Signature or thumbprint

__________________________________________________________________________________
Name of witness Date Signature
(if patient is illiterate)

__________________________________________________________________________________
Name of Person taking consent Date Signature

2 copies: 1 for patient, 1 for the patient’s confidential Trial folder
Appendix 4: Management of expected adverse events

Section A : Major Toxic Reactions

If any one of the major reactions listed below occurs, all anti-tuberculosis treatment should be stopped immediately. If the toxic reaction requires the patient to be admitted to hospital, the Chief Investigator should be notified within 24 hours.

1. 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 red rash. When the fever and rash have subsided, proceed to confirm hypersensitivity and identify the causative drug (if such re-challenge is not contraindicated by the severity of the reaction) or drugs to which the patient is hypersensitive. The steps to be followed are described below:

   To identify the drug causing the reaction:
   NB: In all cases test for hypersensitivity to all the drugs in use at the time of the hypersensitivity reaction. This testing must be done with the patient admitted to hospital and never on an out-patient basis.

First, test for isoniazid; then, for the other drugs in any order.

To test for hypersensitivity to a drug:
   a. Give the drug at the usual dose.
   b. If there is no reaction to a., repeat the same dose for another two days.
   c. If there is no reaction to b., test for another drug in the same way until the offending drug has been identified.
   d. If a reaction occurs after any of the tests, it should be allowed to subside completely before starting to test the next drug.

Once the offending drug(s) has been identified, it should never again be given to the patient.

2. Other Cutaneous Reactions

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

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

3. Hepatitis

Hepatitis occasionally occurs in patients receiving isoniazid, rifamycins 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. Once the tests are normal, treatment can be resumed but the liver function tests should be regularly monitored. It may be necessary to stop the offending drug.
4. Neurotoxicity

**Ethambutol**: Loss of visual acuity due to optic neuritis is dose-related and reversible if the drug is stopped promptly. This complication is uncommon at doses used in TB therapy.

Headaches, dizziness, mental confusion, hallucinations and peripheral neuritis have all been reported infrequently. The drug should be stopped immediately and never given again.

**Isoniazid**: Peripheral neuritis and mental confusion may occur. Pyridoxine 10 mg daily or a vitamin B compound containing pyridoxine should be tried. Because peripheral neuritis is common among those with HIV infection, malnutrition and alcoholism, pyridoxine is given routinely as part of the study regimen.

5. Other

**Rifampicin/rifapentine**: The “Flu” Syndrome. This is associated almost exclusively with the intermittent administration of rifamycins. It is characterised by episodes of fever, chills, headaches, dizziness and bone pain most commonly during the third to sixth month of treatment. The symptoms start one to two hours after each dose and last for up to eight hours. Symptoms can almost always be arrested by changing from intermittent to daily administration. This can be done by giving one capsule (150 mg) on the first day, two on the next and increasing the dose by a capsule a day until the normal daily dosage is reached – usually in three to four days.

**Moxifloxacin**: Quinolones are known to trigger seizures and should be used with caution in patients with CNS disorders. Moxifloxacin has been shown to prolong QTc interval on the electrocardiogram. Tendon inflammation and rupture may occur particularly in elderly patients and those on corticosteroids. Loss of visual acuity may occur. Fever, nausea, dizziness, vomiting, insomnia and joint pains may occur in a very small number of patients. Moxifloxacin should not be given to patients on current or planned therapy with quinidine, procainamide, amiodarone, sotalol, disopyramide, ziprasidone, or terfenadine during the intensive phase of TB therapy. Fluoroquinolones including moxifloxacin may result in an impairment of the patient’s ability to drive or operate machinery. Antacids, anti-retroviral drugs (eg, didanosine), and other preparations containing magnesium or aluminum, sucralfate and agents containing iron or zinc should be administered at least 4 hours (h) before or 2 h after ingestion of an PO moxifloxacin dose.

Section B: Minor Toxic Reactions

**Isoniazid**: Side-effects are negligible

**Rifampicin/rifapentine**: The urine may be coloured red; this is normal and no action is necessary.

**Pyrazinamide**: Anorexia and nausea may occur and be of no importance. It should be remembered, however, that these symptoms may be fore-runners to hepatitis (see below).

Arthralgia and swelling of one or more joints (gouty syndrome) may occur in patients who are receiving pyrazinamide – due to increased serum uric acid levels. Treatment with aspirin or ibuprofen may be successful without interruption of the regimen.

Section C: Other

Although this is not an adverse event it is a notifiable event. Should a woman become pregnant during treatment, this should be reported on the appropriate reporting forms (Form 7 and Form 8). The outcome of the pregnancy should be recorded on Form 13.
Appendix 5: Algorithm for HIV testing

Each centre will follow their usual algorithm.

The suggested steps to be followed are:

1. Consent to participate in the study must include agreement to provide blood for an HIV test.

2. All patients will receive pre-test counselling from trained counsellors and will be asked if they would like to know their result. No patient will be required to receive his/her result. The treating doctor will be informed of the result. All patients should be encouraged to receive their HIV results (in Botswana this will be mandatory for inclusion in the trial). However, the local laws regarding disclosure will be respected.

3. If a patient requests the result of his/her test, they should receive post-test counselling. The doctor should request the laboratory to report the result, in a sealed envelope, to the counsellor. Should the test be positive, the patient should be referred to the local facility providing follow-up care for HIV infected persons.

4. The suggested procedure for testing is as follows:

   A. Pre-test counselling
   B. Patient sent for blood test
   C. Sample is tested using two rapid tests with a confirmatory test if results from these tests are discordant.

   If the patient asks for result
   D. Laboratory sends result in sealed envelope to counsellor
   E. Counsellor gives result to patient
   F. Counsellor carries out post test counselling
   G. Counsellor destroys result in front of the patient
   H. For those patients who are HIV-infected referral to local care facilities

   Test results to be sent to trial statistician at intervals to be agreed during the trial.

5. Each centre will use the kits agreed at the start of the study (any changes must be notified to the CI). Details of the local algorithm and the kits used must be filed in the Trial Master File.

6. Cotrimoxazole is recommended by WHO as part of the initial management of HIV infected TB patients. INTERTB will not be responsible for providing any antiretroviral treatment (ART) for HIV positive patients. The local PI should ensure that patients requiring ART at any time during the trial are referred to the appropriate facility. Details of ART should be recorded on case record forms.
Appendix 6: ART for HIV/tuberculosis co-infection\textsuperscript{27}

1. Start ART in all HIV-infected individuals with active tuberculosis (TB) irrespective of CD4 cell count. (Strong recommendation, low quality of evidence)

2. Start TB treatment first, followed by ART as soon as possible after starting TB treatment. (Strong recommendation, moderate quality of evidence)

3. Use efavirenz (EFV) as the preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) in patients starting ART while on TB treatment. (Strong recommendation, high quality of evidence)

NB: Each centre will follow the local treatment policy.

Appendix 7: Recommendations for initiating anti-retroviral therapy in adults and adolescents with documented HIV infection\textsuperscript{27}

1. Start antiretroviral treatment in all patients with HIV who have CD4 count $\leq 350$ cells/mm\textsuperscript{3} irrespective of clinical symptoms. (Strong recommendation, moderate quality of evidence)

2. CD4 testing is required to identify if patients with HIV and WHO clinical stage 1 or 2 disease need to start antiretroviral treatment. (Strong recommendation, low quality of evidence)

3. Start antiretroviral treatment in all patients with HIV and WHO clinical stage 3 or 4 irrespective of CD4 count. (Strong recommendation, low quality of evidence)

NB: Each centre will follow the local treatment policy.
Appendix 8: WHO staging system for HIV infection and disease in adults and adolescents

<table>
<thead>
<tr>
<th>Clinical Stage I</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Asymptomatic</td>
</tr>
<tr>
<td>2. Generalized lymphadenopathy</td>
</tr>
<tr>
<td>Performance scale 1: asymptomatic, normal activity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Stage II</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Weight loss &lt;10% of body weight</td>
</tr>
<tr>
<td>4. Minor mucocutaneous manifestations (seborrhoeic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)</td>
</tr>
<tr>
<td>5. Herpes zoster within the last five years</td>
</tr>
<tr>
<td>6. Recurrent upper respiratory tract infections (i.e. bacterial sinusitis)</td>
</tr>
<tr>
<td>And/or performance scale 2: symptomatic, normal activity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Weight loss &gt;10% of body weight</td>
</tr>
<tr>
<td>8. Unexplained chronic diarrhoea, &gt;1 month</td>
</tr>
<tr>
<td>9. Unexplained prolonged fever (intermittent or constant), &gt;1 month</td>
</tr>
<tr>
<td>10. Oral candidiasis (thrush)</td>
</tr>
<tr>
<td>11. Oral hairy leucoplakia</td>
</tr>
<tr>
<td>12. Pulmonary tuberculosis</td>
</tr>
<tr>
<td>13. Severe bacterial infections (i.e. pneumonia, pyomyositis)</td>
</tr>
<tr>
<td>And/or performance scale 3: bedridden &lt;50% of the day during last month</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Stage IV:</th>
</tr>
</thead>
<tbody>
<tr>
<td>14. HIV wasting syndrome a</td>
</tr>
<tr>
<td>15. Pneumocystic carinii pneumonia</td>
</tr>
<tr>
<td>16. Toxoplasmosis of the brain</td>
</tr>
<tr>
<td>17. Cryptosporidiosis with diarrhoea &gt;1 month</td>
</tr>
<tr>
<td>18. Cryptococcosis, extrapulmonary</td>
</tr>
<tr>
<td>19. Cytomegalovirus disease of an organ other than liver, spleen or lymph node (e.g. retinitis)</td>
</tr>
<tr>
<td>20. Herpes simplex virus infection, mucocutaneous (&gt;1 month) or visceral</td>
</tr>
<tr>
<td>21. Progressive multifocal leucoencephalopathy</td>
</tr>
<tr>
<td>22. Any disseminated endemic mycosis</td>
</tr>
<tr>
<td>23. Candidiasis of oesophagus, trachea, bronchi</td>
</tr>
<tr>
<td>24. Atypical mycobacteriosis, disseminated or pulmonary</td>
</tr>
<tr>
<td>25. Non-typhoid Salmonella septicaemia</td>
</tr>
<tr>
<td>26. Extrapulmonary tuberculosis</td>
</tr>
<tr>
<td>27. Lymphoma</td>
</tr>
<tr>
<td>28. Kaposi’s sarcoma</td>
</tr>
<tr>
<td>29. HIV encephalopathy b</td>
</tr>
<tr>
<td>And/or performance scale 4: bedridden &gt;50% of the day during last month</td>
</tr>
</tbody>
</table>
Appendix 9: PK-Interaction assessments

The pharmacokinetics of MOXIFLOXACIN in tuberculosis patients during and after completion of continuation phase treatment with moxifloxacin and rifapentine.

Assessments during: AN INTERNATIONAL MULTICENTRE CONTROLLED CLINICAL TRIAL TO EVALUATE HIGH DOSE RIFAPENTINE AND A QUINOLONE IN THE TREATMENT OF PULMONARY TUBERCULOSIS; RIFAQUIN (International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis; INTERTB)

GENERAL INFORMATION

This document describes ancillary assessments of the RIFAQUIN trial to be conducted at the Worcester site, Western Cape, in 15 participants randomised to Study Regimen 1 and 15 to Study Regimen 2.

Sponsor:

St. George’s Hospital Medical School
Centre for Infection
Department of Cellular and Molecular Medicine
St. George’s Hospital Medical School
Jenner Wing, Cranmer Terrace
London SW17 0RE
United Kingdom

Main Contacts in addition to those listed in the RIFAQUIN study protocol; Pharmacokinetic consultants & Investigators:

Dr. Helen McIlleron, Prof. Peter Smith, Prof. Gary Maartens
Division of Clinical Pharmacology, University of Cape Town
K45 Old Main Building
Groote Schuur Hospital
Observatory
Cape Town 7925
South Africa
Tel: +27-21 406 6008
Fax: +27-21 4481989
e-mail: hmciller@uctgsh1.uct.ac.za

Principal Investigator:

Dr. Mark Hatherill
Satvi, Institute of Infectious Disease & Molecular Medicine, University of Cape Town
Room 2.01, Wernher Beit South
Anzio Road
Observatory
Cape Town 7925
South Africa
Tel: SATVI (Worcester) +27-23 347 7424
SATVI (Cape Town) +27-21 406 6014
Fax: 021 406 6081
E-mail: mark@rmh.uct.ac.za
Table of Contents

1. Summary ................................................................. 67
   1.1 Lay summary .......................................................... 67
   1.2 Summary of assessment design ................................. 67
   1.3 Trial interventions and procedures ............................. 67
   1.4 Outcome measures ..................................................... 67
   1.5 Duration .................................................................. 67
   1.6 PK data recording .................................................... 68

2. Background ............................................................. 68

3. Ethical and regulatory requirements ......................... 69

4. Selection of Patients ................................................ 69
   4.1 Patient inclusion criteria ............................................. 69
   4.2 Patient exclusion criteria ............................................. 69
   4.3 Number of participants .............................................. 69

5. Clinical procedures .................................................. 69
   5.1 Pre-PK procedures .................................................... 69
   5.2 PK sampling procedures ............................................ 70

6. Study treatments ....................................................... 72
   6.1 Treatments to be taken on PK study days: ..................... 72
   6.2 Source of drugs ....................................................... 72
   6.3 Drug supplies and accountability ............................... 72

7. Withdrawal of patients ............................................... 72

8. Analytical methods .................................................... 73

9. PK analysis .............................................................. 73
   9.1 Non-compartmental analysis ....................................... 73
   9.2 Statistics ................................................................ 73

10. PK-interaction assessment documentation ................ 74

11. Trial Monitoring ....................................................... 74

12. Safety Reporting ..................................................... 74

13. Ethical Considerations ............................................. 74

14. Indemnity ............................................................... 75

15. Trial Committees .................................................... 75

16. Publication ............................................................ 75

17. References ............................................................. 75

Annexes ..................................................................... 76

Annex1: Patient Information Sheet (PK-interaction assessments) 76
Annex 2: Consent Form for Interaction PK assessment enrolment 79
Annex 3: Table p-glycoprotein inhibitors and inducers ............. 80
1. Summary

1.1 Lay summary

These assessments will be conducted in 30 patients taking part in the RIFAQUIN study (15 in each of the two experimental arms). The purpose is to determine whether a pharmacokinetic (PK) drug-drug interaction between moxifloxacin and rifapentine significantly affects the levels of moxifloxacin when they are given together as part of anti-tuberculosis treatment.

1.2 Summary of assessment design

Type of design
Open-label, non-randomised, cross-over study of the PK of moxifloxacin with and without rifapentine.

Patients studied
Fifteen RIFAQUIN study participants attending the Worcester study site, receiving rifapentine 900 mg plus moxifloxacin 400 mg 2 x weekly during the continuation phase of Study Regimen 1 and 15 receiving rifapentine 1200 mg and moxifloxacin 400 mg once weekly during continuation phase of Study regimen 2; patients providing informed consent to participate in the PK-interaction assessments.

1.3 Trial interventions and procedures

The PK of moxifloxacin as part of the continuation phase of Study Regimens 1 and 2 (during a single dosing interval) will be compared to the single dose PK of moxifloxacin in the same patients once antitubercular treatment is completed (control). Participants will receive a single 400 mg dose of moxifloxacin at least 1 month after completion of antitubercular treatment in accordance with Study Regimens 1 and 2. Plasma concentrations of moxifloxacin will be determined from serial blood samples drawn up to 48 hours after dosing. Validated LC/MS (liquid chromatography/ mass spectroscopy) analytical methods will be used.

1.4 Outcome measures

Primary outcome measure
Area under the curve for plasma moxifloxacin concentration vs. time, until 48 hours after dosing ($AUC_{48}$).

Secondary outcome measure
- Peak plasma concentration of moxifloxacin ($C_{max}$).
- Plasma concentration of moxifloxacin at 48 hours after dosing ($C_{48}$).
- $AUC$ to infinity ($AUC_{i}$).
- Time to peak plasma concentration ($T_{max}$).
- Half-life of moxifloxacin ($T_{1/2}$).
- Adverse events: Adverse events reported during the 48 h period following the additional dose of moxifloxacin after completion of antitubercular treatment will be reported. Adverse events will also be recorded as part of the parent RIFAQUIN study.

1.5 Duration
As part of the RIFAQUIN study, patients will be followed up for 18 months from the commencement of chemotherapy. Follow-up visits will occur monthly until 12 months then at 15 and 18 months. The PK interventions take place during the 4th month of TB treatment, and during the 2nd month after completion of TB treatment, respectively. The PK sampling will coincide with scheduled visits.

1.6 PK data recording

PK-interaction assessment case report forms (PK-CRFs), recording participant, treatment and sampling details will be kept at the clinical study site. Copies of the CRFs will be sent to the Division of Clinical Pharmacology, University of Cape Town, where the information will be stored into a database for the assessments (using double data entry) together with the drug concentration data.

2. Background

Previous evidence on drug interactions with moxifloxacin suggest that drug-drug interaction with the rifamycins is unlikely because moxifloxacin excretion does not occur through the P450 system [Stass 2001], and in vitro studies suggest that p-glycoprotein inhibition has little effect on moxifloxacin disposition [Gibbons 2003]. However, a recent study amongst 16 participants found a 27% reduction in moxifloxacin concentrations when it was given together with rifampicin [Weiner 2006], and, in the same study, a p-glycoprotein mediated mechanism was suggested by an association of moxifloxacin levels with the MDR1 genotype. Rifampicin and rifapentine induce similar metabolic pathways although the effect of rifapentine is putatively less potent [Burman 2001]. It is therefore important to study this potential PK drug-drug interaction as part of this investigation as a PK interaction could contribute to regimen efficacy or safety.

Fifteen patients enrolled to each of Study Regimens 1 and 2 of the RIFAQUIN study will be studied. Patients will be recruited at the Worcester study site as its proximity to the analytical site and infrastructure are suitable for the PK sample preparation, storage and transfer. Separate consent to participate in the PK-interaction sub-study will be sought from eligible patients during the continuation phase. Moxifloxacin levels will be measured during the 4th month of treatment and again 4-8 weeks after treatment completion (thus allowing the level of drug metabolizing enzymes and transporters to return to baseline levels), when a single moxifloxacin dose of 400 mg will be given for the purposes of the PK assessments.

The sequential design avoids the problems of multiple rifapentine doses (which would be required to establish induction effects) and long wash out periods of a cross-over design. It was decided to study patients late during the treatment period to avoid the complicating effects of illness and acute phase reactants; patients are likely to be in relatively stable physiological state. Although the multiple dose PK of moxifloxacin (1st PK sampling during the continuation phase of treatment) will be compared to a single dose (2nd PK sampling after TB treatment completion), the dose prior to that of the 1st PK sampling interval will be at least 72 hours. Thus the washout period approximates 5 half-lives of moxifloxacin. Although the half-life of moxifloxacin increases with consecutive daily doses (10.6 h to 14.9 h in one healthy participant study; p<0.01; [Burkhardt 2002]), this accumulating effect is unlikely with twice weekly dosing, and even more unlikely with once weekly dosing.

Patients with CD4+ cell counts<350/mm³ will not be enrolled as they are at greater risk of acquiring the confounding factors of concomitant illness and medications prior to the PK assessments completion.

Patients with treatment failure or relapse of TB prior to the single dose of moxifloxacin at the 2nd PK sampling will be withdrawn as the appropriate management may interfere with the PK of
moxifloxacin and to minimize the risk of quinolone resistant TB developing. The risks of participation in the PK-interaction assessments are minimal: those of an additional dose of moxifloxacin and venepuncture.

3. Ethical and regulatory requirements

The PK-interaction assessments will be conducted in compliance with the protocol, ICH guidelines for GCP, and the Guidelines for good clinical practice in the conduct of clinical trials in human participants in South Africa (Clinical Trials Guidelines 2000. Department of Health, Republic of South Africa). The PK-interaction assessments will be submitted as part of the RIFAQUIN study for ethical approval to the Research Ethics Committee of the University of Cape Town and to the South African Medicines Control Council for approval of the use of the study treatments. No participant will be enrolled prior to the approval of both authorities.

4. Selection of Patients

4.1 Patient inclusion criteria

1. Participants receiving rifapentine 900 mg plus moxifloxacin 400 mg 2 times weekly as part of RIFAQUIN Study Regimen 1, or rifapentine 1200 mg and moxifloxacin 400 mg once weekly as part of Study Regimen 2.
2. Participants well enough to receive ambulatory treatment.
3. Afrikaans, English or Xhosa speaking participants.
4. Participants providing informed consent to participate in the PK-interaction assessments.

4.2 Patient exclusion criteria

A patient will not be eligible for participation in the assessments if he/ she:
1. Is receiving concomitant medications other than the study medications.
2. Has a CD4+ cell count < 350/mm³ during screening for RIFAQUIN study.
3. Multiple blood sampling is relatively contra-indicated (e.g. severe anaemia, bleeding diathesis, poor venous access).
4. Is unlikely or unable to cooperate with sampling procedures.
5. Has Moxifloxacin intolerance.

4.3 Number of participants

The number of participants required to detect a 25% difference in the AUC₄₈ of moxifloxacin when given with rifapentine and when given without rifapentine assuming the %CV for rifapentine is 20%, is 12 (power 0.9 and alpha 0.05). Fifteen patients will be recruited in each of the experimental study arms to ensure that at least 12 complete the PK-interaction sub-study.

5. Clinical procedures

5.1 Pre-PK procedures

RECRUITING AND ENROLMENT:
All eligible patients at the Worcester RIFAQUIN study site will be invited to participate and enrolled consecutively, until 15 patients have been enrolled in each experimental arm. A screening log will be kept as a record of all eligible patients and the reasons for non-participation if relevant.
CONSENT TO PARTICIPATE:
The assessment procedures, conditions and risks will be described orally and in writing (Patient Information and Consent Leaflet, which will be available in Afrikaans, English and Xhosa as in ANNEX 1) to eligible participants of the RIFAQUIN study. Participants providing written informed consent will be enrolled and their details will be entered in the PK-interaction assessment enrolment log.

INDIVIDUAL PARTICIPANT VISIT SCHEDULING:
The 2 PK sampling days will be scheduled and the proposed dates for PK sampling will be recorded in the PK-interaction assessment enrolment log. The PK sampling days will be scheduled for days when the previous dose is planned to be at least 72 hours prior to 8 am on the PK sampling day and will coincide with RIFAQUIN study visits.

PARTICIPANT INSTRUCTIONS:
Participants will be requested to present at the clinical study site in Worcester at 7h30 on the mornings of PK sampling. They will be instructed not to take that day’s study medication before arrival at the study site, as they will receive their study medication for that day as part of the study procedures. Participants will be requested to bring their RIFAQUIN study treatment cards to the study site on PK sampling days.

PERI-STUDY RESTRICTIONS:
Participants will be requested to avoid strenuous exercise and the use of alcohol, grapefruit juice, black pepper, garlic, over-the-counter medications (including antacids), vitamins or mineral supplements, recreational drugs, and herbal or other medicinal products for 48 hours prior to and during PK sampling admissions.

5.2 PK sampling procedures

REMEMBER:
The study team member designated to study coordination at the Worcester site will contact the participant directly, or the relevant clinic / DOTS worker, during the week prior to the PK sampling visit to remind them of the scheduled date for PK sampling and the instructions and restrictions (see above ‘PARTICIPANT INSTRUCTIONS’ and ‘PERI-STUDY RESTRICTIONS’).

TREATMENT CARD CHECK:
The patient’s treatment card will be checked to verify when the last dose of moxifloxacin was taken. If the treatment card is not available, the patient will be questioned as to when they took their last dose of moxifloxacin. This information will be recorded in the PK-CRF. Should the patient have ingested moxifloxacin within the restricted period (within 72 h for the 1st PK sampling, OR, within 4 weeks for the 2nd PK sampling), the PK sampling will be deferred and another PK sampling day scheduled (and the enrolment log updated).

CONCOMITANT MEDICATION:
The patient will be questioned about the use of concomitant medications, using the standardized questions listed in the PK-CRF, and the answers recorded in the PK-CRF. Should the patient have taken any medicines known to interfere with moxifloxacin disposition or p-glycoprotein metabolism the PK sampling should be deferred, or, if necessary, the patient should be withdrawn from the study. Specifically, antacids containing calcium, aluminium or magnesium, or sucralfate, or oral iron, zinc or magnesium supplements, should be avoided for the 2 days prior to PK sampling and during the PK sampling period. P-glycoprotein inhibitors and inducers should be avoided for 2 weeks prior to and during PK sampling (see ANNEX 2 for a list of p-glycoprotein inhibitors and inducers).

VENOUS ACCESS:
On arrival at the study site, the participant will be admitted to the clinic, a cannula (Introcan®, 20 G, Braun), will be inserted into a suitable arm vein and the pre-dose blood sample collected. Shortly thereafter, the first blood sample will be drawn before the standardized meal and study treatment are given. The exact time of sampling will be recorded in the case record form.
STUDY TREATMENT ADMINISTRATION:
The standardized study meal (2 hard boiled eggs and bread – as detailed in the RIFAQUIN study protocol) will be given. Immediately (within 15 minutes) thereafter, the study treatment will be taken with 240 ml of water. Study treatment ingestion will be carefully observed by a study team member. The exact time of drug ingestion will be recorded in the PK-CRF.
Should the patient vomit within 30 minutes after treatment administration, PK sampling will be deferred, and another PK sampling day scheduled.

FOOD, BEVERAGES AND ACTIVITY:
After drug ingestion patients will be requested to sit upright for 30 minutes. No food or beverages will be allowed until 4 hours after treatment administration, except water which will be allowed freely after 1 hour. After 4 hours light meals, snacks and fluids will be provided (alcohol, black pepper, garlic and caffeine will be avoided) until 12 hours after treatment administration when participants will be discharged. Participants will return on each of the 2 subsequent days for the 26 and 50 hour sampling.

PK SAMPLING SCHEDULE:
Blood sampling will be performed at the following times:

- Sample 0: -0.25 h (15 minutes prior to treatment administration)
- Sample 1: 1 h after treatment administration
- Sample 2: 3 h after treatment administration
- Sample 3: 5 h after treatment administration
- Sample 4: 7 h after treatment administration
- Sample 5: 10 h after treatment administration
- Sample 6: 12 h after treatment administration
- Sample 7: 26 h after treatment administration
- Sample 8: 50 h after treatment administration

Each 4 ml sample will be drawn into a lithium-heparin coated tube with a gel separator. The exact times of sampling will be recorded in the source documents and the PK-CRF. This is the time when the sample is complete i.e. the blood collection tube is filled. Reasons will be noted in the PK-CRF for deviations from the given times of more than 1 minute for samples up to 12 h; and for deviations of more than 5 minutes for samples later than 24 h.
For each PK sampling occasion in each subject, a laboratory request form (appendix P4) must be completed and dispatched with the samples to the Division of Clinical Pharmacology when the samples are transferred. The laboratory request forms comprise the inventory of samples despatched to the laboratory. They should be reconciled with the number of samples sent. The completed forms are necessary for the release of the laboratory results and copies can be used as the sampling source documents to be filed in the patient’s study folder.

SAMPLE HANDLING and STORAGE:
Blood samples will be centrifuged (to fully separate the plasma) within 30 minutes of collection. Whilst awaiting spinning they will be kept in crushed ice.

From each sample, approximately 1.0 ml of plasma will be aliquotted into each of 2 dry polypropylene 1.5 ml microcentrifuge tubes.

Each microcentrifuge tube will be labelled using a permanent marker pen as illustrated below:

[RIFAQUIN participant ID number]-[PK sampling occasion 'I' (for 1st PK sampling) or 'II' (for 2nd PK sampling)]-[sample 0, 1, 2, 3, 4, 5, 6, 7, or 8]

E.g.: XXX-II-3

i.e. participant ID number: XXX; 2nd PK sampling occasion; sample 3 at 5 hours.

The plasma samples will be immediately (within 5 minutes) stored in a – 80 ºC freezer, or they will be kept in dry ice until transfer to a – 80 ºC freezer.
On completion of the collection of PK samples for each site, the samples will be transferred as to the Division of Clinical Pharmacology, UCT, for analysis. The duplicate samples will be transferred as a separate batch. Samples will be stored at – 80 °C until analysis for drug concentrations. Duplicates will be stored for 1 year after study completion (issue of final PK-interaction assessment report).

6. Study treatments

6.1 Treatments to be taken on PK study days:

1\textsuperscript{st} PK sampling: 400 mg moxifloxacin (1x400 mg tablet \textit{PLUS} 900 mg rifapentine (6x150 mg tablets) as part of Study Regimen 1; or 400 mg moxifloxacin and 1200 mg rifapentine as part of Study Regimen 2.

2\textsuperscript{nd} PK sampling: 400 mg moxifloxacin (1x400 mg tablet)

6.2 Source of drugs

All the drugs will be supplied by INTERTB, London as for the RIFAQUIN study.

Moxifloxacin for the PK assessments will be provided from the same batch.

The manufacturer, batch number and expiry dates will be recorded for moxifloxacin in the PK-CRF.

6.3 Drug supplies and accountability

The Study Regimen 1 of the RIFAQUIN study will be managed and accounted for according to the procedures for that study.

The study treatment for the 2\textsuperscript{nd} PK sampling (moxifloxacin: 15 x 400 mg doses plus 5 additional tablets), will be accounted for as follows: The site investigator or pharmacist will inventory and acknowledge receipt of all shipments of the investigational products. The investigational products must be kept in a locked area with restricted access. The investigational products must be stored and handled in accordance with the manufacturer's instructions. The investigator or pharmacist will also keep accurate records of the quantities of the investigational products dispensed and used by each subject. At the conclusion of the study, all unused investigational products will be destroyed and all medication containers will be stored with the study documents.

7. Withdrawal of patients

Participants may withdraw from the PK-interaction assessments at any stage for their own reasons and without necessarily having to justify their decision to withdraw. The investigator should make reasonable effort to ascertain the reason for withdrawal and this should be noted in the PK-CRF.

It may be necessary to withdraw patients if they require concomitant medication that might interfere with moxifloxacin PK (see ‘CONCOMITANT MEDICATION’ in section 5.2), or if they develop serious concomitant illness.
Patients with treatment failure at the end of the 4 month treatment period and patients who develop a relapse of TB before the 2nd PK sampling, will be withdrawn from the PK-interaction assessment.

The investigator may withdraw the participant at any stage if it is deemed to be in the participant's interest.

Participants will not be replaced unless the number of participants completing the PK-interaction assessments drops below 12 and eligible patients are still available for recruiting from the RIFAQUIN study.

8. Analytical methods

Rifapentine and Moxifloxacin will be analyzed by fully validated methods using liquid chromatography-tandem mass spectrometry on an Applied Biosystems API 2000 tandem mass spectrometer. High performance liquid chromatography will be conducted using an Agilent 110 HPLC system.

Chromatography will be on a Thermo Hypersil Gold C18 column (20 x 2.1 mm) in a mobile phase comprising 70/30 acetonitrile/0.1% formic acid. For Mass Spectrometric detection, Q1 for rifapentine will be optimized at an m/z of 877.30 and product ions will be monitored at a transition of 877.30 to 845.1. For Moxifloxacin, Q1 will be optimized at an m/z of 402.1 and product ions monitored at a transition of 402.1 to 261.4.

The analytical laboratory is ISO17025 compliant and accredited for the purpose of quantifying drug concentrations in biological samples including assay development.

9. PK analysis

9.1 Non-compartmental analysis

On each series of the drug plasma concentrations the following pharmacokinetic parameters will be determined using the software package Pharsight Win Nonlin Enterprise 3.3 (Pharsight Corporation)

- Area under the curve for plasma moxifloxacin concentration vs. time, until 48 hours after dosing (AUC_{48}).
- Peak plasma concentration of moxifloxacin (C_{max}).
- Plasma concentration of moxifloxacin at 48 hours after dosing (C_{48}).
- AUC to infinity (AUC).
- Time to peak plasma concentration (T_{max}).
- Half-life of moxifloxacin (T_{1/2}).

Sparse sampling and analysis using a population approach and nonlinear mixed effects modeling will also be used to assess the PK of moxifloxacin and rifapentine in a wider group of patients participating in the RIFAQUIN study. The data from this assessment will contribute to that analysis.

9.2 Statistics

The PK measures will be summarized using parametric or nonparametric methods (as appropriate) for moxifloxacin with and without rifapentine, and for rifapentine from the 1st PK sampling. The significance of differences between the pharmacokinetic measures (for moxifloxacin with and without
rifapentine) will be determined using the students t-test (parametric data) and the Wilcoxon signed rank test (nonparametric data).

Bioequivalence analysis will be conducted using ANOVA. The geometric mean ratios and their 90% confidence intervals will be reported for the pharmacokinetic measures of importance for bioavailability ($C_{\text{max}}$, $AUC_r$, $AUC_{48}$). In addition the interindividual and total variability will be reported for each PK measure.

No interim analyses are planned.

## 10. PK-interaction assessment documentation

The following documents should be added to the **Investigator’s Study File at the clinical site:** signed PK-interaction assessment procedures, sample PK-CRF, sample information and consent leaflet, Independent Ethics Committee/Institutional Review Board approval of the PK-interaction assessments with related correspondence, copies of the South African Medicines Control Council approval of the RIFAQUIN protocol including the PK-interaction assessments with related correspondence, all other relevant study documents/correspondence etc.

PK-interaction assessments documents to be added to the **subject clinical source documents** include the signed informed consent forms for the PK-interaction assessments and the PK sampling records.

For each patient enrolled, a **PK-CRF (study documentation of pharmacokinetic assessments)** will be completed in triplicate and signed by the Principal Investigator or the designated Clinical Research Assistant (CRA) authorised delegate from the study staff.

All forms must be completed using indelible ink, and must be legible. Any change or correction to a CRF must be dated, initialled, and should not obscure the original entry.

The original copy of the CRF will remain at the study site; a copy will be transferred the Division of Clinical Pharmacology at the University of Cape Town, where the relevant data will be entered into an electronic database.

## 11. Trial Monitoring

The PK-interaction assessments will be monitored as part of the RIFAQUIN study.

## 12. Safety Reporting

Safety will be recorded and reported as for the RIFAQUIN study.

## 13. Ethical Considerations

Separate written informed consent will be obtained from the sub-group of RIFAQUIN Study participants enrolled into the PK-interaction assessments.

The information will be provided in Afrikaans, English or Xhosa (according to the participant’s preference) with the aid of a translator if necessary. All subjects will be conversant in at least one of the three languages (see selection criteria). Participants will be informed that they are free to withdraw from the PK-interaction assessments at any stage without prejudice to them for doing so, and without their decision to withdraw affecting their participation in the RIFAQUIN study, or their medical care. Participants will be informed that they will be compensated for inconvenience and travel expenses. Participants will be given a copy of the signed consent form which will include the contact details for the ethical and drug regulatory authorities.
The risks to patients of participation in the PK-interaction assessments are minimal. The benefits to the individual participants are negligible, over-and-above those of participation in the RIFAQUIN study. Participants will be compensated for inconvenience and transport costs (R150 per visit for PK-interaction assessments).

14. Indemnity

The sponsor of the trial is St. George’s, University of London.

All personnel involved in the trial will be expected to be indemnified by their employing authority.

Patients will be indemnified, for non-negligent harm, through a separate policy taken out by the trial sponsor.

15. Trial Committees

The PK-interaction assessments will be subject to the decisions of the RIFAQUIN Study’s Trial Management Group (TMG), Trial Steering Committee (TSC), and Independent Data Monitoring Committee (IDMC).

16. Publication

The Trial Management Group of the RIFAQUIN study will form the basis of the Writing Committee and will advise on the nature of publications.

Named authors will be in accordance with the publication policy of the journal and will include (at least) the RIFAQUIN study’s Chief Investigator(s) and the PK study investigator(s).

17. References


Annexes

Annex 1: Patient Information Sheet (PK-interaction assessments)

You are invited to take part in the assessments for: The pharmacokinetics of MOXIFLOXACIN in tuberculosis patients during and after completion of continuation phase treatment with moxifloxacin and rifapentine.

These assessments will be amongst 30 of the people taking part in the RIAQUIN Study (investigating the role of rifapentine and moxifloxacin in TB treatment). Only people taking RIFAPENTINE and MOXIFLOXACIN once or twice a week at the Worcester site/centre will be invited to take part in these assessments.

This additional research will add information to the RIFAQUIN study, in which you are already taking part. This information will help to optimize tuberculosis (TB) drug combinations and treatment, thereby benefiting future patients with TB. Your decision to take part, or not, in this additional research, will not affect your participation in the RIFAQUIN study. Refusal to take part will not affect your access to treatment in any way.

Before agreeing to take part, it is important that you read and understand the following explanation of the purpose of the research, and the procedures, benefits, risks, discomforts, and precautions. You should fully understand what is involved before you agree to take part. You should not agree to take part unless you are satisfied about all the procedures involved. If you have any questions, do not hesitate to ask the study doctor.

It is your right to withdraw from these procedures at any time. Your access to medical treatment will not be affected in any way if you withdraw.

For the assessments to be useful, it is important that all the information you give the study doctor is truthful and that you follow the study instructions carefully.

If you decide to take part in this procedure, you will be asked to sign and date this document to confirm that you understand the procedures and agree to take part. You will be given a copy to keep.

Purpose:

The purpose of this assessment is to determine whether the amount of the anti-TB medicine moxifloxacin in your body is affected by taking rifapentine at the same time. It will also provide information about the amount of the medicines in the bodies of TB patients taking rifapentine 900 mg and moxifloxacin 400 mg doses 2 times a week, and rifapentine 1200 mg and moxifloxacin 400 mg once per week.

Procedures:

If you decide to take part in this assessment:

1) You will receive 1 extra dose of moxifloxacin 400 mg between 4 and 8 weeks after you have finished your TB treatment.

AND

2) You will undergo additional blood tests on 2 occasions:
1st occasion: During the 4th month of your TB treatment.

2nd occasion: On the day you receive the additional dose of moxifloxacin (4 to 8 weeks after your TB treatment is finished).

On each of these occasions you will need to arrive at the study centre in Worcester early in the morning. You will be given your TB treatment and breakfast (of 2 boiled eggs and bread) at the clinic. It is important NOT to take any medicines before your arrival at the study centre.

Nine blood samples of less than one teaspoonful each will be taken over the 48 hours after you take you medicine at the study centre. All meals and refreshments will be provided. You will be allowed to return home after the first 12 hours, but you will be required to visit the study site to give a blood sample for each of the 2 following mornings.

The blood samples will be used for the purpose of measuring drug concentrations only.

Risks:
The risks of taking part in this study are minimal. The blood samples will be drawn from a suitable arm vein using a cannula (a flexible plastic needle, like a drip needle), and needles (for the later samples). Although experienced and qualified study staff will draw the blood, there is a risk of bruising and slight bleeding. The additional moxifloxacin will be given at the same dose that you are receiving as part of your TB treatment. There is a small risk of the side effects associated with the drug but these are unlikely if you have not experienced them by the end of your treatment.

If you experience any changes in your condition (for example, faintness, dizziness, rash, nausea, vomiting, difficulty sleeping, difficulty with your vision, joins pains, or any other new medical problem) you should report this immediately to the study doctor or other study team member.

Benefits:
There will be no direct medical benefits to you from this procedure. Information that will be obtained from this procedure may be useful scientifically and may benefit future TB patients.

Compensation:
You will be compensated (R150 for each visit to the study site for blood sampling), for the inconvenience and for transport costs to and from the study centre. If you participate for only a part of the procedures you will be compensated accordingly on a pro-rata basis.

Specimen storage:
The samples from your blood will be stored for a year after completion of the procedure. The specimens will then be destroyed.

Confidentiality:
All information concerning your person and the data collected will remain confidential and anonymous. By taking part in the present procedures, you agree that data recorded will be computerised. The information cannot be used by anyone other those involved in the procedure, the regulatory authority or research ethics committees.

If you have questions about this procedure you should discuss them with the study team of your doctor or the ethics committee (contact details as provided on this form).

Important contact details:
If you are concerned about your health or have any questions at any given time during the course of the study, please do not hesitate to contact the study doctor or a study team member.

Study doctor: Name ________________________________
If you want any information regarding your rights as a research participant, or have complaints regarding this research study, you may contact Dr Marc Blockman, the Chairperson of the Research Ethics Committee at the University of Cape Town (021 406 6492).

After you have consulted your doctor or the ethics committee and they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:
The Registrar, SA Medicines Control Council Department of Health, Private Bag X 828
PRETORIA 0001

*One copy of this form to be given to the patient to keep*
Annex 2: Consent Form for Interaction PK assessment enrolment

(TO BE PRESENTED ON LOCAL HEADED PAPER)

Study No.: ............................ Date and version: dd/mm/yyyy, Vxx.x

RIFAQUIN - AN INTERNATIONAL MULTICENTRE CONTROLLED CLINICAL TRIAL TO EVALUATE HIGH DOSE RIFAPENTINE AND A QUINOLONE IN THE TREATMENT OF PULMONARY TUBERCULOSIS

INTERACTION PK ASSESSMENT

Please initial box to agree

1. I confirm that I have read (or had read to me) and understand the information sheet dated ............................ (version ............) for the above study and have had the opportunity to ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at by responsible individuals involved in the running of the trial or from regulatory authorities where it is relevant to my taking part in research, and that I will followed up through usual National Tuberculosis Programme Services. I give permission for these individuals to have access to my records.

4. I agree to take part in the above study.

________________________ ________________ ____________________
Name of Patient Date Signature or thumbprint

_______________________ ________________ ____________________
Name of witness Date Signature
(if patient is illiterate)

_________________________ ________________ ____________________
Name of Person taking consent Date Signature

2 copies: 1 for patient, 1 for the patient’s confidential Trial folder

RIFAQUIN Protocol Version 1.8, 15 April 2011
Annex 3: Table p-glycoprotein inhibitors and inducers

<table>
<thead>
<tr>
<th>P-gp inhibitors</th>
<th>P-gp Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Mefloquine</td>
</tr>
<tr>
<td>Bepridil</td>
<td>Mepacrine</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>Niacardipine</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Nifedipine</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Progestrone</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Dilatazem</td>
<td>Quindine</td>
</tr>
<tr>
<td>Dipyriramol</td>
<td>Quinine</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Tamofoxan</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>Trifluperazine</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Valinomycin</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Verapamil</td>
</tr>
</tbody>
</table>

\(^a\) This agent causes initial inhibition and subsequent induction of P-gp.
\(^b\) This agent can act as a P-gp inhibitor or inducer, depending on the concentration.

Appendix 10: Flow chart for assessing and notifying adverse events

Adverse Event
(Any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment)
Assessed for causality, seriousness and expectedness

Serious
- Resulted in death
- Life-threatening
- Required in-patient hospitalization/extension of existing hospitalization
- Congenital abnormality/birth defect
- Other medically important condition
All serious Adverse Events to be reported on SAE/NAE Form 8

Assess seriousness

Serious Adverse Reaction (SAR)
Drug-Related causal relationship to protocol drugs:
- Definitely
- Probably
- Possible

Assess causality

Expected
Listed in protocol, SPC, IB
SSAR/SAR
(Suspected/Serious Adverse Reaction)
- Notify MRC immediately via SAE/NAE Form 8

Unexpected
Not listed in protocol, SPC, IB
SUSAR
(Suspected Unexpected Serious Adverse Reaction)
- Notify MRC immediately via SAE/NAE Form 8

Notify MRC immediately via SAE/NAE Form 8

Serious Adverse Event (SAE)
Causal relationship to protocol drugs:
- Unlikely
- Not related

Assess expectedness

Notifiable Adverse Event (NAE)
- Pregnancy
- Grade 3 toxicity or event
- Worsening of pre-existing condition to grade 3
- Study drug discontinued
- Study drug dose reduced for toxicity
- Identification of Rifamycin monoresistance
All NAEs to be recorded on SAE/NAE Form 8

Adverse Reaction (AR)
Drug-Related causal relationship to protocol drugs:
- Definitely
- Probably
- Possible
All ARs to be recorded on Form 7

Notify MRC immediately via SAE/NAE Form 8

Adverse Event (AE)
Causal relationship to protocol drugs:
- Unlikely
- Not related
Details of all AEs to be recorded in the patient’s medical notes.

Assess causality

Not Serious

No notification to Sponsor
## Appendix 11: Patient Treatment Cards

<table>
<thead>
<tr>
<th>Ethambutol (E) (daily)</th>
<th>Isoniazid (H) (daily)</th>
<th>Rifampicin (R) (daily)</th>
<th>Pyrazinamide (Z) (daily)</th>
<th>Pyridoxine (daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C= Clinic staff  
D=Domiliary monitor  
N=Not taken  
T=Taken, not observed  
U=Unknown

<table>
<thead>
<tr>
<th>Month/Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Month/Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patient must receive a minimum of 40 and maximum of 56 DOT doses for the intensive phase of treatment*

Total no. doses taken this month:  
No. doses left for intensive phase:  

---

### Intensive phase:

**Month 1**

Date started: / /  
Date finished: / /  
Control regimen  
2EHRZ/4HR

**RIFAQUIN**

An international multicentre controlled clinical trial to evaluate high dose rifampentine and a quinolone in the treatment of pulmonary tuberculosis

Remember - TB can be cured!

Please hand in this card at your next visit and collect a new one next time you come. After this month, you will only have 5 months of treatment left.

**STUDY NO.**  
**PATIENT INITIALS**  
**SEX:** M F  
**BASELINE WEIGHT** Kg

---

RIFAQUIN Protocol Version 1.8, 15 April 2011  
Page 82 of 97
<table>
<thead>
<tr>
<th>Ethambutol (E) (daily)</th>
<th>Isoniazid (H) (daily)</th>
<th>Rifampicin (R) (daily)</th>
<th>Pyrazinamide (Z) (daily)</th>
<th>Pyridoxine (daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C= Clinic staff  D= Domiciliary monitor  N= Not taken  T= Taken, not observed  U= Unknown

<table>
<thead>
<tr>
<th>Month/Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>15</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>22</td>
<td>23</td>
<td>24</td>
<td>25</td>
<td>26</td>
<td>27</td>
<td>28</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patient must receive a minimum of 40 and maximum of 56 DOT doses for the intensive phase of treatment

Total no. doses taken this month: [ ]  Total no. doses taken for intensive phase: [ ]

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>4+59</th>
<th>5+59</th>
<th>6+59</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>300mg</td>
<td>300mg</td>
<td>300mg</td>
</tr>
</tbody>
</table>

Remember - TB can be cured!

Please hand in this card at your next visit and collect a new one.

After this month, you will only have 4 months of treatment left!

Intensive phase:

Month 2

Date started: / / 
Date finished: / / 

Control regimen
2EHR/4IHR

RIFAQUIN

An international multicentre controlled clinical trial to evaluate high dose rifampicin and a quinolone in the treatment of pulmonary tuberculosis.

<table>
<thead>
<tr>
<th>STUDY NO:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENT INTIALS</td>
<td></td>
</tr>
<tr>
<td>SEX: M</td>
<td>F</td>
</tr>
<tr>
<td>BASELINE WEIGHT</td>
<td>Kg</td>
</tr>
</tbody>
</table>
**RIFAQUIN Protocol Version 1.8, 15 April 2011**

<table>
<thead>
<tr>
<th>Isoniazid (H) (daily)</th>
<th>Rifampicin (R) (daily)</th>
<th>Pyridoxine (daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. tablets</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| C= Clinic staff  | D=Domieiliary monitor | N= Not taken  | T= Taken, not observed | U= Unknown |

<table>
<thead>
<tr>
<th>Month/Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>15</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>22</td>
<td>23</td>
<td>24</td>
<td>25</td>
<td>26</td>
<td>27</td>
<td>28</td>
<td>29</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patient must receive a minimum of 90 and maximum of 126 DOT doses for the continuation phase of treatment.

Total no. doses taken this month: [ ]

No. doses left for continuation phase: [ ]

---

**Continuation phase:**

**Month 3**

Date started: [ ]

Date finished: [ ]

Control regimen

2EHRZ/4HR

**RIFAQUIN**

An international multicentre controlled clinical trial to evaluate high dose rifapentine and a quinolone in the treatment of pulmonary tuberculosis.

Remember - TB can be cured!

Please hand in this card at your next visit and collect a new one. After this month, you will only have 3 months of treatment left!

**RIFAQUIN** contact:

RIFAQUIN contact number:

<table>
<thead>
<tr>
<th>STUDY NO:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PATIENT INITIALS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SEX: M</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BASELINE WEIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Kg</td>
</tr>
</tbody>
</table>

RIFAQUIN Protocol Version 1.8, 15 April 2011

Page 84 of 97
<table>
<thead>
<tr>
<th>Mg</th>
<th>Isoniazid (H) (daily)</th>
<th>Rifampicin (R) (daily)</th>
<th>Pyridoxine (daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. tablets</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C=Clinic staff  D=Domiciliary monitor  N=Not taken  T=Taken, not observed  U=Unknown

<table>
<thead>
<tr>
<th>Month/Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patient must receive a minimum of 96 and maximum of 126 DOT doses for the continuation phase of treatment*

Total no. doses taken this month: [ ]  No. doses taken for continuation phase including this month: [ ]  No. doses left for continuation phase: [ ]

---

**Continuation phase:**

**Month 4**

Date started: / / 
Date finished: / /

Control regimen: 2EHRZ/4HR

**RIFAQUIN**

An international multicentre controlled clinical trial to evaluate high dose rifapentine and a quinolone in the treatment of pulmonary tuberculosis

---

**Remember - TB can be cured!**

Please hand in this card at your next visit and collect a new one.

After this month, you will only have 2 months of treatment left!

RIFAQUIN contact:

RIFAQUIN contact number:

---

**STUDY NO:**

**PATIENT INITIALS**

**SEX:** M [ ] F [ ]

**BASELINE WEIGHT**

Kg
### Isoniazid (H) (daily)  Rifampicin (R) (daily)  Pyridoxine (daily)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mg</td>
<td>No. tablets</td>
<td></td>
</tr>
</tbody>
</table>

C=Clinic staff  D=Domiliary monitor  N=Not taken  T=Taken, not observed  U=Unknown

<table>
<thead>
<tr>
<th>Month/Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>15</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>22</td>
<td>23</td>
<td>24</td>
<td>25</td>
<td>26</td>
<td>27</td>
<td>28</td>
<td>29</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patient must receive a minimum of 50 and maximum of 128 DOT doses for the continuation phase of treatment

Total no. doses taken this month: [ ]  No. doses taken for continuation phase including this month: [ ]  No. doses left for continuation phase: [ ]

### RIFAQUIN Protocol Version 1.8, 15 April 2011

**Continuation phase:**

**Month 6**

- **Date started:** / / 
- **Date finished:** / / 
- **Control regimen:** 2EHRZ/4HR

**RIFAQUIN**

An international multicentre controlled clinical trial to evaluate high dose rifapentine and a quinolone in the treatment of pulmonary tuberculosis

**Remember - TB can be cured!**

Please hand in this card at your next visit and collect a new one.

RIFAQUIN contact:

- **RIFAQUIN contact number:**

**STUDY NO:**

- [ ]

**PATIENT INITIALS:**

- [ ]

- [ ]

**SEX:**

- [M]
- [F]

**BASELINE WEIGHT:**

- [ ]
- [ ] Kg

RIFAQUIN Protocol Version 1.8, 15 April 2011  
Page 86 of 97
Isoniazid (H) (daily)  Rifampicin (R) (daily)  Pyridoxine (daily)

<table>
<thead>
<tr>
<th>Mg</th>
<th>Rifampicin</th>
<th>Pyridoxine</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. tablets</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C=Clinic staff  D=Domiciliary monitor  N=Not taken  T=Taken, not observed  U=Unknown

<table>
<thead>
<tr>
<th>Month/Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patient must receive a minimum of 50 and maximum of 126 DOT doses for the continuation phase of treatment

Total no. doses taken this month:  
Total no. doses taken for continuation phase:  

**Continuation phase:**

**Month 6**

Date started: / /  
Date finished: / /

**Control regimen**

2EHRZ4HR

**RIFAQUIN Protocol Version 1.8, 15 April 2011**

Page 87 of 97
### Ethambutol (E) (daily) | Isoniazid (H) (daily) | Rifampicin (R) (daily) | Pyrazinamide (Z) (daily) 
--- | --- | --- | ---
| No. tablets | | | |

<table>
<thead>
<tr>
<th>C= Clinic staff</th>
<th>D= Domiciliary monitor</th>
<th>N= Not taken</th>
<th>T= Taken, not observed</th>
<th>U= Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month/Year</td>
<td>Month/Year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patient must receive a minimum of 40 and maximum of 56 DOT doses for the intensive phase of treatment*

**Total no. doses taken this month:**  
**No. doses left for intensive phase:**  

---

### Intensive phase

**Month 1**

- Date started:  |
- Date finished:  |

**Study regimen 1**

2EMRZ/2P<sub>2</sub>M<sub>2</sub>

---

**RIFAQUIN**

An international multicentre controlled clinical trial to evaluate high dose rifapentine and a quinolone in the treatment of pulmonary tuberculosis.

---

**RIFAQUIN**

*Study No.*  
*Patient initials*  
*Sex:* M/F  
*Baseline weight:* Kg

---

**RIFAQUIN Protocol Version 1.8, 15 April 2011**

Page 88 of 97
<table>
<thead>
<tr>
<th>No. tablets</th>
<th>Ethambutol (E) (daily)</th>
<th>Isoniazid (H) (daily)</th>
<th>Rifampicin (R) (daily)</th>
<th>Pyrazinamide (Z) (daily)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>C= Clinic staff</th>
<th>D= Domiciliary monitor</th>
<th>N= Not taken</th>
<th>T= Taken, not observed</th>
<th>U= Unknown</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Month/Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patient must receive a minimum of 40 and maximum of 56 DOT doses for the intensive phase of treatment.

Total no. doses taken this month: [ ]

Total no. doses taken for intensive phase: [ ]
Moxifloxacin (M) (twice weekly)  Rifapentine (P) (twice weekly)

<table>
<thead>
<tr>
<th>Mg</th>
<th>No. tablets</th>
</tr>
</thead>
</table>

C=Clinic staff  N=Not taken  T=Taken, not observed  U=Unknown

<table>
<thead>
<tr>
<th>Month</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
</tr>
<tr>
<td>Month</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
</tr>
<tr>
<td>Month</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
</tr>
<tr>
<td>Month</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
</tr>
<tr>
<td>Month</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
</tr>
<tr>
<td>Month</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
</tr>
</tbody>
</table>

For example:

<table>
<thead>
<tr>
<th>Month</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
</tr>
</thead>
<tbody>
<tr>
<td>June</td>
<td>15th</td>
<td>17th</td>
<td>20th</td>
<td>23rd</td>
</tr>
<tr>
<td>June</td>
<td>G</td>
<td>N</td>
<td>G</td>
<td>G</td>
</tr>
</tbody>
</table>

*Patient must receive 18 DCT doses for the continuation phase of treatment*

Total no. doses taken this month:  
No. doses left for continuation phase:  

---

**Continuation phase**

**Month 3**

Date started:  
Date finished:  

**Study regimen 1**

2EMRZ/2P₂M₂

---

**RIFAQUIN**

An international multicentre controlled clinical trial to evaluate high dose rifapentine and a quinoline in the treatment of pulmonary tuberculosis

---

**STUDY NO:**

**PATIENT INITIALS:**

**SEX:** M  F  

**BASELINE WEIGHT:** Kg
Please complete a treatment card for each month of treatment during the continuation phase.

<table>
<thead>
<tr>
<th>Month</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For example:

<table>
<thead>
<tr>
<th>Month</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
</tr>
</thead>
<tbody>
<tr>
<td>June</td>
<td>19th C</td>
<td>19th C</td>
<td>26th C</td>
<td>26th C</td>
</tr>
<tr>
<td>June</td>
<td>32nd C</td>
<td>33rd C</td>
<td>40th C</td>
<td>40th C</td>
</tr>
</tbody>
</table>

*Patient must receive 18 DOT doses for the continuation phase of treatment.

Total no. doses taken this month:  
Total no. doses taken for continuation phase:  

**Continuation phase**

**Month 4**

**Study regimen 1**

2EMRZ2PJM_{L}

**RIFAQUIN**

An international multicentre controlled clinical trial to evaluate high dose rifapentine and a quinolone in the treatment of pulmonary tuberculosis.

---

Remember - TB can be cured!
This is your last month of treatment!

<table>
<thead>
<tr>
<th>RIFAQUIN contact name</th>
<th>RIFAQUIN contact number</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>STUDY NO.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENT INITIALS</td>
</tr>
<tr>
<td>SEX: M</td>
</tr>
<tr>
<td>BASELINE WEIGHT</td>
</tr>
<tr>
<td>Ethambutol (E) (daily)</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Mg</td>
</tr>
<tr>
<td>No. tablets</td>
</tr>
</tbody>
</table>

C = Clinic staff  
D = Domiciliary monitor  
N = Not taken  
T = Taken, not observed  
U = Unknown

<table>
<thead>
<tr>
<th>Month</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

*Patient must receive a minimum of 46 and maximum of 56 DOT doses for the intensive phase of treatment*

Total no. doses taken this month:  
No. doses left for intensive phase:  

---

**Intensive phase**

**Month 1**

Date started:  
Date finished:  

**Study regimen 2**

**2EMRZ/4P,M,2**

**RIFAQUIN**

An international multicentre controlled clinical trial to evaluate high dose rifapentine and a quinolone in the treatment of pulmonary tuberculosis

---

**REMINDER - TB can be cured!**

Please hand in this card at your next visit and collect a new one. After this month, you will only have 3 months of treatment left.

RIFAQUIN contact:  
RIFAQUIN contact number:
### Moxifloxacin (M) (weekly) vs Rifapentine (P) (weekly)

<table>
<thead>
<tr>
<th>Mg</th>
<th>Rifapentine (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. tablets</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C= Clinic staff</th>
<th>N= Not taken</th>
<th>T= Taken, not observed</th>
<th>U= Unknown</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Month</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For example:

<table>
<thead>
<tr>
<th>Month</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
</tr>
</thead>
<tbody>
<tr>
<td>June</td>
<td></td>
<td>24th</td>
<td>25th</td>
<td>26th</td>
</tr>
</tbody>
</table>

*Patient must receive 16 DOT doses for the continuation phase of treatment*

Total no. doses taken this month:   
No. doses left for continuation phase:  

### Continuation phase

**Month 3**

Date started:  
Date finished:  

**Study regimen 2**

2EMRZ/4P:(P;

**RIFAQUIN**

An international multicentre controlled clinical trial to evaluate high dose rifapentine and a quinolone in the treatment of pulmonary tuberculosis

**REMINDER**

TB can be cured!

Please hand this card at your next visit and collect a new one.

After this month, you will only have 3 months of treatment left.

RIFAQUIN contact: [Contact number]

STUDY NO:  

PATIENT INTIALS:  

SEX: M F  

BASELINE WEIGHT:  

Kg
<table>
<thead>
<tr>
<th>Month</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C = Clinic staff  
N = Not taken  
T = Taken, not observed  
U = Unknown

For example:

<table>
<thead>
<tr>
<th>Month</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
</tr>
</thead>
<tbody>
<tr>
<td>June</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>June</td>
<td>Day</td>
<td>Day</td>
<td>24th</td>
<td>28th</td>
</tr>
</tbody>
</table>

"Patient must receive 18 DOT doses for the continuation phase of treatment"

Total no. doses taken this month: ☐  
No. doses taken for continuation phase including this month: ☐  
No. doses left for continuation phase: ☐

**Continuation phase**

**Month 4**

Date started: / /  
Date finished: / /

**Study regimen 2**  
2EMRZ/4P:M1

RIFAQUIN

An international multicentre controlled clinical trial to evaluate high dose rifampicin and a quinolone in the treatment of pulmonary tuberculosis

**Remember** - TB can be cured!

Please hand in this card at your next visit and collect a new one. After this month, you will only have 2 months of treatment left.

RIFAQUIN contact number:

STUDY NO:  
PATIENT INTIALS  
SEX: M □ F □  
BASELINE WEIGHT  
Kg
Moxifloxacin (M) (weekly) | Rifapentine (P) (weekly)
---|---

<table>
<thead>
<tr>
<th>No. tablets</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>C= Clinic staff</th>
<th>N= Not taken</th>
<th>T= Taken, not observed</th>
<th>U= Unknown</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Month</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 1</td>
<td>[Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
</tr>
<tr>
<td>Month 2</td>
<td>[Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
</tr>
<tr>
<td>Month 3</td>
<td>[Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
</tr>
<tr>
<td>Month 4</td>
<td>[Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
</tr>
<tr>
<td>Month 5</td>
<td>[Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
</tr>
<tr>
<td>Month 6</td>
<td>[Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
<td>Day</td>
</tr>
</tbody>
</table>

For example:

<table>
<thead>
<tr>
<th>Month</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
</tr>
</thead>
<tbody>
<tr>
<td>June</td>
<td>[Day</td>
<td>Day</td>
<td>24th</td>
<td>25th</td>
</tr>
</tbody>
</table>

*Patient must receive 18 DOT doses for the continuation phase of treatment.

Total no. doses taken this month: [ ]
No. doses taken for continuation phase including this month: [ ]
No. doses left for continuation phase: [ ]

---

**Continuation phase**

**Month 5**

*Date started: [ ]
Date finished: [ ]

**Study regimen 2**

2EMRZ/4P+M 1

**RIFAQUIN**

An international multicentre controlled clinical trial to evaluate high dose rifapentine and a quinolone in the treatment of pulmonary tuberculosis.

---

**MEDICATION**

<table>
<thead>
<tr>
<th>Number of tablets to be taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>800mg/day</td>
</tr>
</tbody>
</table>

**Number of tablets to be taken**

<table>
<thead>
<tr>
<th>Number of tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>800mg/day</td>
</tr>
</tbody>
</table>

**RIFAQUIN contact number:**

---

Remember - TB can be cured!

Please hand in this card at your next visit and select a new one.

After this month, you will only have 1 month of treatment left.

**RIFAQUIN contact:**

---

**STUDY NO:**

**PATIENT INITIALS:**

**SEX:** M [ ] F [ ]

**BASELINE WEIGHT:**

**Kg**
Moxifloxacin (M) (weekly)  Rifapentine (P) (weekly)

<table>
<thead>
<tr>
<th>Mg</th>
<th>No. tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C= Clinic staff  N= Not taken  T= Taken, not observed  U= Unknown

<table>
<thead>
<tr>
<th>Month</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For example:

<table>
<thead>
<tr>
<th>Month</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
</tr>
</thead>
<tbody>
<tr>
<td>June</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patient must receive 18 DOT doses for the continuation phase of treatment.

Total no. doses taken this month:  
Total no. doses given in continuation phase:  

---

**Continuation phase**

**Month 6**

Date started:  
Date finished:  

**Study regimen 2**

2EMRZ/4P+M_{1}

---

**RIFAQUIN**

An international multicentre controlled clinical trial to evaluate high dose rifapentine and a quinolone in the treatment of pulmonary tuberculosis.

---

**Remember - TB can be cured!**

This is your last month of treatment!

**RIFAQUIN contact:**

**MEDICATION**

Number of tablets to be taken:

- Rifampicin (600mg)
- Moxifloxacin (400mg)

---

**STUDY NO:**

**PATIENT INITIALS:**

**SEX:** M □ F □

**BASELINE WEIGHT:** □□□□ Kg