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*Pre-Authorisation Evaluation of Medicines for Human Use*

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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)**

**DRAFT**

# ADDENDUM TO THE NOTE FOR GUIDANCE ON EVALUATION OF MEDICINAL PRODUCTS INDICATED FOR TREATMENT OF BACTERIAL INFECTIONS

# TO SPECIFICALLY ADDRESS THE CLINICAL DEVELOPMENT OF NEW AGENTS TO TREAT DISEASE DUE TO MYCOBACTERIUM TUBERCULOSIS

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## EXECUTIVE SUMMARY

This addendum to the *Note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections* (CHMP/EWP 558/95 Rev 1) has been produced in response to recent advances in the development of new agents intended for the treatment of clinically apparent disease due to *Mycobacterium tuberculosis*. The preparation of specific guidance to be included in an addendum was considered to be appropriate due to the differences in approaches to treatment of tuberculosis compared with almost all other types of bacterial infections.

The overall content of the clinical development programme, including the patient populations selected for study, will need to be tailored according to the properties of each new agent intended for the treatment of tuberculosis. This addendum focuses on two modes of use of new agents that seem to be at the forefront of current clinical development programmes. These are:

- 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.*

Examples of other types of clinical development programmes include the evaluation of new agents expected to have an improved safety profile and/or a lesser potential for drug-drug interactions compared to available agents. These anticipated benefits might occur with or without the possibility of shortening the overall duration of therapy and/or demonstrating activity against MDR-TB and XDR-TB. Much of the guidance provided in this addendum would be generally applicable to these scenarios but sponsors may wish to obtain specific advice from EU Regulators on a case by case basis.

*In vitro* and *in vivo* non-clinical studies can be used to assess the potential efficacy of new agents in various dose and combination regimens and provide some indication of the need for and extent of exploratory clinical studies to be performed before selecting a regimen or small number of regimens to be evaluated in confirmatory studies of efficacy.

In exploratory clinical investigations of efficacy the selection of regimens for further study may be based on biomarkers that are evaluated during or at the end of treatment. Nevertheless, none of the biomarkers discussed in this addendum has been shown to predict clinical outcomes at 24 months post-therapy.

The most straightforward designs for confirmatory clinical studies involve addition of a new agent to a standard combination regimen or to individually-tailored optimised therapeutic regimens or replacement of an agent within a standard regimen with a new agent. If it appears likely that a new agent could confer clinically important benefits it may be acceptable to base an initial application for marketing authorisation on a pre-planned interim analysis provided that this does not adversely affect the overall integrity of the study and the final interpretation of the data that should be obtained up to at least 24 months post-therapy.

The evaluation of the safety profile of a new agent for treating tuberculosis is confounded by the need to administer it as part of combination regimens in clinical studies. Identification of adverse reactions to the new agent should be possible when all other components of the regimens that are compared can be kept the same. However, this becomes more difficult when the new agent has to be administered as part of a wide variety of combination regimens tailored to the susceptibility profiles of MDR-TB or XDR-TB in individual patients. A well-constructed and comprehensive Risk Management Plan is therefore very important.

There are special considerations for the evaluation of new agents for the treatment of tuberculosis in some populations (e.g., children, patients with HIV) that are only briefly considered in this addendum. Detailed advice should be obtained from EU Regulators on a case by case basis.

## 1. INTRODUCTION (background)

Disease caused by *Mycobacterium tuberculosis* is currently treated with combination therapy and for many months. The choice of regimen and the duration of therapy depend on the characteristics of the disease (e.g., localised to the respiratory tract, extrapulmonary or widely disseminated), the past treatment history (if any), the resistance profile of the organism, the potential for drug interactions (a

particular potential difficulty in those being treated with combination anti-retroviral therapy regimens for HIV) and the ability of patients to tolerate certain agents. Long and complex regimens and/or high pill burdens can result in poor patient compliance, which may affect relapse rates, transmission rates and the selection of resistant strains.

Simpler and shorter treatment regimens and agents with less potential for drug interactions and better tolerability are needed for the management of disease due to *M. tuberculosis*, regardless of its susceptibility pattern. There is a need for antibacterial agents that are effective against disease caused by multi-drug-resistant (MDR-TB) and extensively resistant (XDR-TB) *M. tuberculosis*. MDR-TB is resistant to at least rifampicin and isoniazid and requires prolonged therapy with second-line drugs, which may have more side-effects. XDR-TB is resistant to at least rifampicin and isoniazid among the first-line therapies as well as to any fluoroquinolone and to at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin) so that treatment options are very limited.

There are several antibacterial agents currently at various stages of development that are intended for the treatment of disease due to *Mycobacterium tuberculosis*. These are all referred to as "new agents" for the treatment of tuberculosis in this addendum. However, some of these agents have been or may be developed for the treatment of other types of bacterial infections.

## 2. SCOPE

This addendum covers the evaluation of new agents for the treatment of disease due to *Mycobacterium tuberculosis*. It does not cover any other possible mode of use of anti-tuberculosis agents (e.g., it does not cover the treatment of latent infection, post-exposure prophylaxis or the management of disseminated Bacillus Calmette Guerin after immunisation). Much of the guidance provided in CPMP/EWP/558/95 Rev 1 is relevant to the evaluation of new agents for the treatment of disease due to *M. tuberculosis*. However, there are some special issues that are addressed in this addendum.

The focus is on the evaluation of a single new agent within regimens that contain licensed anti-tuberculosis agents. It is possible that some sponsors may wish to evaluate co-administration of more than one new agent within a single regimen, which might also involve development of a fixed combination formulation of the new agents. Although much of the content of this addendum would be of relevance to co-administration of new agents it is recommended that advice should be sought from EU Regulators on a case by case basis.

It is assumed that all test combination regimens (i.e., including at least one new agent) that will be evaluated in clinical studies will comprise at least three potentially active agents for a defined initial period of therapy with the possibility of reduction to a minimum of two agents thereafter up to the end of treatment. The guidance provided would apply regardless of whether the new agent is given throughout the treatment course or is stopped after a specified period with continuation of other therapies to the end of the course.

Brief guidance is provided on the range of *in-vitro* and *in-vivo* non-clinical studies that may provide at least an indication of the range of doses and/or durations of therapy that might be suitable for evaluation in clinical studies.

It is anticipated that the overall content of the clinical development programme may be very variable, depending on the properties of the new agent and the results of non-clinical studies. It is not possible to cover every possible scenario for clinical development in this addendum and it is recommended that specific advice from EU Regulators should be sought. However, some guidance is provided on the approach to clinical development programmes that focus on:

- The investigation of agents potentially suitable for use in shortened regimens for the treatment of disease due to susceptible *M. tuberculosis* (i.e., susceptible to first line agents).
- The investigation of agents potentially suitable for use in the treatment of disease due to MDR-TB and/or XDR-TB.

It is not considered possible to extrapolate a demonstration of efficacy against susceptible *M. tuberculosis* to the treatment of MDR-TB or XDR-TB or *vice versa*. Each type of use must be evaluated separately in appropriate clinical studies. This is because of the major differences in regimen composition and duration of therapy between the two modes of use. It is recognised that some new

agents may be suitable for both types of use, in which case clinical studies that investigate each mode of use may be conducted in parallel or in tandem.

The interpretation of the safety data will not be straightforward because studies will inevitably involve use of the new agent as part of combination treatment regimens. Some approaches to the review of these data are discussed depending on the range of regimens evaluated.

Once the safety and efficacy of a test combination regimen have been established in the above types of patients it is anticipated that sequential studies may investigate use in some special patient populations. A brief consideration of these studies is provided.

## 3. MAIN GUIDELINE TEXT

### 3.1 Efficacy

#### 3.1.1 Non-clinical evaluation of efficacy

Some caution is needed in the interpretation of the data obtained from non-clinical studies. Conflicting results have sometimes been observed between in-vitro antibacterial activity and studies of efficacy in animal models and between each of these and clinical study results. Any discrepancies that are observed should be taken into account when considering the design of the overall clinical development programme for a new agent.

3.1.1.1 In-vitro antibacterial activity

*In vitro* studies should usually include at least the following:

- Characterisation of the antibacterial activity of the new agent against *M. tuberculosis*, including assessment of activity against strains that demonstrate resistance to one or more licensed therapies.
- Assessment of synergy or antagonism between the new agent and an appropriate range of other agents active against *M. tuberculosis.*
- Assessment of any bactericidal activity of the new agent against strains of *M. tuberculosis* in log and stationery phases of growth (the latter may indicate a potential for the agent to demonstrate sterilising activity *in vivo*).
- The potential risk of selection of organisms with reduced susceptibility to the new agent. The estimated frequency of selection of resistant organisms on exposure of wild-type *M. tuberculosis* to the new agent *in vitro* may not predict the risk of this happening during combination therapy *in vivo*. Nevertheless, if there is a relatively high risk of selecting for resistant strains then this may influence the design of clinical studies (e.g., even short-term monotherapy should probably be avoided).

Every effort should also be made to characterise the following:

- Mode of action.
- Mechanism(s) of resistance.
- Intracellular activity in macrophages.

3.1.1.2 Efficacy in animal models

These studies may be used to:

- Assess the efficacy of the new agent alone.
- Assess the contribution of the new agent to the efficacy of test combination regimen(s).
- Identify potentially effective dose regimen(s) to be evaluated in clinical studies.

Animal models can be used to assess the bactericidal activity (i.e., initial rapid killing) and sterilising activity (i.e., reduction of bacillary counts during longer-term treatment) of the new agent when administered alone and with a range of other agents. *M. tuberculosis* strains that demonstrate reduced susceptibility to the new agent may be assessed in animal models for their fitness to cause and maintain clinically apparent infections.

There is no perfect animal model for predicting clinical efficacy. Consideration should be given to performing some studies in the mouse and possibly in at least one other species. Currently it is not known which biomarkers that can be assessed in animal models (e.g., lung and spleen colony-forming unit counts when treatment is initiated at different stages of disease, time to relapse of infection) might correlate best with clinical efficacy. Animal models can be used to evaluate the possible contribution of an individual agent to a test combination regimen but it may not always be possible to obtain unequivocal results.

3.1.1.3 PK/PD studies

Although the application of PK/PD analyses is less advanced in the field of treatment of tuberculosis compared to the treatment of more common bacterial infections their use is encouraged. PK/PD analyses may help identify potentially efficacious treatment regimens that, ideally, have a low risk of selecting for drug-resistant organisms. These investigations should take into account *in vitro* and *in vivo* non-clinical data and human pharmacokinetic data including potentially relevant data on sputum and tissue penetration.

### 3.1.2 Clinical evaluation of efficacy

3.1.2.1 Patient selection

Protocols should provide clear instructions regarding the minimum clinical, imaging and laboratory investigations that should be performed to characterise the extent of pulmonary tuberculosis and any extrapulmonary disease.

It is essential that the laboratories involved in any one study should be accredited with respect to the diagnosis of tuberculosis and drug resistance testing of *M. tuberculosis* and should use the same validated methodologies. The results of any rapid tests for detection of *M. tuberculosis* and/or resistance determinants that might be used to screen patients before randomisation should be confirmed at some time after enrolment by more conventional methods.

*Patients with disease due to susceptible organisms*

Patients may be considered eligible for enrolment based on a positive smear performed on a suitable respiratory tract specimen and may be randomised before the results of culture and susceptibility testing are available. Eligible patients should be 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 between species and/or detect drug resistance determinants.

*Patients with disease due to MDR-TB 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 outlined in the next section.

*Extrapulmonary disease*

Patients may be considered eligible for enrolment into clinical studies if they meet the relevant criteria described in section 3.1.2.1 and have evidence of extrapulmonary tuberculosis unless the body site(s) involved would require special or prolonged therapy (e.g., CNS infection or possibly osteomyelitis).

3.1.2.2 Design of clinical studies

Applicants are strongly advised to enter into early discussions with EU Regulators regarding appropriate clinical development programmes.

Detailed CHMP guidance is already available regarding the pharmacokinetic evaluation of new drugs and should be consulted. It is essential that adequate and appropriate drug-drug interaction studies are performed as early as possible in the clinical development programme to facilitate co-administration of the new agent with an appropriate range of other agents in clinical studies of safety and efficacy. In addition, it is recommended that detailed (subset) and sparse sampling pharmacokinetic data should be obtained during clinical studies. These data should be used for analyses of population pharmacokinetics and to explore relationships between systemic exposure and efficacy.

It is recommended that in all clinical studies direct observation of therapy (DOT) should be employed. If this is not considered to be feasible the lack of DOT should be justified and every effort should be made to assess compliance (e.g., consideration of home visit "spot-checks" to perform interim drug accountability).

The safety and efficacy of a new agent for the treatment of tuberculosis may be studied when it is administered with a standard regimen and/or with regimens tailored to the susceptibilities of organisms in individual patients as outlined below. It is expected that any indication for use that is approved would state that the new agent should be administered as part of an appropriate combination regimen, which would be selected in accordance with available official guidance and the results of drug susceptibility testing. A concise and balanced description of the most relevant clinical study data would be included in the SmPC.

#### *3.1.2.2.1 Populations to be analysed*

There are two major populations to consider in the analyses:

- Patients who have a positive culture of *M. tuberculosis* obtained from a suitable respiratory tract specimen that was collected before therapy commenced and have no major protocol violations i.e., per protocol population.
- All randomised patients i.e., an ITT population.

Other populations may be pre-defined in the protocol, such as all treated patients and all patients with a positive culture regardless of protocol compliance.

Since a positive culture from a suitable respiratory specimen provides the most definitive evidence of pulmonary tuberculosis and allows for determination of the baseline susceptibility of organisms it may be appropriate to base the primary analysis on the per protocol population regardless of whether the study aims to demonstrate non-inferiority between regimens or superiority of one regimen over another.

In all instances:

- The primary analysis population should be pre-defined and justified in the protocol.
- There should be a clear plan to analyse efficacy in all other pre-defined populations, including an analysis of the ITT population in which all unknown outcomes are relegated to failures.
- Consistency of results between per protocol and ITT populations is expected and any inconsistency should be explored and discussed.

#### *3.1.2.2.2 Endpoints for the evaluation of efficacy*

Primary endpoint

The primary analysis of efficacy should usually be based on the comparison of rates of cure of pulmonary tuberculosis. Alternative primary endpoints (such as one or more of the secondary endpoints listed below) would need careful justification and it is recommended that these should be discussed with EU regulators before initiation of studies. Regardless of the pre-defined primary endpoint all clinical studies that evaluate efficacy should follow up patients for at least 24 months post-therapy.

The definition of cure of pulmonary tuberculosis should require negative cultures to have been obtained at some time during therapy and up to the time of cessation of treatment with no relapse detected during a post-therapy follow-up period of 24 months. Protocols should set out the timings of study visits (e.g., every 3 months post-therapy) and the assessments to be performed at each timepoint.

Relapse may be defined as the return of microbiologically confirmed tuberculosis with the same strain that caused the first episode of disease. All relapses should be counted as treatment failures. Most relapses occur within 6 months of completion of the initial course of therapy but in any recurrence of disease relapse should be distinguished from a new infection by appropriate typing methods. If it is not possible to distinguish relapse from new infection (e.g. a clinical recrudescence is not accompanied by a positive culture to allow for typing) then the case should be counted as a failure.

Treatment failure is often defined as persistently positive cultures at 4 months after commencement of therapy. It may also be defined as persistence of a positive smear at 5 months or later during treatment. Protocols should provide a specific definition of failure, which should take into account any reductions in the duration of therapy with test combination regimens.

Secondary endpoints

Patients should be evaluated for clinical and, if possible, bacteriological resolution of any extrapulmonary disease that was detected at the time of enrolment based on assessments made at pre-defined time points, including 24 months post-therapy. However the outcome of extrapulmonary disease should be regarded as a secondary endpoint in these patients.

Secondary endpoints may include one or more of mycobacterial and/or host biomarkers of treatment response. Unfortunately, all the existing biomarkers have several shortcomings and none has been formally demonstrated to predict 2-year post-therapy relapse rates. Nevertheless, biomarker endpoints that may be used include (note that several others have been proposed and/or are being evaluated, such as immunogenic secreted antigens of *M. tuberculosis*):

- Early bactericidal activity

For new agents that show rapid bactericidal activity *in vitro*, an evaluation of the early bactericidal activity (EBA) of a new agent when administered alone (i.e., short-term monotherapy) or as part of combination regimens may be made in patients. EBA is most likely to pick up any differences that might exist between regimens in the first two days after commencement of therapy. When comparing combination regimens it may not always be possible to demonstrate that EBA is superior in one or more groups that receive the new agent compared to one or more control groups, especially if a rapidly bactericidal agent (such as isoniazid) is included in the control regimen. Nevertheless, the data generated could indicate whether there is any antagonism between the new agent and other agents co-administered. EBA does not assess the potential for a drug to clear residual bacteria (i.e., sterilisation).

- Sputum culture conversion at 2 months after starting therapy

This is considered to be a marker of sterilising activity. However, the relapse rate at 24 months post-therapy is influenced not only by the treatment administered in the first 2 months but by the sequential therapy. In addition, not all patients can expectorate at this time point and induced sputa may not be adequate to pick up residual viable organisms.

In order to strengthen the validity of sputum culture conversion as an endpoint it is important that the quality of the sputum examined should be assessed (e.g., in terms of numbers of polymorphonuclear cells *vs.* epithelial cells) and that protocols should pre-define “acceptable” sputa. Nevertheless, it is not clear which cellular criteria are most important for a reliable conclusion to be drawn regarding culture conversion. These considerations also apply to the validity of other biomarkers that are based on detection of *M. tuberculosis* in specimens obtained from the respiratory tract.

- Culture conversion at the end of therapy

This is an additional possible time point for assessing sterilising activity.

- Time to culture conversion

This has recently been proposed as an improvement over sputum culture conversion for assessing the efficiency of sterilising activity. This endpoint may be particularly relevant for selection of short-course regimens (e.g., 3-4 months total duration).

- Serial sputum colony counting (SSCC)

SSCC measured over at least the first 28 days of treatment can also give an indication of the sterilising activity of a regimen. Mathematical approaches to the analysis of serial counts have been proposed that may improve on the ability of SSCC to distinguish between regimens.

- Mortality at 4 or 6 months

This might be an important endpoint in studies of patients with XDR-TB since there is currently an appreciable early mortality rate despite institution of the best tailored therapy available.

- Other host factors

For example, serial measurements of body weight, haematology data, clinical chemistry data and results of imaging studies.

#### *3.1.2.2.3 Exploratory investigations of efficacy*

Due to the uncertainties surrounding the prediction of clinically efficacious regimens based solely on non-clinical studies and PK/PD analyses some exploratory investigations of efficacy might be considered appropriate to evaluate a range of doses and/or durations of regimens before proceeding with clinical development. 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 investigations of efficacy may be used to:

Assess the contribution of a new agent to a combination regimen

For example, EBA associated with short-term monotherapy (i.e., up to a maximum of 7 days) with a new agent that is rapidly bactericidal *in vitro* could be evaluated in patients with susceptible *M. tuberculosis* unless laboratory studies suggest there might be a high risk of selection of resistant strains within one week. Several dose regimens of the new agent may be compared with one standard regimen of licensed agents that includes the rapidly bactericidal agent isoniazid. The effect of monotherapy cannot be evaluated based on other biomarkers because this would require an unacceptable duration of exposure to a single agent.

A preliminary assessment of the contribution made by a new agent to a combination regimen could be assessed by comparing EBA and other biomarker data between combination regimens with and without addition of the new agent (i.e., add-on studies). Patients with susceptible *M. tuberculosis* could receive a standard regimen with or without addition of the new agent. In patients with MDR-TB or XDR-TB the comparison would have to be made between groups in which patients receive individually tailored OBT with or without the new agent.

In patients with susceptible *M. tuberculosis* biomarker data could be used to perform a preliminary assessment of the effect of replacing one component of a standard regimen with the new agent (i.e., substitution studies). Substitution studies can assess whether the new agent improves the efficacy of the test combination regimen compared to a standard regimen but cannot establish definitively the contribution of the new agent.

Identify one or a small number of regimens for further evaluation

If one or more exploratory studies are performed it is likely that the selection of doses to be evaluated in confirmatory studies would be based on biomarker data obtained during the first 2-4 months of treatment. Nevertheless, it is recommended that exploratory studies should continue to follow-up patients since the data obtained up to 24 months post-therapy for one or treatment groups might contradict previous assumptions made regarding efficacy based on biomarker data.

If there is any intent to use data from an ongoing study to make a decision regarding regimen selection for another study then there should be a pre-planned interim analysis of the ongoing study. Similarly, if data from an ongoing study could be used to indicate the need to discontinue a treatment arm in the same study or in another ongoing study there should be a pre-planned assessment of futility at an interim analysis with decisions based on statistical hypothesis tests.

The possibility that the results of an interim analysis could lead to re-examination of the assumptions underpinning the design of a study and that major amendments to the protocol might be envisaged should be addressed during the planning stage. Sponsors should consult the *CHMP Reflection Paper on methodological issues in confirmatory clinical trials planned with an adaptive design* (CHMP/EWP/2459/02) when designing and reporting these exploratory and confirmatory studies.

Protocols may also allow for switching of patients from discontinued arms to other regimens under evaluation within the same study. The analysis of final outcomes in patients who are switched should be carefully pre-defined in the protocol and the statistical analysis plan.

#### *3.1.2.2.4 Confirmatory studies*

Depending on the accumulation of data from previous non-clinical and clinical investigations there are several possible options for the overall clinical development programme. Therefore confirmatory studies might include one or a small number of treatment regimens (varying by dose and/or duration) containing the new agent. Employing multiple treatment groups that include the new agent in a single study would have important implications for the planned statistical analyses that are beyond the scope of this guideline. Existing CHMP guidance should be consulted.

Shortened regimens for the treatment of disease due to susceptible *M. tuberculosis*

The most straightforward study designs would involve either addition of the new agent to a recommended standard regimen or replacement of one of the agents in a recommended standard regimen with the new agent. Studies should compare the test combination regimen(s) administered for a pre-defined period to the standard regimen in a double-blind fashion using matching placebo formulations as necessary.

Ideally the primary objective would be to demonstrate at least non-inferiority of one or more regimens that contain the new agent to the standard regimen with respect to cure rates at 24 months post-therapy. Applicants should consult available CHMP guidance on the choice of a non-inferiority margin. A pre-requisite of a non-inferiority trial is that reliable data are available from historical studies to document the effect of the reference treatment. Care should be taken to construct each non-inferiority margin (delta) such that incremental losses of efficacy are avoided. Due to lack of differentiation between relapse and re-infection in many previous studies the true relapse rate in any one geographical setting may not have been clearly established. In this case a conservative approach to the choice of delta is appropriate and a supportive comparison of relapse and re-infection rates should be provided.

As an alternative, taking into account the fact that most relapses in these patients occur within 6 months of completion of therapy and the relapse rate at 4 months post-therapy has been estimated to be around 10%, it may be justifiable to base the primary analysis of efficacy on a demonstration of non-inferiority with respect to relapse rates that occur up to at least 4 months post-therapy. This approach would facilitate an earlier application for a marketing authorisation application. Nevertheless, patients should still be followed for relapses up to 24 months post-therapy.

Treatment of disease due to MDR-TB and/or XDR-TB

In this instance a double-blind comparative study design is considered to be appropriate only if enrolment is restricted to patients with organisms susceptible to at least three licensed agents.

In the most straightforward study design patients would be randomised to receive the new agent (single regimen or small number of regimens) or a matching placebo for a prescribed period from the time of randomisation in a double-blind fashion. The new agent or placebo would be administered together with three licensed agents that would be selected by investigators for individual patients based on susceptibility testing results (i.e., an open-label optimised background treatment regimen [OBT]).

The primary aim would be to demonstrate superiority of the new agent + OBT over placebo + OBT for cure rates at 24 months post-therapy. However, it may be appropriate to base an initial application for marketing authorisation on demonstration of one or more specific benefits for the new agent over placebo, such as reduced mortality at 4-6 months or proportions with negative smears and cultures documented at 3-monthly intervals after the first 6 months.

Patients with disease due to *M. tuberculosis* that is susceptible to less than three licensed treatments are not suitable for enrolment into this type of study. Sponsors are encouraged to include such patients in clinical studies in which the new agent is co-administered as part of the best regimens that can be constructed from available agents rather than collect data only from compassionate use protocols.

- One design that might be considered feasible in carefully selected patients (i.e., not considered to be in urgent need of add-on therapy with the new agent) would be a comparison of groups that receive the new agent + OBT from the outset or receive placebo + OBT for an initial prescribed period and then switch to new agent + OBT. The comparison of biomarker and clinical data would be made before switching all patients to the new agent.
- Alternatively, patients could be invited to enrol into an additional open label non-comparative treatment arm of an otherwise double-blind comparative study as described above. The treatment responses documented in this group would be analysed separately and descriptively.

It should be noted than an initial application for marketing authorisation should not be based solely on non-comparative efficacy data obtained from patients with XDR-TB.

### 3.2 Safety

Unless the new agent has been studied as monotherapy for other types of bacterial infections, which will very likely reflect only relatively short-term use (e.g., up to 10-14 days), it is inevitable that almost all the safety data obtained in patients with tuberculosis will be derived from use in combination regimens.

In studies in patients with disease due to susceptible *M. tuberculosis* the most likely study design would employ overlap between the agents included in the test and control combination regimens. Therefore detailed comparisons between treatment arms may highlight adverse reactions likely to be specific to the new agent and/or adverse reactions that occur more commonly when the combination regimen includes the 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. Nevertheless, overall comparisons between new agent and placebo groups are feasible and informative based on the premise that in double blind studies the range of OBTs employed in the two randomised treatment groups should be comparable. Exploratory analyses of safety based on comparisons between patients that did and did not receive specific co-administered agents may also be informative if numbers are sufficient for interpretation.

The duration of therapy with the new agent will very likely be shorter in patients with susceptible *M. tuberculosis* compared to patients with MDR-TB or XDR-TB. If studies are conducted in both populations attempts should be made to identify any adverse reactions that tend to occur early or late during courses of therapy.

For some new agents it may be considered necessary to plan for a formal interim analysis of safety during exploratory or confirmatory studies. As with interim analyses of efficacy care should be taken to avoid compromising the integrity of the study as a result of any interim review of data.

Whatever the focus of the clinical development programme and design of individual studies the RMP should fully describe the limitations of the safety database. The RMP should also take into account the non-clinical data and any drug class-related information that may be applicable. Consideration should be given to the possible need to conduct a specific study of safety that may commence before or after initial approval.

### 3.3 Special considerations

It is strongly recommended that each of the following should be discussed with EU Regulators.

#### 3.3.1 Use in children

For any new agent for treatment of tuberculosis it will be necessary to submit a Paediatric Investigation Plan. Some possible considerations for development of this plan include:

- If adolescents were excluded from initial clinical studies but the new agent would be suitable for this age group it should be possible to obtain data on pharmacokinetics, safety and efficacy in patients aged from approximately 12-17 years. If safety and efficacy have already been

demonstrated in adults it may be acceptable to provide only limited and non-comparative data in adolescents.

- There are difficulties in obtaining satisfactory respiratory tract specimens from younger children. For example few children (around 10%) aged < approximately 12 years who are considered to have pulmonary disease actually have smear and culture-confirmed pulmonary disease.
- If a new agent is considered suitable for use in children aged approximately < 12 years it may be possible to extrapolate safety and efficacy data obtained in adults to children provided that age-specific dose regimens can be identified. Thus, pharmacokinetic studies could be performed in children during therapy for tuberculosis that has been diagnosed in accordance with the criteria laid down by an internationally-recognised expert body. These children should also be followed to obtain some data on safety and efficacy.

### 3.3.2 HIV positive patients

The efficacy of a new agent for the treatment of tuberculosis may be expected to be generally similar between adults who do not have HIV and HIV-infected individuals with a sustained virological and cellular response to highly active anti-retroviral therapy (HAART) that is expected to result in long-term survival. Sponsors may choose to study such patients separately or to include them in clinical studies along with HIV-negative individuals provided that the efficacy of test regimens is not expected to be adversely affected by such factors as poor compliance, additive toxicities and/or drug-drug interactions.

If such patients are to be included in the same study as HIV-negative individuals there should be pre-stratification by HIV status. Sufficient patients should be enrolled in each important sub-group so that internal consistency can be assessed. Particular attention should be given to the possibility of higher longer-term relapse rates in HIV-infected patients even if a good response to HAART is maintained.

In contrast the efficacy of a new agent may be reduced in patients with low CD4 counts or in those failing their HAART regimen. Different and/or longer duration combination regimens may be necessary and will require specific investigation. The assessment of outcomes is complicated by the need to evaluate responses to test combination regimens for treatment of tuberculosis in the light of the success of concurrent HAART in individual patients. Details of possible studies are beyond the scope of this addendum.

The assessment of safety of a new agent for treatment of tuberculosis in HIV-infected patients is especially complicated due to the large number of medications that will need to be co-administered and the potentially extensive range of drug-drug-interactions, which may change over time as HAART regimens are adjusted. The possible occurrence of immune reconstitution syndrome is also a complicating factor for the overall safety assessment of these patients.

### 3.3.3 Patients taking drugs that predispose to the development of tuberculosis and/or potentially affect the outcome of therapy

Whenever possible drugs that may have predisposed to the development of disease due to *M. tuberculosis* (e.g., immunosuppressive therapy such as with TNF alpha antagonists) are stopped when the diagnosis is made and treatment for tuberculosis commences. However, it may not always be possible to stop these treatments or they may have to be re-commenced during the treatment of tuberculosis because of the pressing need to control the concomitant diseases for which they were prescribed.

Assessing responses to a test combination regimen in patients who must continue or re-commence treatment with agents that predispose to the development of disease due to *M. tuberculosis* is only likely to be possible in very small numbers and in an uncontrolled fashion. However, if substantial and well-documented clinical experience were to be accumulated it might be considered appropriate to mention this in the SmPC.

### *3.3.4 Disease affecting the Central Nervous System (CNS)*

The composition and duration of combination regimen(s) containing a new agent shown to be efficacious in pulmonary disease and in any types of extrapulmonary disease that might have been

included in clinical studies would not necessarily be suited to treatment of CNS disease. It is not expected that prospective randomised studies could be conducted in patients with CNS disease. However, if it is expected that the new agent will penetrate into the CNS to a potentially useful extent then sponsors are encouraged to collect information on use of the new agent to treat CNS disease in a suitable combination regimen. These studies should include detailed pharmacokinetic analyses.

### 3.3.5 M. africanum and M. bovis

It may be possible to use non-clinical data to support some extrapolation of efficacy of test combination regimens against *M. tuberculosis* to these other species that are part of the *M. tuberculosis* complex.

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