



European
Commission



Report from the OFLOTUB Consortium on Gatifloxacin for TB treatment development

Christian Lienhardt
Institut de Recherche pour le Développement (IRD)
Paris

Rationale

- despite a treatment of proven efficacy, TB rates continue to increase in resource-poor countries
 - persistence of high treatment default rates
 - spread of multi-drug resistance
 - high impact of HIV infection
-
- improve access to and delivery of treatment
 - decrease duration of treatment
 - new drugs
 - new combinations of drugs

Ofloxacin

- Proven bactericidal activity against *M. tuberculosis* (Garcia–Rodrigues 1993, Gillespie 1998)
- rapidly absorbed
- high concentrations in respiratory cells, secretions and macrophages
- low cost, included in the WHO essential drug list
- several clinical trials (Tsukamura 1986, Hong Kong Chest Service/MRC 1992)

Ofloxacin

- TRC trial - Chennai: potential for ofloxacin-based shortened regimens (TRC, *Ind J Tub* 2002)

<i>Protocols</i>	<i>% smear conversion</i>	<i>% outcome</i>			<i>% relapse</i>
		<i>Fav.</i>	<i>Doubt.</i>	<i>Unfav.</i>	
	<i>at two months</i>				
3OHRZ	92 to 98 %	90.1	6.6	3.3	8
3OHRZ/ 1RH2		88.6	6.2	5.2	4
3OHRZ/ 2RH2		93.2	2.5	4.3	2
2 OHRZ/2RH2		95.6	1.7	2.7	13

Gatifloxacin

- 8-methoxy-fluoroquinolone active against Gram + and Gram - organisms
- used for the treatment of commune infections (pneumonia, acute bronchitis, sinusitis, skin infections, UTIs and STDs)
- *in vitro* and *in vivo* experiments:
 - more active than ofloxacin against susceptible and resistant M.tb isolates
 - anti-TB activity similar to moxifloxacin (Tomioka 2002; Alvirez-Freites 2002)
- cheaper to manufacture than moxifloxacin
- generic production (low cost)

Gatifloxacin

- free of many of the class effects of quinolone antibiotics (eg. phototoxicity)
- potential cardiotoxicity (QT enlargement), although of minor degree compared to other fluoroquinolone compounds (class effect)
- reported early effect on glucose homeostasis with potentially severe hypo- or hyperglycemia

*Towards a combined gatifloxacin-
containing 4-month duration regimen for
the treatment of TB (WHO-TDR Product
development plan*

Development Workplan:

1. Phase I Toxicology and Pharmacokinetic studies
2. Phase II Trial
3. Phase III RCT

Phase II Trial

Serial Sputum Colony Counts (SSCC) study to assess the sterilizing activity of a gatifloxacin-containing regimen compared with other FQ-containing regimens in TB patients over the initial 2 months intensive treatment phase

Design

- Open label Phase II Randomised Controlled Trial

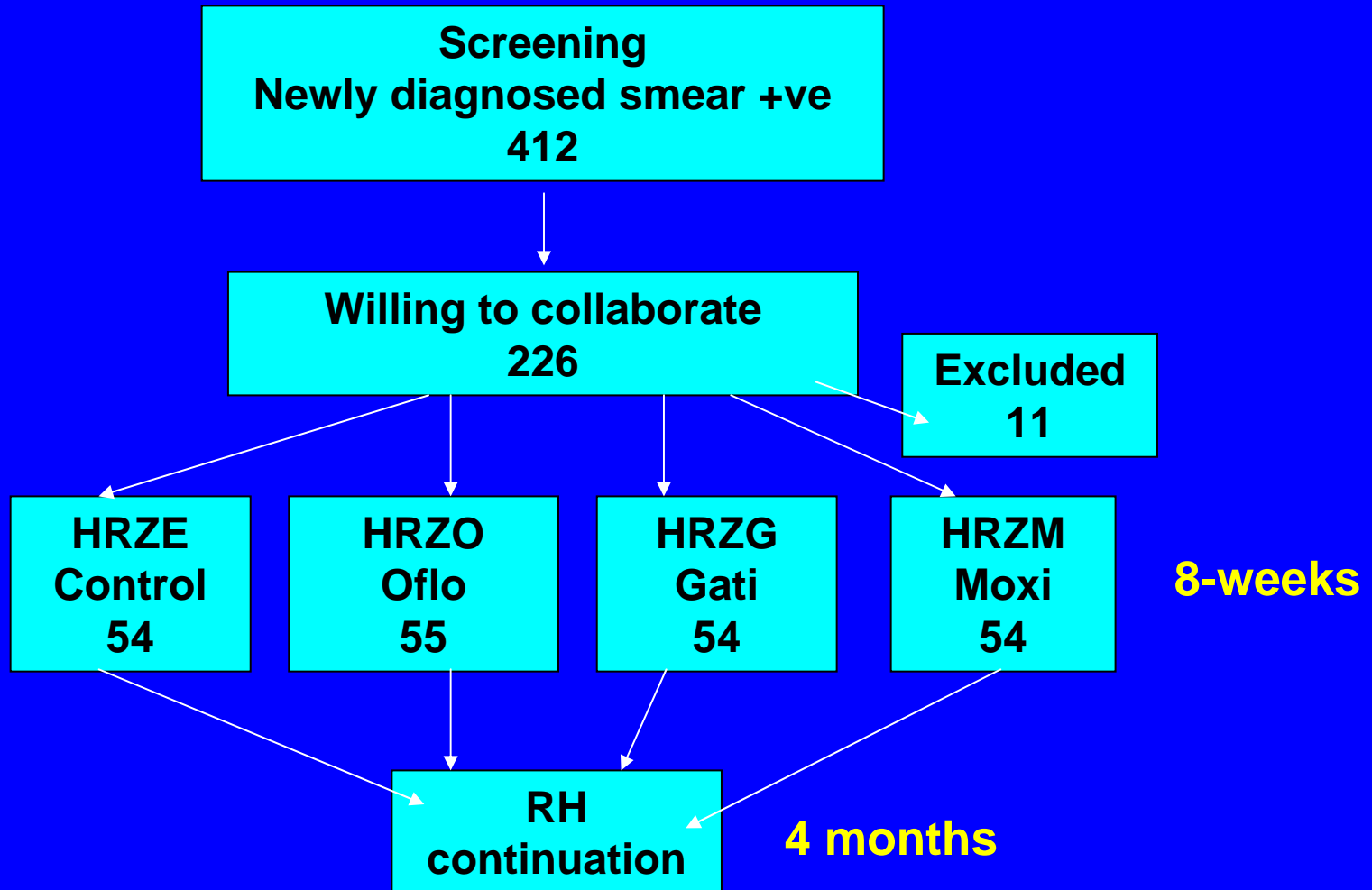
Aims

- Compare three fluoroquinolones substituted for ethambutol in 2HRZE initial phases using serial sputum colony counting (SSCC)

Methods

- Four-arms trial
- Regimens under study
 - 2 months HRZO (Ofloxacin)
 - 2 months HRZM (Moxiflocacin)
 - 2 months HRZG (Gatifloxacin)
 - 2 months HRZE (Ethambutol - control)
- After 8 weeks, all patients shifted to 4 months of RH according to standard practice

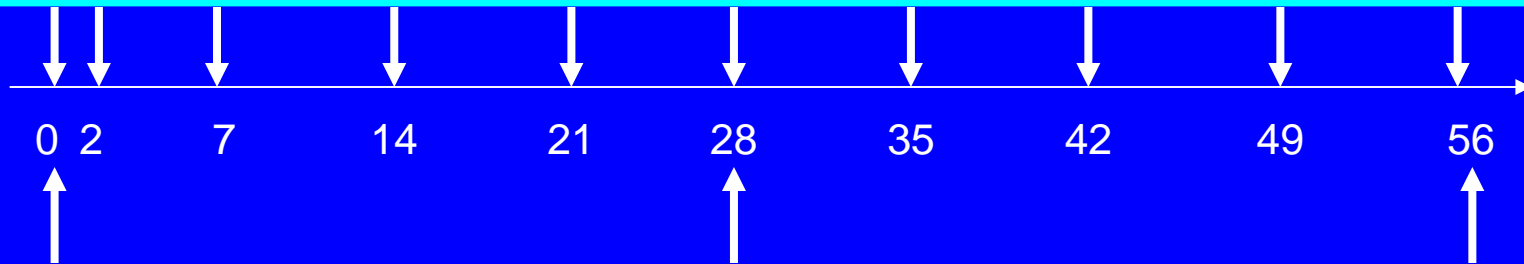
Summary of recruitment



Comparative bactericidal assessments

14 hour sputum collection

Sputum colony counts on selective 7H11 medium without decontamination at 10 time points during initial 8-week phase

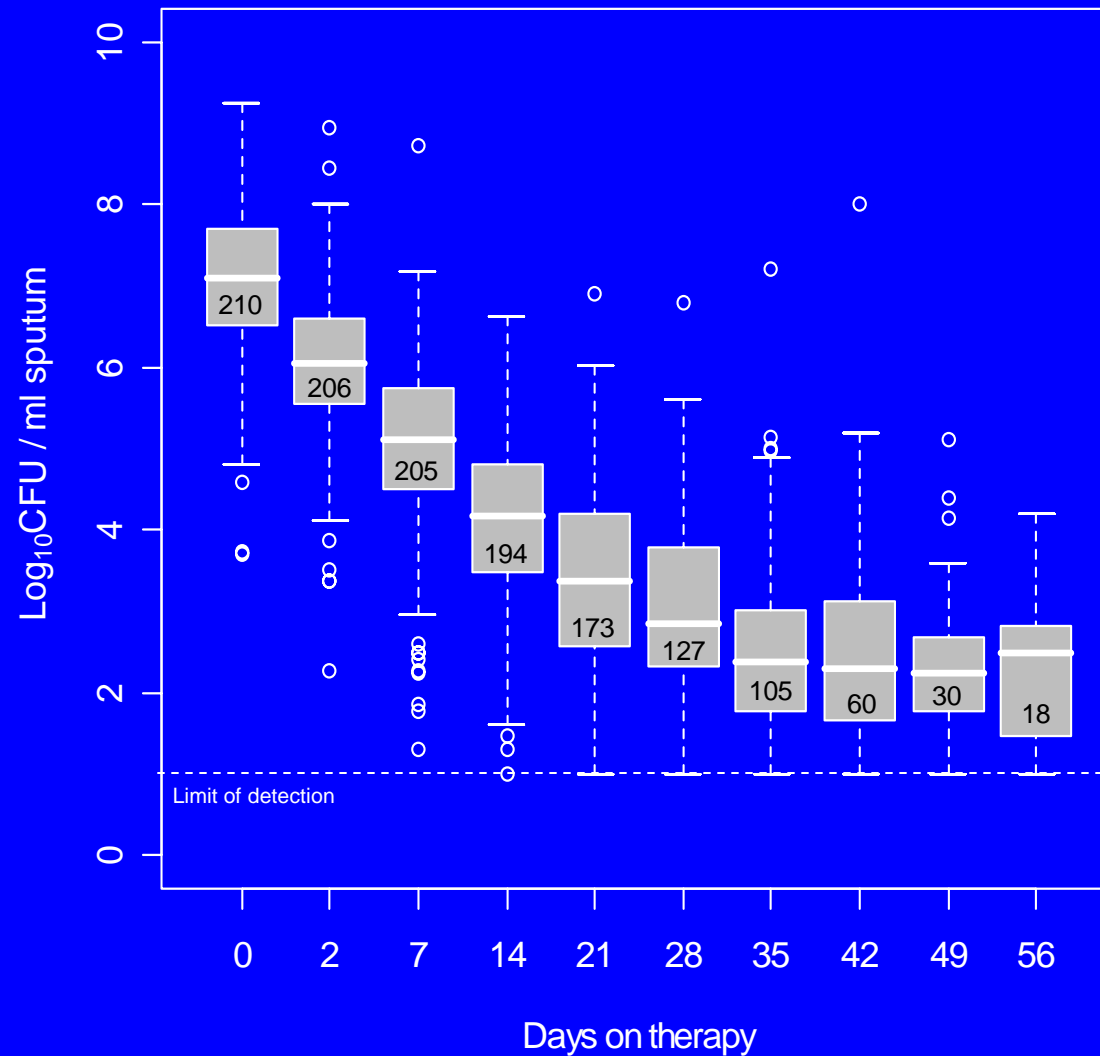


Standard 7H11 culture + indirect susceptibility tests

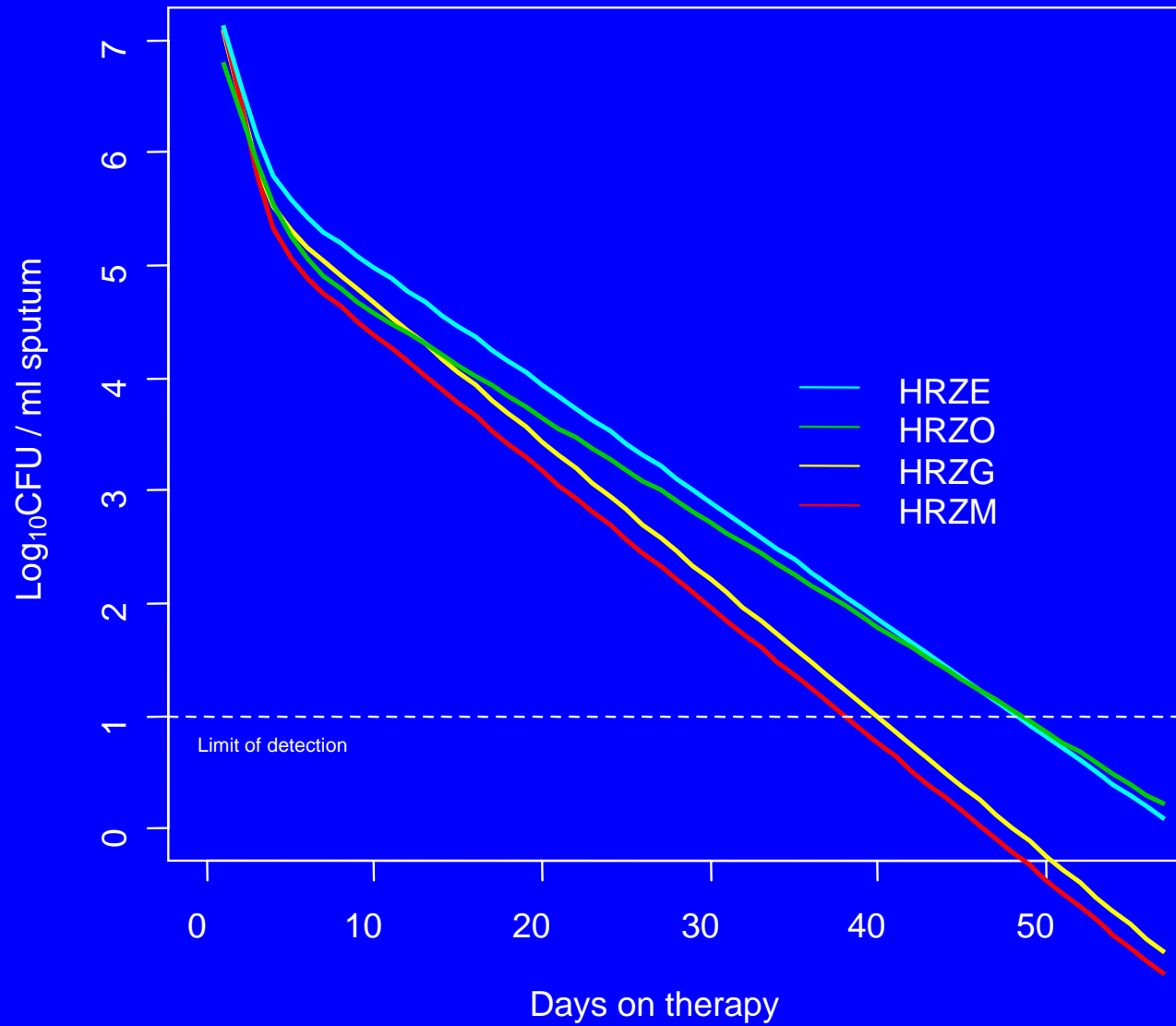
Standard 7H11 culture

Standard 7H11 culture + Liquid culture (MGIT)

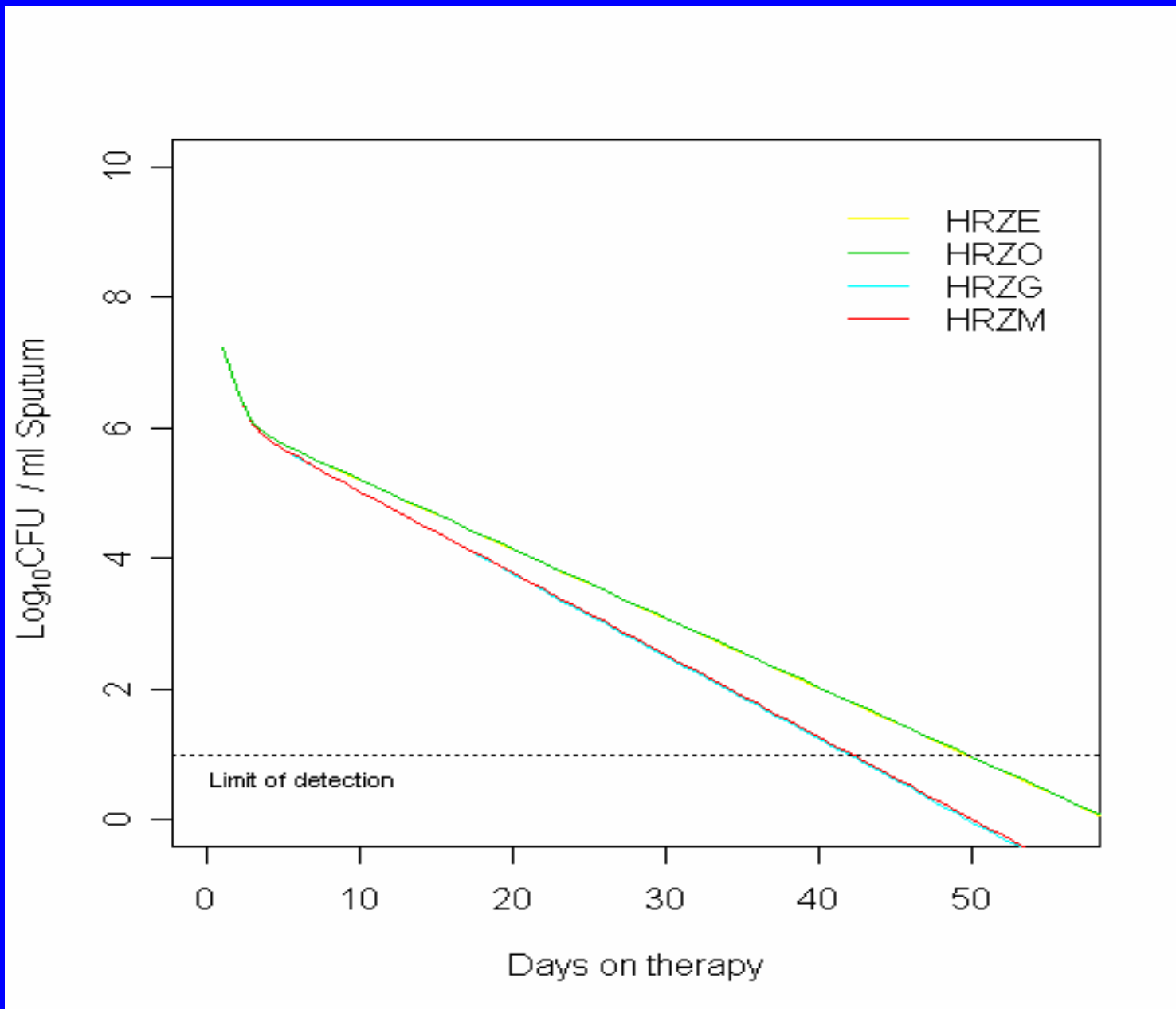
Summary of SSCC results



Estimated treatment effects



Estimated treatment effects after adjustment on age, sex, HIV and CXR extent of disease



Conclusions

- When substituted for Ethambutol, both Moxifloxacin and Gatifloxacin killed significantly faster and at equal rates in the early and late phases than control
- Ofloxacin substitution had no significant effect
- The observed increases in late phase killing with these regimens support a probable reduction in the duration of therapy of at least one month
- SSCC modelling could be the basis of future phase II studies aiming at evaluating new regimens suggested by mouse studies.

Phase III RCT

Phase III Multicentre open-label Randomised
Controlled Trial of a 4-month Gatifloxacin-
containing Short-Course regimen vs Standard
6-month regimen for the treatment of
Pulmonary Tuberculosis

Methods

- Open-label Randomised Controlled Trial
- Non-inferiority
- Treatments :
 - test: 2 months GHRZ / 2 months GHR
 - control: 2 months EHRZ / 4 months RH
- Sample size: 1035 patients/arm
- Followed-up for 2 years after completion of treatment

Randomisation

- randomisation lists, stratified per centre
- individual codes sent to the trial centres in sealed envelopes
- patients and investigators not blind
- microbiology laboratories blind of the origin of sputa

OFLOTUB sites



Recruitment

Inclusion criteria:

patients aged 18 to 65 years, suffering from a recently diagnosed pulmonary tuberculosis and giving informed consent

Recruitment

Exclusion criteria:

- History of TB within the last 3 years
- Concomitant infection requiring additional anti-infectious treatment (including ARV therapy)
- HIV infected patients at WHO stages 3 and 4
- ID or NID diabetes mellitus requiring treatment
- Fasting glycemia > 1.26 g/l (= 6,93 mmol/L)
- Impaired renal or hepatic function
- History of drug hypersensitivity and/or active allergic disease
- Pregnant or lactating women
- Patients with congenital QT interval prolongation > 480 ms
- Patients with significant bradycardia (≤ 40 /mn)

Initial Examination

- Pre-screening of MDR-TB (MGIT)
- Complete clinical examination
- Sputum samples for smear, culture and drug sensitivity test
- CXR
- Blood collection (FBC, fasting glycaemia, LFT, iron, HIV serology, etc)
- ECG
- Urinary pregnancy test
- Sign informed consent

Treatment Phase

- Initial Phase (2 mths): daily drug intake (DOT)
- Continuation phase: weekly delivery
- Regular monthly follow-up visit to assess :
 - observance
 - clinical aspects
 - microbiology tests
 - adverse events
- Check presence of potential AEs/SAEs at each contact with health services

Follow-up after treatment

- patients seen at 1, 2, 4, 6, 9, 12, 15, 18 and 24 months after treatment
- regular clinical examination
- sputum samples collected for smear and culture
- DST if culture positive

End-points

Efficacy:

- Primary outcome:

- Percent relapses at 24 months

- Secondary outcome:

- Time to relapse, defined from the date of treatment cure to date of relapse
- Percent culture conversion at 8 weeks
- Percent patients cured in each arm by the end of treatment
- Time to a composite (unsatisfactory) endpoint of treatment failure/relapse

End-points

Safety:

- *Primary outcome:* percent adverse events in each arm
- *Secondary outcome:* distribution of type and grade of adverse events

Status of recruitment (Nov. 06)

- Phased recruitment - started June 2005

– Benin:	210	patients
– Guinee:	220	"
– Kenya:	94	"
– Senegal:	130	"
– Sth Africa:	305	"
– Total:	959	patients

Problems

- Reported increased risk of hypoglycemia with gatifloxacin as compared to other FQ (aOR: 4.4, 95%CI 2.9 – 6.3) (Park-Wyllie, NEJM 2006)
- overall rate of dysglycaemia (hypo and hyperglycaemia) associated with gatifloxacin : 1.10% ;
- medium age of patients : 78 years
- gatifloxacin related hypoglycaemia overwhelmingly found in diabetic patients (57/61)
- Change in drug label by BMS in Febr 2006 : diabetes is a formal contra-indication for prescription of gatifloxacin
- Return of license from BMS to Kyorin (April 2006)

Problems

- *Strengthened exclusion criteria and glycemia monitoring within the trial:*
 - Exclusion of patients with fasting glucose test (finger-prick) values outside the range 70-115 mg/dl (3.9 – 6.4 mmol/l)
 - Enhanced glycemia monitoring (FGT) during the first 2 months of treatment (0, 0+4h, 8, 15, 28, 56) + questions on signs and symptoms of hypo/hyperglycaemia

All modifications discussed with and agreed by the trial DMC, and amendments re-submitted to IRBs/IECs

MCC audited SA clinical site, reviewed information and recommended trial continuation

Thanks to the partners involved in the project

The **OFLOTUB** Consortium :

- Hopital Ignace Deen, Conakry, Guinée : O. Bah-Sow, M. Diallo, B. Bah, MT Barry
- Institute of Tropical Medicine, Belgium: F. Portaels, A. Martin, D. Affolabi
- IRD, Senegal: A. Ndiaye, JP. Nguessan, JF. Gomis
- KEMRI, Kenya: J. Odhiambo, E. Amukoye, W. Githui
- LSHTM, London, UK: K. Fielding, B. Sismanidis, C. Merle
- MRC, South Africa : R. Rustomjee, J. Allen, T. Mthiyani
- Programme National de lutte anti-TB, Benin: M. Gninafon, F. Kassa, G. Monteiro
- Programme National de lutte anti-TB, Senegal: H. Diop, N. Konate
- St George's Hospital Medical School, London, UK: D. Mitchison
- Hôpital de Garches, France: C. Perronne

European Commission: A. Hoeveler; H. Laang

WHO/TDR : T. Kanyok, J. Horton, O. Lapujade, J. Karbwang

Lupin Pharmaceuticals Ltd, India: H. Sen