



European
Commission



Report from the OFLOTUB Consortium on gatifloxacin for TB treatment development

Second Open Forum on Key Issues in
TB Drug Development

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

Gatifloxacin

- 8-methoxy-fluoroquinolone active against Gram + and Gram - organisms
- more active than ofloxacin against susceptible and resistant *M.tb* isolates *in vitro* and *in vivo*
- anti-TB activity similar to moxifloxacin
- free of many of the class effects of quinolone antibiotics (eg. phototoxicity)
- potential cardiotoxicity (QT enlargement)
- reported early effect on glucose homeostasis with potentially severe hypo- or hyperglycaemia
- generic production (low cost)

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
- Follow-up: 2 years after completion of treatment

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 <70 mg/dl (3.9 mmol/l) or >115 mg/dl (6.4 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 or with significant bradycardia (≤ 40 /mn)

Treatment Phase

- Initial Phase (2 mths): daily drug intake (DOT)
- Continuation phase: weekly delivery
- Regular monthly follow-up visit to assess :
 - side effects
 - 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
- DNA finger-print of failure/relapse samples

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
 - 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 glycaemia 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 month of treatment (0, 0+4h, 8, 15, 28 days), then monthly till the end of treatment (M 2, 3, and 4)
 - questions on signs and symptoms of hypo/hyperglycaemia at each visit

*All modifications discussed with and agreed
by the trial DMC*

All amendments submitted to IRB/IECs

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

- Submission of a pre-IND application to FDA(08/06)
- Dialogue meeting Nov 2006

Partners involved in the project

- 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, C. 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
- Hopital de Garches, France: C. Perronne

- WHO/TDR : T. Kanyok, J. Horton, O. Lapujade, J. Karbwang
- Lupin Pharmaceuticals Ltd, India: H. Sen
- European Commission: A. Hoeveler; H. Laang