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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE

(CHMP)

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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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@ema.europa.eu http://www.ema.europa.eu

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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 agents intended for the treatment of disease due to *Mycobacterium tuberculosis*. Specific guidance was considered to be appropriate due to the differences in approaches to the treatment of tuberculosis compared with the treatment of other types of bacterial infections.

In-vitro and in-vivo non-clinical studies can be used to assess the potential efficacy of test agents in various dose and combination regimens for the treatment of drug-susceptible and drug-resistant *M. tuberculosis*. The data can provide some indication of the extent of exploratory clinical studies that may be needed before selecting one or a few test combination regimens to be evaluated in confirmatory studies of efficacy.

If non-clinical studies indicate that an agent may be suitable for the treatment of drug-susceptible and drug-resistant *M. tuberculosis* clinical studies that investigate each mode of use may be conducted in parallel or in tandem. It is not considered possible to extrapolate a demonstration of efficacy against drug-susceptible *M. tuberculosis* to the treatment of drug-resistant organisms or *vice versa*. Each type of use must be evaluated separately in appropriate clinical studies.

Patients should be enrolled into studies in the treatment of drug-susceptible or drug-resistant *M. tuberculosis* based on selection criteria intended to maximise the possibility that the results of susceptibility testing will confirm their eligibility. The population enrolled should be as representative as possible of the range of patients presenting with tuberculosis. Stratification according to important baseline factors is recommended (e.g. in terms of age, cavitation, extrapulmonary disease and HIV status).

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 these biomarkers has been shown to predict clinical outcomes at 24 months post-therapy.

Confirmatory studies may assess the safety and efficacy of a test agent under conditions that include but are not limited to:

- Addition to or substitution for another agent within standard regimens to achieve shortened regimens, an improved safety profile, a lower potential for drug interactions or simplification of treatment for drug-susceptible *M. tuberculosis*
- Addition to optimised background treatment (OBT) regimens based on susceptibility test results to achieve superior efficacy to placebo + OBT in the treatment of drug-resistant *M. tuberculosis.*

The demonstration of a clinically important benefit for a test combination regimen in a primary analysis conducted at an appropriate time point may be considered sufficient to support an indication for use. Studies should plan to follow-up patients to 24 months post-therapy.

An extrapolation of safety and efficacy in adults to some paediatric age groups may be justifiable, in which case it would be sufficient to establish appropriate age-specific dose regimens based on pharmacokinetic data obtained in children with tuberculosis. Nevertheless, children should also be followed for safety and efficacy using age-specific criteria for diagnosis and outcome assessments as appropriate.

The evaluation of the safety profile of a test 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 test agent should be possible when all other components of the regimens that are compared can be kept the same. However, this is not possible when the test agent has to be administered as part of a wide variety of combination regimens tailored to the susceptibility profiles of drug-resistant organisms in individual patients. In all cases, a well-constructed and comprehensive Risk Management Plan is very important.

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 “test 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 agents for the treatment of disease due to *Mycobacterium tuberculosis*. It does not cover other modes of use of anti-tuberculosis agents such as 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 agents for the treatment of disease due to *M. tuberculosis* and should be read in conjunction with this addendum. In all instances sponsors are advised to discuss the development programme with EU Regulators at an early stage and at intervals as necessary.

The focus of this addendum is on the evaluation of a single test 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 test agent within regimens, which might also involve development of a fixed drug combination formulation. Although much of the content of this addendum would be of relevance to co-administration of test agents it is recommended that advice should be sought from EU Regulators on a case by case basis.

It is assumed that test combination regimens (i.e. including at least one test agent) will initially comprise at least three potentially active agents with the possibility of reduction to a minimum of two agents after a defined period of time. The guidance provided would apply regardless of whether the test 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.

Detailed guidance is not provided on the evaluation of pharmacokinetics of test agents for the treatment of tuberculosis. It is very important that a full range of clinical pharmacokinetic studies is conducted, including appropriate drug-drug interaction studies relevant to the anticipated content of combination regimens and drugs that are most likely to be co-administered (e.g. anti-retroviral agents). 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. Existing CHMP guidance should be consulted.

The safety and efficacy studies included in the clinical development programme may be very variable, depending on the properties of the test agent and the results of non-clinical studies. This addendum pays particular attention to:

- 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 drug-resistant *M. tuberculosis.*

Other possible scenarios for clinical development (e.g. to identify regimens that provide an improved safety profile, a lower risk of drug-drug interactions or a simplified regimen or address other objectives) are not covered in detail.

Guidance is provided on approaches to patient selection and to enrolment of representative patient populations with stratification according to important factors such as presence of cavitation, extrapulmonary disease and co-infection with HIV. The extrapolation of data in adults to younger age groups is discussed.

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

3. EFFICACY

3.1 Non-clinical evaluation of efficacy

In-vitro and in-vivo non-clinical studies form an important part of the preliminary assessment of efficacy of a test agent for the treatment of disease caused by *M. tuberculosis*. Nevertheless, some caution is needed in the interpretation of the data. 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.

3.1.1 In-vitro antibacterial activity

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

- Characterisation of the antibacterial activity, including bactericidal activity, of the test agent against *M. tuberculosis* strains in log and stationery phases of growth (the latter may indicate a potential for the agent to demonstrate sterilising activity *in vivo*). Strains should come from a range of geographic locations and should include a representative sample of *M. tuberculosis* that express resistance to one or more licensed therapies. Susceptibility testing should employ standardised methods.
- Assessment of the potential risk of selection of organisms with reduced susceptibility to the test agent. The estimated frequency of selection of resistant organisms on exposure of wild-type *M. tuberculosis* to the 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 *in vitro* 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 and potential for cross-resistance with other agents
- Activity against intracellular organisms.

The results of in-vitro assessments of synergy or antagonism between the test agent and an appropriate range of other agents active against *M. tuberculosis* may not reliably predict the in-vivo situation. If such studies are performed and suggest that antagonism could occur then particular attention should be paid to exploring this possibility during pre-clinical and clinical efficacy studies.

It is recommended that sponsors should decide early in the development programme if they will participate in an agreement that will allow the breakpoints for susceptibility to be set by EUCAST (REF to SOP) since this decision may have implications for the range of studies performed and the methods used.

3.1.2 Efficacy in animal models

These studies may be used to:

- Assess the efficacy of a test agent alone
- Assess the contribution of an agent to the efficacy of test combination regimen(s)
- Identify potentially effective dose regimens to be evaluated in clinical studies
- In conjunction with in-vitro data, support an extrapolation of efficacy of test combination regimens against *M. tuberculosis* to other species that are part of the *M. tuberculosis* complex.

Animal models, including immunocompetent and immunodeficient 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 an agent when administered alone and with a range of other agents. *M. tuberculosis* strains that demonstrate reduced susceptibility to an 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.

3.1.3 PK/PD studies

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. However, advances have been made recently and the use of PK/PD analyses is encouraged. These analyses may help identify potentially efficacious treatment regimens that, ideally, have a low risk of selecting for drug-resistant organisms.

Analyses 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. Early explorations of the PK/PD relationship may be based on endpoints such as time to sputum conversion and sputum conversion rates.

3.2 Clinical evaluation of efficacy

3.2.1 General issues for clinical studies

3.2.1.1 Content of the clinical development programme

This section is based on the conduct of separate studies in patients with drug-susceptible or drug-resistant M. tuberculosis in parallel or in tandem. It is preferred that two randomised and controlled studies are provided to support each indication for use. If a single confirmatory study is proposed the CHMP guidance on submission of a single pivotal study will apply. Sponsors should discuss alternative approaches to the overall clinical development programme with EU Regulators before study initiation.

It is not considered possible to extrapolate the results of clinical studies with a new agent in the treatment of drug-susceptible M. tuberculosis to the treatment of drug-resistant organisms or vice versa. The safety and efficacy of each type of use must be evaluated in appropriate clinical studies. This is because of differences in the study objectives and hypotheses, regimen composition, duration

of therapy, disease characteristics (e.g. extent of underlying lung damage), general health of patients and other factors.

Depending on the patient population to be enrolled, test agents for the treatment of tuberculosis will be administered as part of standardised regimens or regimens that are tailored to the susceptibilities of individual organisms. It is expected that any indication for use that is approved would state that the test 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.

It is recommended that clinical studies should employ a double blind design with respect to study groups that do and do not receive the test agent and that direct observation of therapy (DOT) should be employed.

Protocols should plan to follow-up patients for 24 months after treatment completion. Measures should be in place minimise numbers that are lost to follow-up during this period, especially if it follows a long duration of treatment for drug-resistant tuberculosis.

3.2.1.2 Efficacy endpoints

The most appropriate efficacy endpoints for an individual exploratory or confirmatory clinical study will depend on the pre-defined primary and secondary efficacy analyses as discussed in sections 3.2.3 and 3.2.4 below. This section considers the range of primary and secondary endpoints that may be considered appropriate.

The definition of cure of pulmonary tuberculosis should require a mycobacterial response (i.e. sputum culture conversion; see below) to have been obtained at some time during therapy with no relapse detected up to the end of therapy or during a defined post-therapy follow-up period. A mycobacterial response should be accompanied by documentation of improvement or resolution of clinical signs and symptoms associated with active tuberculosis.

Protocols should provide a specific definition of primary treatment failure. This may be defined as persistently positive cultures at a specified time point after commencement of therapy determined in accordance with the type of disease (i.e. drug-susceptible or drug-resistant) being treated.

All relapses should be counted as treatment failures. Relapse may be defined as the return of microbiologically confirmed tuberculosis with the same strain that caused the first episode of disease based on the use of 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.

Protocols may plan to count all deaths as failures or to count as failures all deaths excluding those that were clearly not related to M. tuberculosis (e.g. deaths from trauma). Early deaths on treatment (e.g. within the first 4 or 6 months) may be a particularly important endpoint in patients with multidrug-resistant tuberculosis due to the appreciable early mortality rate despite institution of the best tailored therapy currently available.

Patients should be evaluated for clinical and, if possible, bacteriological resolution of any extrapulmonary disease that was detected at the time of enrolment. The outcome of extrapulmonary disease should be regarded as secondary to the outcome of pulmonary disease in these patients.

Efficacy endpoints may also include mycobacterial and host biomarkers of treatment response. Currently, all the existing biomarkers have shortcomings and none has been demonstrated to predict 2-year post-therapy relapse rates. Nevertheless, endpoints may include:

- Early bactericidal activity (EBA)

The evaluation of the EBA is based on the serial determination of viable counts of *M. tuberculosis* in sputa that have been collected under standardised conditions before and for a short period following initiation of therapy. EBA is often expressed as the rate of fall of colony forming units (log10 cfu/day) during the first 2 days of treatment but several alternative definitions and approaches to analysing the data have been used.

For those agents that elicit EBA, estimates may be obtained during short-term monotherapy with different dose regimens or during therapy with different combination regimens. EBA data are most likely to pick up any differences that might exist between agents and between dose regimens in the first few days after commencement of therapy. EBA does not assess the potential for a drug to clear residual bacteria (i.e. sterilisation).

- Sputum culture conversion (SCC)

The validity of SCC-related endpoints requires that the quality of the sputum examined should be assessed, that culture methods should maximise the possibility of detecting residual organisms and on a definition based on three consecutive negative cultures of specimens obtained at timed intervals.

SCC may be measured in different ways as follows:

SCC at 2 months or other time point up to end of therapy

Early SCC is considered to be a marker of sterilising activity. However, not all patients can expectorate after a few months on treatment and induced sputa may not be adequate to pick up residual viable organisms.

Time to culture conversion

For example, time to the first consecutive negative culture. 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.

- Other host factors

These may include serial measurements of body weight, haematology data, clinical chemistry data and results of imaging studies.

3.2.2 Patient selection and patient populations

3.2.2.1 General issues for patient selection

Protocols should:

- Specify which type(s) of patients are eligible for enrolment. Eligibility may be based on a positive smear performed on a suitable respiratory tract specimen and patients may be randomised before the results of culture and susceptibility testing are available. The results of any rapid tests for detection of *M. tuberculosis*, for speciation of acid-fast bacilli or for preliminary detection of resistance determinants that might be used to screen patients before randomisation should be confirmed at some time after enrolment by more conventional methods.
- Specify the criteria for categorising isolates according to their susceptibility and the methods to be used. 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. Results should be confirmed in a centralised laboratory whenever possible.
- Provide clear instructions regarding the minimum clinical, imaging and laboratory investigations required to characterise the extent of pulmonary tuberculosis.
- Specify how patients found to be infected with strains that do not meet the required susceptibility criteria should be handled in terms of possible need to discontinue study therapy and inclusion or exclusion from populations used for analyses.

- Define patient sub-populations suitable for pre-stratification. For example, presence or absence of lung cavitation, HIV infection or extrapulmonary disease and the total number of drugs to which the infecting organism is resistant.

3.2.2.2 Patients with disease due to susceptible organisms

In order to reduce the chance that patients with drug-resistant organisms are inadvertently enrolled patient eligibility should take 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.

Protocols should specify how patients found to be infected with strains that are resistant to isoniazid but susceptible to rifampicin after enrolment into these studies should be handled in the analyses.

3.2.2.3 Patients with disease due to resistant organisms

Patient eligibility may be based on a history of previous treatment that resulted in primary failure or relapse, contact with persons known to have drug-resistant tuberculosis cases and residence in areas with high rates of drug resistance. Nevertheless, there is a risk not only that patients with drug-susceptible organisms but also that patients infected with drug-resistant *M. tuberculosis* that do not fulfil the inclusion criteria are inadvertently enrolled.

The availability of susceptibility test results before enrolment would be ideal but the availability of data is likely to vary between geographic locations. Sponsors may consider implementing a run-in period after enrolment but before randomisation during which time the susceptibility test results can be obtained.

3.2.2.4 Patients with extrapulmonary disease

Patients with well-documented extrapulmonary disease may be considered eligible for enrolment into clinical studies if they otherwise meet the inclusion criteria. It is recommended that patients should be stratified according to the presence or absence of documented extrapulmonary disease. Consideration of the minimal data that might be considered sufficient to support a specific claim for use in extrapulmonary disease at various sites should follow the guidance on data requirements relating to the treatment of rarely bacterial encountered infections.

Test combination regimens that are shown to be efficacious in pulmonary disease would not necessarily be suited to the treatment of extrapulmonary disease at certain body sites due to the need for special or prolonged regimens (e.g. CNS infection or possibly osteomyelitis). If a test agent is expected to achieve potentially useful concentrations at these sites then sponsors are encouraged to collect information on pharmacokinetics and efficacy within appropriate prospective clinical studies.

3.2.2.5 Paediatric populations

Some considerations for development of Paediatric Investigation Plans, taking into account existing CHMP guidance, may include the following:

- Whenever considered possible, taking into account what is known about the properties of the test agent, children and adolescents aged from approximately 10 years upwards should be included in studies that enrol adults. Data on pharmacokinetics may be obtained from these subjects during treatment.
- If adequately powered randomised and controlled studies of efficacy are not considered to be feasible in children in specific age groups there must be a justification for extrapolation of safety

and efficacy data obtained in adults to children. The presentation of clinical disease may be different compared to adults but the response to treatment may be comparable at least from the age of five years upwards. Below this age an extrapolation of results from studies in adults may be more problematic due to higher rates of extrapulmonary tuberculosis.

- If it is considered acceptable that safety and efficacy data obtained in adults can be extrapolated to children of specific age groups it is required that age-specific dose regimens are identified based on pharmacokinetic studies conducted in children during therapy for tuberculosis. Children should also be followed to obtain data on safety and efficacy.
- The diagnosis of tuberculosis and the assessment of responses to treatment in children enrolled into these types of studies should be based on age-specific criteria recommended by internationally-recognised expert bodies.

3.2.2.6 HIV positive patients

The efficacy of a test combination regimen 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 long-term relapse rates in HIV-infected patients even if a good response to HAART is maintained.

The efficacy of a test combination regimen may be reduced in patients with very low CD4 counts or in those failing their HAART regimen. Different and/or longer duration combination regimens may be necessary and 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.

3.2.2.7 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. Treatment regimens for tuberculosis expected or shown to be efficacious in other patient populations may not be suitable in these cases (e.g. different doses and durations of treatment may be needed).

As a result, the assessment of combination regimens 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 small numbers and in an uncontrolled fashion. However, if well-documented clinical experience were to be accumulated with a combination regimen containing a test agent it might be considered appropriate to mention this in the SmPC.

3.2.2.8 Populations to be analysed

Patient populations should at least comprise:

- A Full Analysis Set (FAS) in accordance with ITT principles.

- A modified ITT population comprising patients who have a positive culture of *M. tuberculosis* obtained from a suitable respiratory tract specimen that was collected before therapy commenced and which shows the required drug susceptibility pattern
- A Per Protocol population comprising the subset of the mITT population defined above that has no major protocol violations.

In all instances:

- The primary or co-primary analysis population(s) should be specified in the protocol and justified according to the pre-defined primary and secondary analyses
- There should be a clear plan to analyse efficacy in all other pre-defined populations, including an analysis of the FAS in which all patients with unknown outcomes and deaths due to any cause are relegated to failures.
- Consistency of results between analysis populations should be assessed and any inconsistency should be explored and discussed.

3.2.3 Exploratory studies

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 may be necessary to evaluate a range of doses and/or durations of regimens before proceeding with clinical development. Exploratory studies may be used to:

i) Assess the in-vivo effect of the test agent

For example, EBA associated with short-term monotherapy over one to two weeks could be evaluated in patients with susceptible *M. tuberculosis* unless laboratory studies suggest there might be a high risk of early selection of resistant strains. However, the EBA exerted by the test agent may not be superior to that of the standard regimen containing isoniazid.

ii) Assess the contribution of a test agent within a combination regimen

A preliminary assessment of the contribution made by a test agent to a combination regimen could be assessed by comparing EBA and other biomarker data between combination regimens with and without the test agent. Patients with susceptible *M. tuberculosis* could receive a standard regimen with or without the new agent. A similar study could be performed in patients with drug-resistant tuberculosis but the interpretation of the results becomes difficult unless enrolment is restricted to those infected with *M. tuberculosis* that are suitable for treatment with the same open label optimised background treatment (OBT) regimen with and without the test 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 test agent (i.e. substitution studies). Substitution studies can assess whether inclusion of the test agent improves the efficacy of the combination regimen compared to the standard regimen but they cannot establish the contribution of the new agent.

iii) Select dose regimens of the test agent for confirmatory studies

The selection of doses to be evaluated in confirmatory studies may be based on biomarker data obtained during the first 2-4 months of treatment in exploratory studies. It is recommended that exploratory studies should continue to follow-up patients since the data obtained up to 24 months post-therapy may support or refute the assumptions made regarding efficacy based on early 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 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.

3.2.4 Confirmatory studies

All studies that are intended to provide a confirmatory assessment of efficacy should be adequately powered to address the study hypothesis. Existing CHMP guidance should be consulted.

Depending on the accumulation of data from previous non-clinical and clinical investigations confirmatory studies might investigate one or more than one test combination regimen in which the test agent is administered at different doses and/or for different durations.

The following sections discuss:

- 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 drug-resistant *M. tuberculosis.*

While there are several other possible scenarios for clinical development recognised (see section 2) these are not covered in detail.

3.2.4.1 Treatment of disease due to susceptible M. tuberculosis

Treatment shortening regimens

The most straightforward study design would involve either addition of the test agent to a recommended standard regimen or replacement of one of the agents in the standard regimen with the test agent.

Taking into account the fact that most relapses in patients with susceptible *M. tuberculosis* occur within 6 months of completion of therapy it may be justifiable to base the primary analysis of efficacy on a demonstration of non-inferiority (test versus standard regimen) with respect to the total of primary treatment failures + relapses + deaths up to a pre-defined time point (e.g. at 12 months post-treatment). All studies should also plan to assess non-inferiority of test combination regimens versus standard regimens with respect to cure rates at 24 months post-therapy.

Applicants should consult available CHMP guidance on the choice of a non-inferiority margin. 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.

Other possible studies

Some test agents may potentially offer superior tolerability, lower risks of significant drug-drug interactions, treatment simplification or address other issues of clinical importance when substituted for an agent in a standard regimen. In these cases, it would still be expected that non-inferiority to the standard regimen in terms of efficacy should be demonstrated as discussed above.

3.2.4.2 Treatment of disease due to drug-resistant M. tuberculosis

Efficacy of test combination regimens

The most straightforward study design would involve randomisation of patients to the test agent or to placebo, each administered with licensed agents selected by investigators for individual patients based

on susceptibility testing results to construct open label optimised background treatment [OBT] regimens.

It is preferred that a double-blind and placebo-controlled comparative study design is used only if enrolment is restricted to patients with organisms that are still susceptible to a pre-defined minimum number of licensed agents. Restriction of the population in this way should make it feasible to maintain sufficient patients on study in the test and controls group to provide meaningful comparisons of responses during treatment and at pre-defined intervals after completion of therapy.

Taking into account the longer duration of therapy that is considered necessary in these types of patients it may be justifiable to base the primary analysis of efficacy on a demonstration of superiority of the test agent over placebo with respect to an endpoint that encompasses SCC plus a documented improvement in clinical status assessed at an appropriate time after initiation of treatment.

All studies should plan to assess cure rates (i.e. based on a pre-defined mycobacterial and clinical response) at intervals after completion of therapy (e.g. at 6-monthly intervals up to 2 years).

Other possible studies

Patients with disease due to *M. tuberculosis* that is susceptible to very few licensed treatments (e.g. less than the minimum applied to patient selection in placebo-controlled studies as suggested above) should be enrolled into clinical studies in which the test agent is co-administered as part of the best regimens that can be constructed. Examples of possible study designs that could provide information on the utility of a test agent in these types of patients include (but are not limited to):

- Patients who are screened for enrolment into placebo-controlled studies but are found not to meet the required criteria when susceptibility test results become available could be enrolled (or switched if already enrolled) into an additional open label non-comparative treatment arm of an otherwise double-blind comparative study as described above. Treatment responses documented in this parallel group should be analysed separately and descriptively.
- A separate placebo-controlled study might be feasible in carefully selected patients who are not considered to be in urgent need of add-on therapy with the new agent. These patients could be randomised to receive the test agent + OBT from the outset or to receive placebo + OBT for an initial prescribed period (e.g. a few weeks) and then switch to test agent + OBT. A comparison of biomarker and clinical data should be made immediately before switching.

4. SAFETY

Unless the test 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 designs 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 test agent and/or adverse reactions that occur more commonly when the combination regimen includes the test agent.

In studies in patients with drug-resistant *M. tuberculosis* the interpretation of the safety data becomes much more complex due to the variable content of the OBT. Nevertheless, overall comparisons between test 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 will differ between patients with drug-susceptible and drug-resistant *M. tuberculosis*. 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.

In studies that aim to demonstrate a benefit in terms of safety for test combination versus standard regimens the parameters on which the assessment of superior tolerability will be based should be pre-defined in the protocol.

The assessment of safety in HIV-infected patients with tuberculosis is especially complicated due to the large number of medications that will need to be co-administered with the test agent 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.

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.

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