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Addendum to the 'guideline on the evaluation of medicinal products indicated for treatment of bacterial infections' to address the clinical development of new agents to treat disease due to *Mycobacterium tuberculosis*

Draft

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This addendum replaces 'Addendum to the note for guidance on evaluation of medicinal products indicated for the treatment of bacterial infections to specifically address the clinical development of new agents to treat disease due to *Mycobacterium tuberculosis* (EMA/CHMP/EWP/14377/2008)'.

Comments should be provided using this template. The completed comments form should be sent to idwpsecretariat@ema.europa.eu

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Addendum to the 'guideline on the evaluation of medicinal products indicated for treatment of bacterial infections' to address the clinical development of new agents to treat disease due to *Mycobacterium tuberculosis*

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Executive summary

This revision of the Addendum to the *Note for guidance on the evaluation of medicinal products for treatment of bacterial infections to address the clinical development of new agents to treat disease due to Mycobacterium tuberculosis* (EMA/CHMP/EWP/14377/2008 Rev 1) has been produced in response to recent advances and changes in focus in the field.

Since the adoption of the prior guidance advances have been made in the application of pharmacokinetic-pharmacodynamic (PK-PD) analyses to identify potentially efficacious doses and regimens for further clinical evaluation. In particular, the use of in-vitro pharmacodynamic models early on in the development programme, with further refinement when human PK data become available, may play an important role in minimising the extent of dose- and/or regimen-finding clinical trials.

To facilitate appropriate patient selection for efficacy trials, the use of rapid diagnostic tests to detect *Mycobacterium tuberculosis* complex and to detect certain types of resistance mechanisms is addressed. Also addressed is the confirmation of *M. tuberculosis* and its susceptibility in baseline specimens and the need for thorough evaluation of the validity of negative cultures of sputa collected while patients are still on active therapy, i.e. to minimize the risk of false negatives.

There has been a shift in focus towards the development of new regimens that include one or more new agents that can allow for a shortening of the duration of therapy in patients infected with organisms that are susceptible to the agents in the regimen, regardless of their susceptibility to other anti-tuberculosis agents. These new regimens may be presented for clinical use as fixed drug combinations or as individual agents for co-administration in specific regimens (in terms of composition, doses and durations).

Depending on the content of the treatment shortening regimen and issues such as the anticipated safety profile and route of administration, it may be considered suitable for evaluation in patients infected with organisms treatable with first-line therapies. In this case the proposed treatment shortening regimen could be compared with a widely-recommended first-line regimen with the aim of demonstrating non-inferior efficacy. Although the demonstration of efficacy is obtained in a population with many remaining treatment options, results may support an approval for use of the test regimen for the duration that has been studied in patients infected with organisms susceptible to all agents in the regimen, regardless of their susceptibility to other existing anti-tuberculosis agents. If the test regimen is not considered suitable for evaluation in patients with many remaining therapeutic options, one possibility would be to compare various durations of the proposed treatment shortening regimen in patients with highly drug-resistant *M. tuberculosis*. Alternatively or in addition, one or more durations of the test regimen could be compared with a control group that receives current standard of care tailored to organism susceptibility. In either case, identifying a margin for concluding non-inferior efficacy is not straightforward.

Recent data suggest that superiority is not likely to be shown when a single new agent is added to an optimised background regimen and compared with addition of placebo in patients with limited treatment options. However, it cannot be ruled out that adding a single new agent could provide superiority, perhaps in a population infected with highly drug-resistant organisms. In addition, it remains possible that a new regimen containing more than one very active new agent could be superior to regimens consisting of only existing agents that are tailored to the susceptibility of individual patients' organisms. If such a strategy is pursued the primary comparison between the test

regimen and standard of care regimens should be over at least 6 months from randomisation and sustained SCC rates should be documented for at least 24 months from randomisation.

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.

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 trials. In all cases, a well-constructed and comprehensive Risk Management Plan is very important.

1. Introduction

Disease caused by *Mycobacterium tuberculosis* is currently treated with combination therapy 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, extra-pulmonary 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), the ability of patients to tolerate certain agents and other host factors.

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 drug-resistant *M. tuberculosis* (DR-TB), including rifampicin-resistant (RR-TB), multi-drug-resistant (MDR-TB) and extensively drug resistant (XDR-TB) *M. tuberculosis*, all of which require prolonged therapy with second-line or third-line drugs.

Much of the guidance provided in CPMP/EWP/558/95 rev 2 and in EMA/456046/2015 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. This addendum focusses on the features of the development programme that are specific to new agents for treatment of tuberculosis. In this guideline:

- A new agent is defined as an agent that has not been approved in any EU country for the treatment of *M. tuberculosis*. New agents include those that have been approved for treatment of other types of infections but are not widely recommended for treatment of tuberculosis.
- An existing agent is defined as one that is already approved for treatment of *M. tuberculosis* in any EU country or one that is not actually approved for this use but is nonetheless widely recommended for inclusion in combination regimens.

In all instances sponsors are advised to discuss the development programme with EU Competent Authorities at an early stage and at intervals as necessary.

2. Scope

This addendum covers the evaluation of new agents for the treatment of pulmonary disease due to *Mycobacterium tuberculosis,* with or without concomitant extrapulmonary infection. Reflecting current development strategies, the main focus of this addendum is on the evaluation of regimens that contain at least one new agent, including regimens that may consist of multiple new agents or wholly of new agents. Other less likely development strategies are considered briefly. The guidance is relevant

whether a new agent is to be developed as a standalone formulation and/or as a component of one or more fixed drug combinations (FDCs), including FDCs that represent single treatment regimens (STRs).

This addendum 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. Detailed guidance is not provided on the evaluation of in-vitro antibacterial activity or pharmacokinetics of test agents for the treatment of tuberculosis. Existing CHMP guidance should be consulted.

3. Legal basis and relevant guidelines

This guideline has to be read in conjunction with the introduction and general principles (4) and part I and II of the Annex I to Directive 2001/83/EC as amended as well as all other pertinent EU and ICH guidelines and regulations, especially those listed in the following:

Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections – CPMP/EWP/558/95 rev 2

Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections – EMA/CHMP/351889/2013

Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products - EMA/456046/2015;

4. Microbiological data

4.1. In vitro activity

For each new agent the general principles laid out in the Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 2) regarding in-vitro studies should be followed. In addition, for new agents active against *M. tuberculosis* it is relevant to evaluate activity against intracellular organisms and the effect of combining each new agent with other selected new or existing agents

Consideration should be given to the use of one or more in-vitro pharmacodynamic models to obtain an early indication of the effects of different concentrations of a new agent on antibacterial activity when it is used alone and when it is combined with other agents selected by the sponsor as potentially suitable for co-administration. These models may be used to evaluate the contribution of each new agent when used within selected combination regimens, to assess the possible synergy or antagonism between the new agent and other selected agents (although the results may not necessarily predict the clinical efficacy of combined treatment regimens) and to estimate the risk of selecting for resistant organisms. Such models can also take into account the effects of growth phases on activity and intracellular accumulation of the new agent.

4.2 Efficacy in animal models

The results of in-vitro studies, including in-vitro pharmacodynamic models, should be used to decide on the need for in-vivo nonclinical efficacy studies.

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) and possibly the rate of relapse 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 in tuberculosis. 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.

4.3 Microbiological data obtained during clinical trials

The following considerations are important for the validity of the data obtained from clinical trials and must be adequately addressed:

Isolation, identification and susceptibility testing of *M. tuberculosis* at trial entry

Patient eligibility for enrolment into clinical trials may be based on prior documentation of the identity and susceptibility of the infecting organism at local laboratories and/or regional reference laboratories, which may have used a range of different methodologies, or on rapid diagnostic tests applied to appropriate specimens obtained at screening visits (see section 6). These tests may be designed to detect *M. tuberculosis* complex and specific drug resistance mechanisms. The same commercially available rapid diagnostic tests should be used at all trial sites for the purposes of patient selection purposes. Recognising the global nature of clinical development programmes, rapid diagnostic tests that are used for the purposes of determining patient eligibility for enrolment do not necessarily have to be CE marked. Whether or not a test is CE marked, details of the performance of each test (e.g. estimated sensitivity and specificity) should be provided in the clinical trial report.

Whether eligibility was based on prior culture and/or on rapid testing at screening, it remains important to attempt to culture *M. tuberculosis* from appropriate baseline specimens in order to confirm the identity of organisms belonging to *M. tuberculosis* complex and to assess susceptibility at least to the agents included in trial regimens. Primary culture may occur in accredited local laboratories or in designated central laboratories with appropriate expertise. It is generally recommended that primary culture should employ an appropriate selective liquid medium. Consideration may be given to using a solid culture medium in addition, in which case patients with a positive result using either method may be considered to have confirmed *M. tuberculosis*. Isolates should be shipped to one or more designated central laboratories for confirmation of identity and susceptibility testing.

The determination of susceptibility may use various methods, which should be discussed in detail in the application dossier. If non-commercialised tests are used for specific purposes (e.g. to detect specific resistance mechanisms for which no commercial tests are available) it is recommended that these are conducted in single central laboratories.

Detection of residual viable organisms

The same culture method(s) selected for confirmation of *M. tuberculosis* at baseline should be applied to the isolation of residual organisms in post-baseline specimens. If more than one method is used, a positive result obtained using any method may be used for the primary analysis.

The interpretation of negative cultures obtained while the patient is still on therapy should be supported by adequate in-vitro studies to estimate the potential carry over effects of drug

concentrations in sputum when using the selected processing and culture methods. For some drugs residual concentrations even at 24 h after the last dose could be sufficient to result in false negative cultures, i.e. no growth despite the fact that viable organisms persist in respiratory secretions. In addition, for interpretation of on-therapy and post-therapy culture results, the minimum number of residual viable organisms that can be detected using the selected methodology for sample processing and culture should be assessed.

Contaminated cultures

The application of a sensitive PCR method to detect *M. tuberculosis* may assist in assigning contaminated cultures to positive or negative. A positive test may not equate with the presence of viable organisms. A negative PCR test result is useful if the method used is very specific and sensitive.

5. Pharmacokinetic-Pharmacodynamic (PK-PD) analyses

Recent advances in the field indicate that PK-PD analyses may be used to identify potentially efficacious treatment regimens for tuberculosis and to assess the risk of selecting for drug-resistant organisms. Sponsors should consult the Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products (EMA/456046/2015), which is of considerable relevance to the development of anti-tuberculosis agents.

As human PK data are accumulated, in-vitro pharmacodynamic models may be particularly useful for the selection of regimens to be evaluated for efficacy. PK-PD analyses using PK and efficacy endpoint data from dose-finding trials (such as log drops in organism loads, SCC rates and time to SCC) should be conducted to support the regimen(s) assessed in pivotal trials. Furthermore, it is recommended that sufficient PK data should be obtained from patients in pivotal trials to support analyses of the exposure-response relationship.

6. Patient selection

It is recommended that patients are not enrolled into trials solely on the basis of a positive smear and clinical signs and symptoms.

Patient eligibility for entry into clinical trials may be based on prior documentation of active positive pulmonary tuberculosis at local or reference laboratories and/or the results of rapid diagnostic tests applied to appropriate specimens obtained at the screening visit.

Protocols should specify the clinical, imaging and laboratory investigations required to characterise the extent of pulmonary tuberculosis (e.g. number of lobes affected and presence of cavitation) and, for patients considered to have extra-pulmonary disease, to confirm that this is present.

7. Assessment of efficacy

7.1 General considerations for trial design and analysis

It is recommended that clinical trials should employ direct observation of therapy (DOT).

Although a double-blind and double-dummy design is preferred it is acknowledged that this may not always be a practical option due to the need to co-administer multiple agents and, to address some strategies, the need to tailor regimen content to the individual patient's organism. In addition, if rifampicin is included in some but not all regimens patients may become aware of urinary or lachrymal

colouration. If a sponsor concludes that a double-blind design is not feasible it is important to consider the potential consequences of an unequal number of withdrawals from test and comparative regimens. Measures should be in place to minimize numbers that are lost to follow-up, especially during the post-therapy phase.

Protocols should address the following issues:

- Retention in the trial of patients found to have negative baseline cultures after they have been randomised and commenced therapy. If it is considered that these patients can be retained in the trial based on the clinical picture plus prior documented *M. tuberculosis* and susceptibility results or positive rapid diagnostic tests at screening, the protocol and statistical analysis plan should state whether they would be eligible for the primary analysis or only for specified secondary analyses.

- Handling of patients found to be infected with organisms that are resistant to one or more assigned drugs after they have been randomised and commenced therapy. These patients will usually need to be removed from the trial. There may be exceptions, including retention of patients with rifampicin-susceptible but isoniazid-resistant organisms in some types of trial. The approach in this situation should take into account the anticipated proportion of the total enrolled who may have this susceptibility pattern (based on local site data) and the potential for introducing bias in favour of the new regimen(s) assessed in the trial.

- Handling of contaminated cultures obtained at one or more visits in the primary analysis based on positive or negative results of PCR for *M. tuberculosis*. It would be acceptable that contaminated cultures that are negative for *M. tuberculosis* by PCR are counted as negative in the primary analysis but a sensitivity analysis should be conducted in which all contaminated cultures are designated as positive.

7.2 Efficacy endpoints

This section considers some of the endpoints (whether designated primary or secondary in any one trial) that may be considered and how they may be defined and analysed.

- 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 ($\log_{10}$ cfu/day) during a pre-specified number of days from the start of treatment but several alternative definitions and approaches to analysing the data have been used. Sponsors should explain and justify their selected mode of analysis.

For those agents that elicit EBA, estimates may be obtained during short-term monotherapy with different dose regimens. EBA may also be determined during therapy with different combination regimens in dose and/or regimen-finding trials. These trials may be conducted in randomly-selected subsets or at specific trial sites with appropriate laboratory capacity and expertise.

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 as an endpoint requires that specimen quality and culture methods should maximise the possibility of detecting residual viable organisms. Confirmed SCC should be based on at least two (and preferably three) consecutive negative cultures of specimens obtained at timed intervals. The time to SCC may be based on the date of the first of the consecutive negative cultures. Sustained SCC should be defined based on persistently negative cultures from the time of first SCC up to the last post-therapy visit.

Not all patients can expectorate after a few months on treatment even with sputum induction. Protocols and statistical analysis plans should pre-specify how these missing data will be handled in the analyses of efficacy.

- Time to positivity (TTP)

The TTP is the number of days taken for a culture to give a positive result. This may provide an assessment of early differences in antimycobacterial activity between regimens provided that adequate attention has been paid to the potential that results are affected by carryover effects. The rate of change in TTP may also be calculated.

- Cure of pulmonary tuberculosis

The definition of cure of pulmonary tuberculosis should require sustained SCC (see above) accompanied by documentation of improvement or resolution of clinical signs and symptoms associated with active tuberculosis. Patients should also be evaluated for clinical and, if possible, bacteriological resolution of any extra-pulmonary disease that was present at enrolment although the outcome of any extra-pulmonary disease may be regarded as secondary to the outcome of pulmonary disease in these patients.

- Primary treatment failure

This may be defined as lack of SCC at a pre-specified time point after commencement of therapy.

- Relapse

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 relapse (i.e. failure) in the primary analysis of efficacy.

- Deaths

The primary analysis may exclude deaths that are clearly not attributable to tuberculosis, including accidents, deaths from deliberate trauma and deaths that result from other diseases (such as disseminated malignancy). All other deaths should be counted as failures in the primary analysis. A sensitivity analysis should be conducted in which all deaths from whatever cause are counted as failures.

- Other host factors

Other potentially relevant host factors to capture and to consider as secondary endpoints include serial measurements of body weight and results of imaging studies.

7.3 Specific trial designs

7.3.1 Short-term trials

Unless in-vitro data suggest that there is a potentially unacceptable risk of selecting for resistance if the new agent is administered alone, a short-term monotherapy trial is usually recommended for agents that show a rapid bactericidal effect *in vitro.* For example, EBA associated with short-term monotherapy with a range of doses of the new agent over one to two weeks could be evaluated in previously untreated patients infected with *M. tuberculosis* that is known or expected to be susceptible to all first line agents. The EBA exerted by the test agent may be compared with an existing bactericidal agent, such as isoniazid, to put the findings into context. Superiority of EBA compared to an existing agent, such as isoniazid, may not be anticipated for the new agent when given alone.

Short-term trials may also be used to provide preliminary evidence of the bactericidal activity of the new agent when given alone and with other new and/or existing agents. Again, a comparison with a known rapidly bactericidal agent may be used to put the results into some context. Nevertheless, superiority of EBA for combinations containing the new agent(s) compared to isoniazid or each new agent given alone may not necessarily be demonstrated. The final selection of regimens to be taken forward should take into account other factors, such as different mechanisms of action of co-administered agents and the risk of the combined regimen selecting for resistance (e.g. taking into account the results of in-vitro pharmacodynamic models).

7.3.2 Further dose- and/or regimen-finding trials

Depending on the strength of evidence obtained from short-term trials and from the PK-PD analyses, it may also be useful to conduct one or more multiple-arm trials over short periods, such as 8 weeks. These trials could assess endpoints that include serial sputum bacterial loads and rates of change in loads, which could be documented in randomised subsets or at specific trial sites, SCC rates, time to SCC and TTP. There should be an appropriate control group. Patients should be previously untreated or already known to be infected with organisms that are fully susceptible to all test agents to which they may be randomised. The primary analysis should be conducted in those who are confirmed to be infected with organisms that are susceptible to all agents in their assigned regimen. These trials are not expected to be fully powered for inferential testing but they should be of sufficient size to allow the sponsor to conduct a descriptive comparison of test and control regimens and to inform the design of appropriate pivotal trial(s).

Following the visit at which data are collected for the primary analysis, protocols may plan that all patients are switched to a standard regimen of existing agents. Alternatively, protocols may allow patients who have achieved SCC to continue on their assigned regimen for a specified period with post-therapy follow-up to assess sustained SCC rates. These data may assist in supporting regimen duration in further trials.

If protocols allow for switching of patients from discontinued arms to other regimens under evaluation within the same trial then the analysis of final outcomes in patients who are switched should be carefully pre-defined in the protocol and the statistical analysis plan.

7.3.3 Pivotal trials

Depending on the accumulation of data from previous non-clinical and clinical investigations, including the extent and results of prior dose- and regimen-finding trials, it is possible that pivotal trials could

investigate more than one regimen containing at least one new agent, different doses of new agent(s) and/or different durations of treatment.

7.3.3.1 Development of new agents within regimens that shorten the duration of treatment

New agent(s) in fixed regimens

Based on current development strategies, the most likely aim is to demonstrate that a fixed regimen containing at least one new agent allows for a shortening of the duration of treatment in patients infected with organisms that are susceptible to all agents in the fixed regimen (which may or may not be presented as a FDC). The patient population in which the new regimen is evaluated will depend on factors such as the anticipated safety profile of the regimen, its simplicity and the route of administration (e.g. whether injections are needed for one or more agents).

The most straightforward approach would be to compare one or more regimens containing at least one new agent in patients infected with organisms susceptible to all agents in each test regimen with the recommended standard regimen for patients infected with organisms treatable with first-line therapies. Although the demonstration of efficacy is obtained in a population with many remaining treatment options, this approach may support an approval for use of the test regimen for the duration that has been studied in patients infected with organisms susceptible to all agents in the regimen, i.e. without regard to the susceptibility of their organisms to any other existing anti-tuberculosis agents. Therefore, the programme should support an indication for a FDC or for the individual new agent(s) in the regimen *for the treatment of pulmonary tuberculosis*.

If the test regimen is considered to be unsuitable for patients with many remaining therapeutic options, the trials may be conducted in patients infected with organisms resistant to a range of licensed agents. In this case, it is recommended that the possible designs for pivotal clinical trials are discussed with EU Competent Authorities. One possibility would be to compare various durations of the same test regimen in a population infected with organisms that are susceptible to each agent in the regimen but are resistant to many other licensed agents. One treatment arm could receive the test regimen for the currently recommended minimum duration of treatment for the type of patient enrolled and the other arm could receive a shorter duration(s) of the same test regimen. Alternatively, or in addition, one or more durations of the test regimen could be compared with a control group that receives current standard of care tailored to individual organism susceptibilities. In either case, identifying a margin for concluding non-inferior efficacy is not straightforward.

Taking into account the fact that most relapses in patients with susceptible *M. tuberculosis* occur within 6 months of completion of therapy, the primary analysis of efficacy may be based on sustained SCC rates determined at a visit conducted at a fixed time elapsed since randomisation and which falls at least 6 months after the last dose of the longest regimen included among the trial treatments. Alternatively, the primary endpoint could be defined as the incidence of bacteriologic failure and clinical failure (i.e. counting all patients who fail to achieve sustained SCC, relapses and deaths as failures). An initial approval may be based on such an analysis.

Secondary analyses should be conducted using all data collected up to a visit conducted at 24 months after randomisation. At this last visit, secondary analyses should compare the sustained SCC and cure rates between regimens. It is possible that these results could be reported in the post-approval period.

Other issues to consider include the nature of any concomitant bacterial therapy that may be considered necessary to treat other infections during the trial treatment period. For example, antibacterial agents with known or potential efficacy against *M. tuberculosis* could interfere with culture

results. In particular, antibacterial agents of the same class as those included in the trial regimens should be avoided.

New agent(s) in variable regimens

One alternative that sponsors may consider is to demonstrate that inclusion of new agent(s) to which the individual patient's organism is susceptible within variable regimens (i.e. in which the additional agent(s) is/are tailored to the susceptibility of the individual patient's organism) allows for a shortening of the duration of treatment. The efficacy of the pooled regimens containing the new agent(s) would have to be at least non-inferior to that of regimens of widely-recommended composition and tailored to individual patients. The total content of the test and control regimens could be selected based on a pre-defined algorithm so that the range of possible regimens is to some extent limited.

This strategy poses additional difficulties for identifying an appropriate non-inferiority margin. It also poses considerable difficulties for interpretation because the efficacy of the short duration regimens of various total compositions may be different. Therefore, it is possible that the primary analysis meets the pre-defined non-inferiority margin but the overall result is driven by good efficacy of certain regimens balancing out poor efficacy of other regimens and by the proportion of patients who receive the better regimen(s). However, the trial will not be powered to assess the efficacy of individual regimens. In addition, the overall result cannot be extrapolated to regimens that were not even included in the trial.

Therefore this strategy is not straightforward and it is not further discussed in this guideline. If sponsors are considering such a strategy it is recommended that early discussions take place with EU Competent Authorities.

7.3.3.2 Development of new agents within regimens that provide superior efficacy

A demonstration of superiority based on a suitable primary endpoint would be an acceptable basis for approval. However, the feasibility of this approach is expected to be low.

It is unlikely that a new regimen will have superior efficacy to that of a standard recommended regimen for patients infected with organisms that are susceptible to first-line agents. Nevertheless, if a non-inferiority trial meets the pre-defined margin set for the primary analysis, it is acceptable that the protocol and statistical analysis plan could pre-specify that the results are then explored for evidence of superiority. In addition, it could be pre-defined that secondary endpoints are explored for evidence of superiority (e.g. based on time to SCC).

Recent data suggest that superiority is not likely to be shown when a single new agent is added to an optimised background regimen and compared with addition of placebo in patients with few remaining treatment options. The possibility of demonstrating superiority for a single new agent compared to placebo when each is added to tailored background regimens is expected to diminish further as more new agents and more efficacious regimens become available, including those suitable for treating organisms with resistance to multiple existing agents. However, it cannot be ruled out that adding a single new agent could provide superiority, perhaps in a population with very limited remaining treatment options. In addition, it remains possible that a new regimen containing more than one very active new agent could be superior to regimens consisting of only existing agents that are tailored to the susceptibility of individual patients' organisms.

If such a strategy is pursued it is recommended that there is stratification according to the extent of resistance in the baseline organism. A suitable primary endpoint should be discussed with EU Competent Authorities. The primary comparison between test and control regimens should not occur

before at least 6 months from start of therapy. It is essential that patients are followed to at least 24 months from the start of therapy and preferably for at least 12 months after the end of trial therapy.

7.3.3.3 Development of new agents with other potential benefits

Sponsors may wish to demonstrate that a fixed regimen containing at least one new agent provides an improved safety profile and/or lower risk of drug-drug interactions compared with an appropriate widely-recommended regimen.

If no change in duration of therapy or improved efficacy is anticipated from regimens containing the new agent(s) then a demonstration of non-inferior efficacy against an appropriate control arm could suffice for approval. Sponsors could consider attempting to demonstrate superior safety for regimens containing new agents based on pre-specified parameter(s) and a pre-defined co-primary endpoint. The assessment of the risk for clinically important drug-drug interactions can be based on a combination on in-vitro data and clinical pharmacology studies.

8. Clinical 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.

Depending on the composition of regimens that are compared in any one trial it is possible that comparisons between treatment arms may highlight adverse reactions likely to be specific to a new agent and/or adverse reactions that occur more commonly when regimens include a new agent. Such an exercise is unlikely to be feasible in trials in which a new agent is co-administered with a wide range of other agents in regimens that are tailored to the susceptibility of individual patients' organisms. Nevertheless, if a trial provides a comparison between adding a new agent or placebo the safety data could be informative based on the premise that in double blind trials the range of other agents co-administered should be broadly 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.

In trials that compare different durations of therapy attempts should be made to identify any adverse reactions that tend to occur early or late during the treatment period.

9. Considerations for special populations

<u>Patients with extrapulmonary disease</u>

Patients with well-documented extra-pulmonary disease may be considered eligible for enrolment into clinical trials if they otherwise meet the inclusion criteria. It is recommended that patients should be stratified according to the presence or absence of documented extra-pulmonary disease. Sponsors seeking a specific claim for use in extra-pulmonary disease at various body sites should consult the guidance on data requirements relating to the treatment of rarely encountered bacterial infections (CPMP/EWP 558/95 Rev 2).

Test combination regimens that are shown to be efficacious in pulmonary disease would not necessarily be suited to the treatment of extra-pulmonary 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 trials.

Paediatric populations

The presentation of clinical disease may be different in children aged less than approximately 10 years compared to adults but the response to treatment may be comparable at least from the age of five years upwards, supporting the possibility of extrapolating efficacy documented in adults (and possibly also adolescents if they are enrolled into the same trials as adults) to children. Below the age of 5 years an extrapolation of efficacy observed in adults is regarded as more problematic due to higher rates of extra-pulmonary tuberculosis. Nevertheless, due to the recognised difficulties in conducting randomised controlled trials in this age group, including the problems of establishing the diagnosis, the approach could be accepted.

The diagnosis of tuberculosis and the assessment of responses to treatment in children should be based on age-specific criteria recommended by internationally-recognised expert bodies. Age-specific dose regimens should be identified based on pharmacokinetic studies conducted in children during therapy for tuberculosis. Children should also be followed to obtain data on safety and descriptive data on treatment response.

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 anti-retroviral therapy. Sponsors may choose to evaluate use in such patients separately or to include them in clinical trials along with HIV-negative individuals provided that the efficacy of test regimens is not expected to be adversely affected by factors such as additive toxicities and/or drug-drug interactions.

When HIV-negative and positive individuals are included in a trial consideration should be given to stratification by HIV status to achieve adequate numbers in each sub-group to be able to assess the possibility of higher long-term relapse rates in HIV-infected patients.

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 HIV regimens are adjusted. The possible occurrence of immune reconstitution syndrome is also a complicating factor for the overall safety assessment of these patients.

Concomitant medications pre-disposing to tuberculosis

Whenever possible, drugs that are known to predispose patients to develop disease due to *M. tuberculosis* (e.g. 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/or 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.

References

Websites consulted:

WHO (http://www.who.int/tb/strategy/en/)

Stop Tb Partnership (http://www.stoptb.org)

TB Alliance (http://tballiance.org)

International Union Against Tuberculosis and Lung Disease (http://www.iuatld.org/index_en.phtml)