EU guidance on the clinical development of new agents for the treatment of tuberculosis
Progress in developing guidance

• Developed as an addendum to the existing antibacterials guideline

• First draft reviewed at Anti-Infectives Drafting Group meeting November 2007

• Focus on two major areas of investigation:
  - Shortened treatment of S MTb
  - Treatment of MDR/XDR MTb
Progress in developing guidance

• Second draft reviewed at SAG meeting February 2008

• Revision post-SAG considered at EWP April 2008

• Forwarded to CHMP for adoption April 2008

• Released for consultation until October 2008
Focus of the addendum

- The use of new agents in shortened combination regimens for the treatment of disease due to *M. tuberculosis* that is susceptible to first-line therapies

- The use of new agents to treat disease due to multi-drug-resistant (MDR-TB) and extensively resistant (XDR-TB) *M. tuberculosis*

- Relevance to other development scenarios
Scope

- Evaluation of a single new agent within regimens that contain licensed anti-tuberculosis agents
- Combination regimens to comprise at least three potentially active agents for a defined initial period of therapy
- New agent may be given throughout the treatment course or stopped after a specified period while others continue
- Cannot extrapolate efficacy against susceptible *M. tuberculosis* to the treatment of MDR-TB or XDR-TB or vice versa
- Sequential studies in special patient populations
Non-clinical studies

• In-vitro activity against *M. tuberculosis*

• Safety and efficacy in animal models

• Contribution of the new agent to the antibacterial activity and efficacy of test combination regimen(s)

• Identify potentially effective dose regimen(s) to be evaluated in clinical studies
Non-clinical studies

• Caution is needed - conflicting results possible

• No perfect animal model for predicting clinical efficacy

• Animal models may not give unequivocal results

• PK/PD – less advanced compared to other antibacterial uses but use is encouraged
Patients

Evidence of pulmonary tuberculosis before randomisation (+ smear and/or + culture)

Patients who also have evidence of extra-pulmonary disease can be enrolled unless they might need a special regimen (e.g. CNS disease, possibly osteomyelitis)

Analyse:
- Patients with a positive culture of *M. tuberculosis* obtained from a suitable respiratory tract specimen obtained pre-study
- All randomised patients
Patients with susceptible MTb

Eligible for enrolment based on a positive smear performed on a suitable respiratory tract specimen

May be randomised before the results of culture and susceptibility testing available if considered likely to be infected with susceptible *M. tuberculosis* after taking into account factors such as:

- Any past exposure to antibacterial agents that have activity against *M. tuberculosis*, whether or not administered for the treatment of tuberculosis
- The time elapsed since any such treatment was given
- Place of residence
- Contact history
- Rapid tests to differentiate species and/or detect drug resistance
Patients with MDR or XDR-TB

It is anticipated that in most cases susceptibility test results will already be available for the organisms causing pulmonary tuberculosis in these patients. This would make it possible to enrol specific populations from the outset and is the preferred approach since it facilitates the study designs suggested.
Primary endpoint

Rate of cure of pulmonary tuberculosis
[ Negative cultures obtained at some time during and up to end of therapy with no relapse detected during a post-therapy follow-up period of 24 months ]

Alternative primary endpoints need justification

Regardless of the pre-defined primary endpoint all clinical studies that evaluate efficacy should follow up patients for at least 24 months post-therapy
Secondary endpoints

Secondary endpoints may include mycobacterial and/or host biomarkers of treatment response.

All the existing biomarkers have several shortcomings and none has been formally demonstrated to predict 2-year post-therapy relapse rates.

Biomarker endpoints that may be used are listed and each is discussed.
Secondary endpoints

- EBA
- Sputum culture conversion at month 2 of therapy
- Culture conversion at the end of therapy and/or time to culture conversion
- Serial sputum colony counting (SSCC)
- Mortality at 4 or 6 months
- Other host factors
Exploratory investigation of efficacy

These investigations could be performed:

• In exploratory studies specifically designed for the purpose of identifying regimens for further evaluation

and/or

• During confirmatory studies
Exploratory investigation of efficacy

Assess contribution to a combination regimen

EBA associated with short-term monotherapy with several dose regimens of the new agent compared with one standard regimen of licensed agents that includes the rapidly bactericidal agent isoniazid

EBA and other biomarker data for combination regimens with and without addition of the new agent

• Patients with susceptible *M. tuberculosis* could receive a standard regimen with or without the new agent
• Patients with MDR-TB or XDR-TB should receive individually tailored OBT with or without the new agent
Exploratory investigation of efficacy

Identify regimen(s) for further evaluation

• Biomarker data after 2-4 months in exploratory studies
  OR
• Proceed directly to confirmatory studies

Results of an interim analysis could be used to:
• Make a decision regarding regimen selection
• Indicate the need to discontinue a treatment arm

• CHMP Reflection Paper on methodological issues in confirmatory clinical trials planned with an adaptive design (CHMP/EWP/2459/02) offers relevant guidance
Confirmatory studies – short regimens for susceptible MTb

Addition of the new agent to a standard regimen
Or
Replacement of one of the agents in a standard regimen

Compare the test combination regimen(s) administered for a pre-defined period to the standard regimen
Double-blind design should be feasible
Confirmatory studies – short regimens for susceptible MTb

Non-inferiority w.r.t. cure rates at 24 months post-therapy

May be justifiable to base the primary analysis of efficacy on non-inferiority w.r.t. relapse rates within first 6 months post-therapy (e.g. at 4 months)

• Earlier MAA
• Possibly conditional approval

[Still follow for relapses up to 24 months post-therapy]
Confirmatory studies
MDR–TB and XDR-TB

MTb S to \( \geq 3 \) licensed agents

Randomise to new agent or placebo (DB) together with three licensed agents [OBT] (open label)

Demonstrate superiority of the new agent + OBT over placebo + OBT for cure rates at 24 months post-therapy

Initial MAA might be based on specific benefits over placebo (e.g. reduced mortality at 4-6 months, % with negative smears and cultures at defined intervals)
Confirmatory studies
MDR–TB and XDR-TB

MTb S to ≤ 3 three licensed treatments

Identify those not in urgent need of new agent + compare
  • new agent + OBT from the outset with
  • placebo + OBT before switching to new agent + OBT at set time point

Comparison of biomarker/clinical data before switching

Additional open label non-comparative treatment arm of DB study and analyse separately and descriptively
Safety

• S MTb - overlap between test and control regimens may allow some identification of ADRs to new agent

• In studies in patients with MDR-TB or XDR-TB the interpretation of the safety data becomes much more complex due to the variable content of the OBT

• Exploratory analyses of safety based on comparisons between patients that did and did not receive specific co-administered agents may be informative
Safety

• If different durations compared might identify ADRs that tend to occur early or late during therapy

• RMP should describe the limitations of the safety database, take into account the non-clinical data and any drug class-related information of relevance

• RMP should include a plan for at least one prospective post-approval study of safety
Children

- Adolescents - limited and non-comparative PK, safety and efficacy data may be acceptable

- Children aged < 13 years - extrapolate safety and efficacy data obtained in adults to children provided that age-specific dose regimens can be identified

- Obtain PK and safety data during therapy for TB diagnosed based on criteria of an internationally-recognised expert body and follow up for efficacy
HIV

Good viral and cellular response to HAART
- Could be included in clinical studies along with HIV-negative individuals
- Might pre-stratify
- Particular attention to risk of longer-term relapse rates

Low CD4 and/or failing HAART
- Different and/or longer duration combination regimens may be necessary and will require investigation
Predisposing therapy

• Drugs that may have predisposed to TB preferably stopped when the diagnosis is made

• May not always be possible to stop these treatments or they may have to be re-commenced during treatment of TB to manage the concomitant disease

• In either case it is likely that experience can be gathered only in relatively small numbers but accumulated data might be reflected in the labelling
Summary

• Draft guidance now in consultation phase

• Comments to be sent via the EMEA

• Further amendments when consultation completed

• Final adoption and release by CHMP end-2008

• Revisions as experience gained in future