



**An international multi-centre
controlled clinical trial to evaluate high
dose rifapentine and a quinolone in the
treatment of pulmonary tuberculosis
(RIFAQUIN)**

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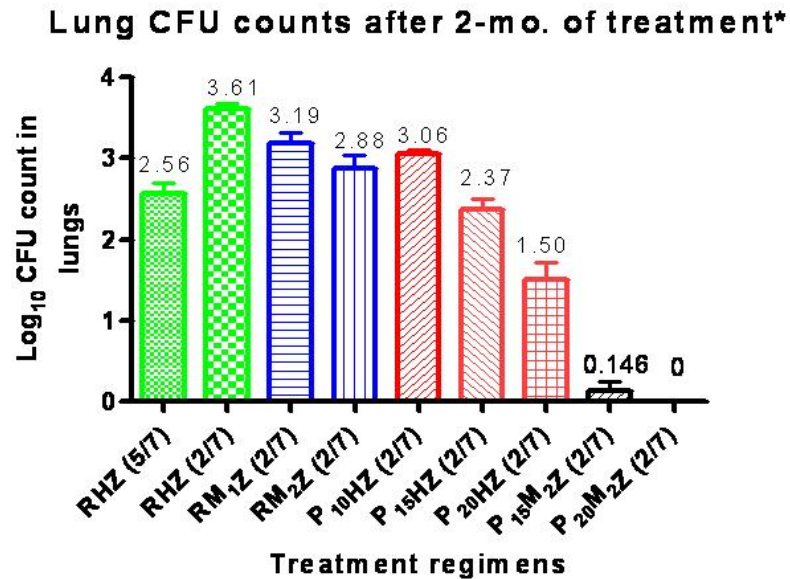
Background

- Rifapentine has a long half life but three trials with once weekly dosing with isoniazid showed it to be sub-optimal in efficacy in the treatment of patients with fully sensitive organisms (9%-12% failure/relapse rates).
- 4 of 5 HIV-infected patients who relapsed in the TBTC study developed rifamycin mono-resistance.
- Increased dose sizes of rifapentine have been proposed as a solution to both of these limitations.

The mouse data

A mouse study of twice weekly rifapentine showed remarkable sterilising activity with increasing dose size of rifapentine dose from 10 mg/kg (equivalent to 600 mg dose in patients of 60 kg) to 15 mg/kg and to 20 mg/kg¹.

When 20 mg/kg rifapentine (P), (equivalent to 1200 mg dose in patients of 60 kg) was given with moxifloxacin and pyrazinamide no bacilli were recovered after only 2 months.



¹ Rosenthal et al (2006)

- Could moxifloxacin be a more effective companion drug to rifapentine than isoniazid in the continuation phase of once weekly-treatment?

Trial design

- Under RCT conditions standard treatment, 2EHRZ/4HR, is highly effective, 95%+.
- It is unrealistic and inappropriate to consider a design in which a new regimen might be more effective.
- An appropriate goal would be a ***simpler, shorter or safer*** regimen.

E ethambutol, H isoniazid, R rifampicin, Z pyrazinamide

Trial Design

RIFAQUIN is multi-centre RCT of **non-inferiority design** comparing:

- 2EMRZ/2M₂P₂, and
 - 2EMRZ/4M₁P₁
- with the standard control regimen
2EHRZ/4HR

in newly diagnosed, previously untreated patients with fully sensitive organisms

E ethambutol, H isoniazid, M moxifloxacin, R rifampicin,
P rifapentine, Z pyrazinamide

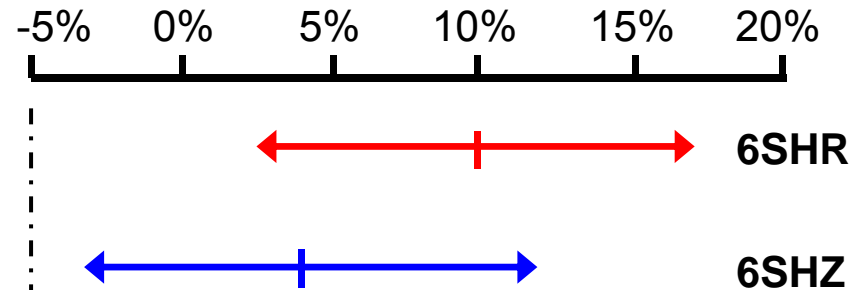
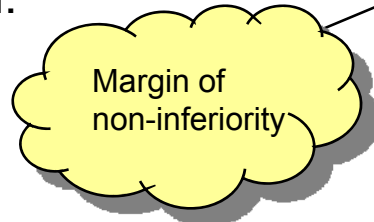
Hypotheses

1. The 4-month rifapentine twice weekly regimen is **not inferior** to the standard control regimen.
2. The 6-month rifapentine once weekly regimen is **not inferior** to the standard control regimen.
3. HIV co-infected patients who relapse **do not** have an increased risk of developing rifampicin resistance if allocated to a rifapentine containing regimen.

Non-inferiority analysis of 1st EA short course

Difference in success rate from 2STH/16/TH

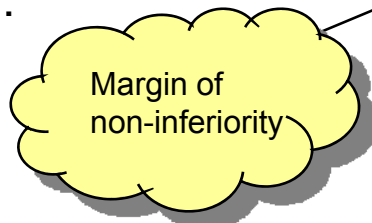
The results analysed on the **modified ITT** population suggest that both the 6SHR and 6SHZ regimen are not inferior to the 2STH/16TH control.



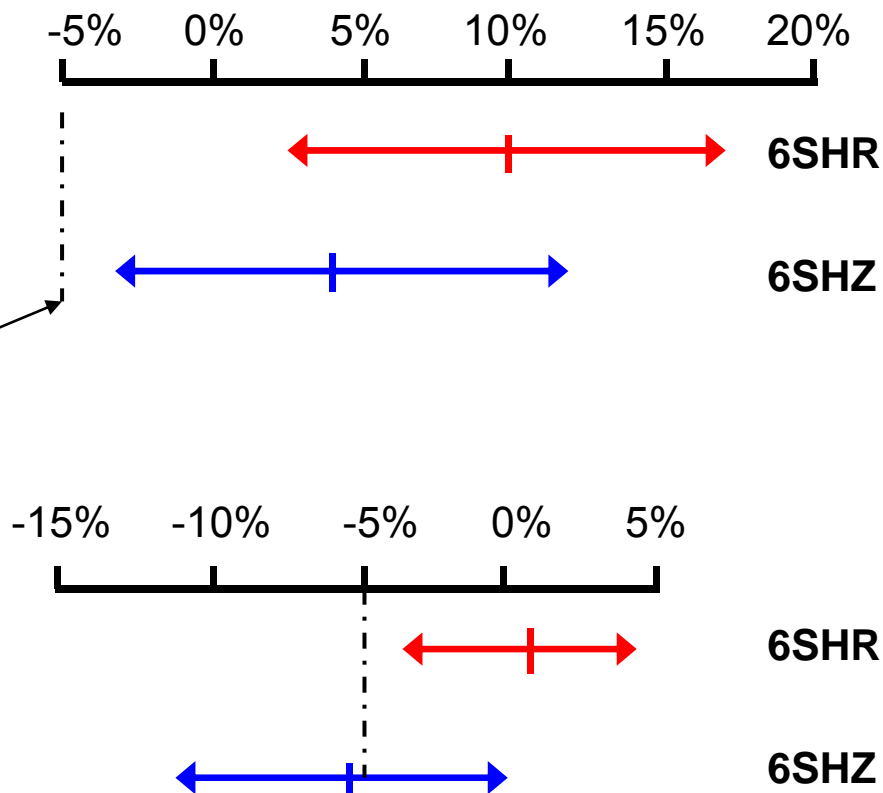
Non-inferiority analysis of 1st EA short course

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In contrast the **per protocol** results show 6SHZ to be significantly *inferior* to the control; 6SHR is no longer significantly superior but remains non-inferior.



Determining non-inferiority

- In contrast to superiority trials the intention to treat (ITT) population is not the most appropriate group of patients for analysing non-inferiority trials because it tends to minimise differences between treatment arms, thereby increasing the possibility of declaring non-inferiority.
- In line with current CPMP guidance RIFAQUIN will be analysed both by ITT and per protocol.

Committee on Proprietary Medical Products

Choosing the margin of non-inferiority

Estimates of relapse (%) based on historical data in trials conducted by the BMRC:

- Control 2EHRZ/4HR regimen 2.7% (1.8%, 3.9%)*
- Control regimen given for 4m 11.8% (8.9%, 15.6%)
(some regimens used streptomycin in place of ethambutol)

* adjusting for trial differences using multilevel mixed-effects logistic regression

Based on the above and following discussions with physicians the margin of non-inferiority employed in RIFAQUIN is the same as that in REMox, i.e. 6%

Sample size assumptions

- A conservative definition of unfavourable outcome, namely all deaths and losses to follow-up during treatment considered to have an unfavourable outcome
- Overall unfavourable outcome 10% in the control arm.
- 15% unassessable due to late exclusions (culture negative or drug resistant) and loss to follow-up after completion of treatment.
- 80% power
- One sided 90% confidence interval.
- Margin of non-inferiority, δ , of 6%.

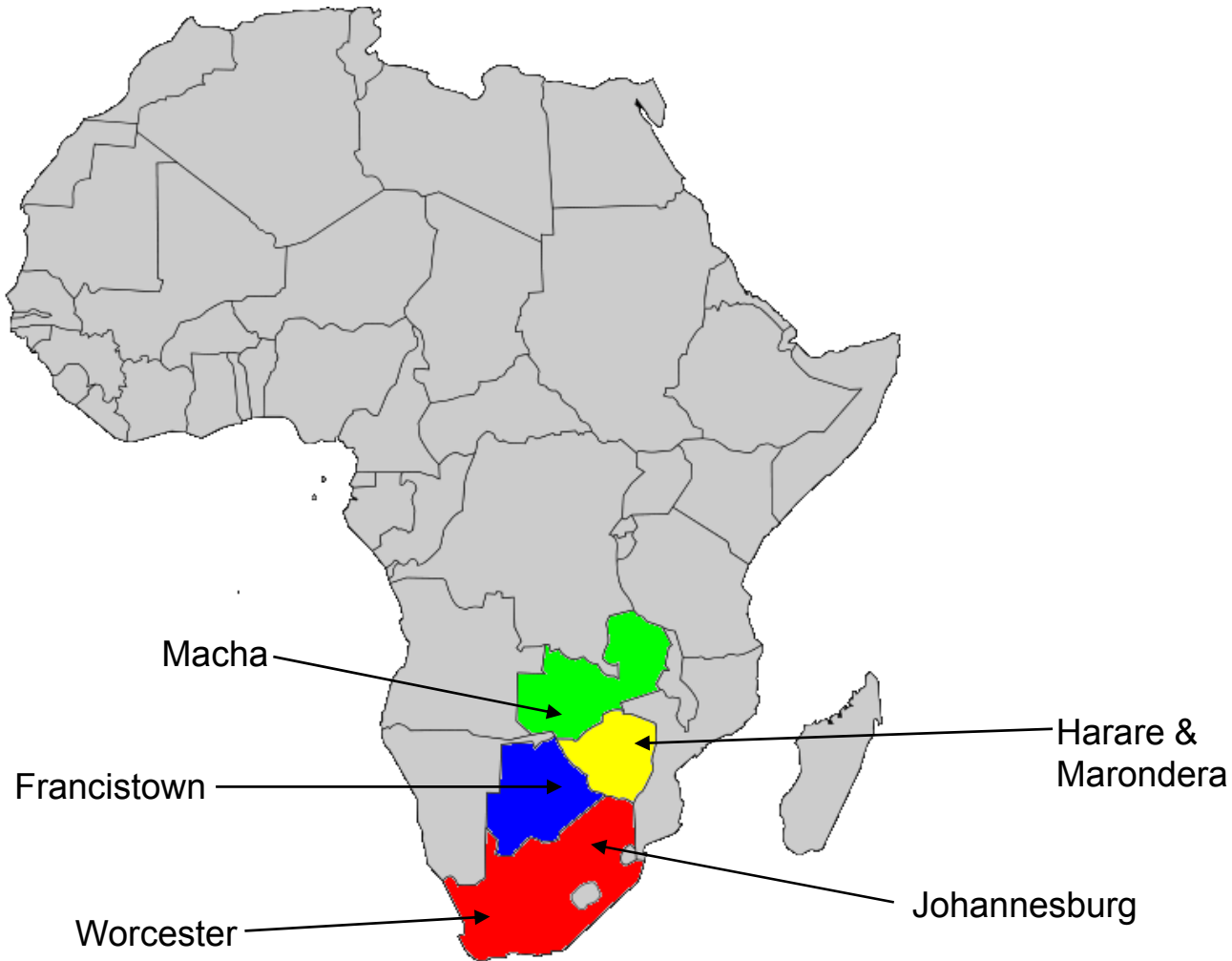
Sample size 365/arm, 1095 total.

Primary endpoints

RIFAQUIN has three primary endpoints:

- Failure during treatment or relapse by 18 months after starting.
- Sensitivity of relapse strains in HIV-infected patients receiving intermittent rifapentine.
- Grade 3 or 4 adverse events

RIFAQUIN sites



Number of patients enrolled to date

(3rd October 2009)

Harare	68
Johannesburg	71
Macha	9
Marondera	31
Worcester	58
<hr/>	
Total	227

- Francistown awaiting approvals
- 35% of patients enrolled to date are HIV-infected

Screening failures

Of the first 85 screening failures:

- 62 were HIV-infected with CD4 < 200/mm³
- 6 were on account of laboratory abnormalities
- 3 were pregnant or breastfeeding

Problems encountered

- Start-up was considerably delayed because of the prolonged time it took to obtain regulatory approval; this was particularly acute in South Africa and Zimbabwe.
- The exclusion of patients with low CD4 counts has considerably reduced the number of eligible patients available and reduced the numbers available for assessment of the second primary endpoint.

South Africa regulatory approval process

- March 2007 protocol submitted
- September 2007 supplementary data requested
- February 2008 final approval
- August 2008 recruitment began

Similar problems were experienced in Zimbabwe

PK studies

(University of Cape Town)

- **Population study:** 400 participants in the two experimental arms of the study in Worcester, Johannesburg and Harare will be sampled during a dose interval in the 4th month of treatment
- **Interaction study:** 30 patients from the Worcester site will be studied to determine whether a pharmacokinetic drug-drug interaction between moxifloxacin and rifapentine significantly affects the levels of moxifloxacin when they are given together.

Other trials in progress

- **OFLOTUB** is a non-inferiority trial assessing a 4-month gatifloxacin regimen compared to the standard control.
- **REMOx TB** is a non-inferiority trial assessing two 4-month moxifloxacin regimens, substituting moxifloxacin for either ethambutol or isoniazid in comparison with the standard control.

RIFAQUIN Investigators

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Thanks

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Thank you!