Progress in the Development of EU Regulatory Guidance on the Clinical Development of New Agents for the treatment of Tuberculosis

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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*

• Guidance:
  - non clinical
  - clinical: (PK), safety/efficacy, patient selection/stratification
Non-clinical studies

- Caution! – conflicting results possible (*in-vitro/in-vivo*; pre-clinical /clinical)

- No perfect animal model predicting clinical efficacy

- PK/PD – less advanced compared to other antibacterial uses
In-vitro studies

- Characterisation of activity
  - Mode of action
  - mechanism resistance/ X-resistance
  - activity versus intracellular organisms

- Potential risk to select *M Tb* with reduced susceptibility

- (Synergism/antagonism?)
In-vivo studies

• Efficacy of test agent alone

• Contribution of test agent to efficacy of test combination regimen(s)

• Identify potentially effective dose regimens for further evaluation
  – Immunocompetent/immunodeficient models
  – Bactericidal activity/sterilising activity
Clinical evaluation – efficacy

General Approach

- no extrapolation S-TB/MDR-TB
- 2 randomised controlled studies *preferred*
- double-blind / DOT
- FU: 24 months
- alternative approaches → early discussion
Efficacy Endpoints

• Possible range, **pre-defined**
• Cure: Negative cultures at some time during and up to end of Rx; no relapse detected during FU of 24 months
• Primary Rx failure defined
• Relapse (typing!) as Rx failure
• Death
  – define what is counted as failure
  – determinant in MDR-TB
Other Endpoints

Other 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 as example:
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)
- Early mortality on Rx (e.g. at 4 or 6 months)
- Other host factors
Patient selection/Population

In general, specify:

• eligibility
  – + smear prior to randomisation
  – rapid screening test

• categorise isolates as S or R
  – accredited lab
  – confirm in centralised lab?

• minimum (clinical/lab/image) to assess extent

• sub-population for pre-stratification
Patients with susceptible MTb

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 drugs resistance

→ specify R-INH / S-RFP handled in analysis
Patients with MDR/XDR-MTb

Ideally – susceptibility test results available before enrolment

Eventually – “Run-in” period + testing
Children

- ≥ 10 years of age – included in adult studies; PK data to be obtained

- Efficacy trial unfeasible → justify extrapolation (for age group < 5 years more EP disease)
  - Age-specific dose regimens

- Diagnosis/Responses: Age specific criteria
Extrapulmonary disease

Patients with evidence of extra-pulmonary disease can be enrolled unless need of special regimen (e.g. CNS disease, osteomyelitis)

→ pre-stratified
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
Exploratory studies

- **In-vivo** effect of test agent
  - short-term (1-2 weeks) – EBA
  - if no anticipated high risk selection R/

- Assess contribution to combination regimen: EBA (other biomarker) data compared
  - S-TB patients could receive standard regimen +/- new agent
  - MDRTB/XDRTB patients receive tailored OBT +/- new agent

  ( <---> substitution studies)
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. primary failure + relapse + death rate (e.g. at 12 months FU)

• Earlier MAA
• Possible conditional approval

(Still follow for relapses up to 24 months post-therapy)
Confirmatory studies MDR-TB and XDR-TB

MTb S to $\geq$ predefined number of agents

Randomise to new agent or placebo (DB) together with individually OBT (open label)

Demonstrate superiority of new agent + OBT over placebo + OBT

- endpoint: scc + clinical
- predefined timing

Serial assessment of cure rates up to 24 months
Confirmatory studies MDR-TB and XDR-TB

MTb S to < predefined number of agents

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 date 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
- Consideration to at least one specific safety study