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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 pulmonary disease due to *Mycobacterium tuberculosis*

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This guideline replaces 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* EMA/CHMP/EWP/14377/2008

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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 pulmonary 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 and reduce the numbers that are discontinued post-randomisation, there is increasing use of rapid diagnostic tests to detect *Mycobacterium tuberculosis* and resistance to some commonly used anti-tuberculosis agents. Currently it remains important to attempt to culture *M. tuberculosis* from appropriate baseline specimens in order to confirm organism identity and to assess susceptibility at least to the agents included in trial regimens. In future it may be acceptable to replace culture as well as current susceptibility testing methods with alternative non-culture-based (e.g. genomic) methods.

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.

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 setting one possible approach would be to randomise patients to receive one or more durations of the test regimen or a widely-recommended first-line treatment regimen. If the test regimen is not considered suitable for evaluation in patients with many remaining therapeutic options, one possible approach would be to evaluate one or more durations of the test regimen in patients with fewer remaining treatment options compared to a regimen likely to be generally appropriate for the population to be enrolled or compared to regimens tailored to the susceptibility of the individual patient's organism. Alternatively or in addition, the test regimen could be compared to an external control group.

It is possible, although unlikely, that adding a single new agent could provide a superior response rate, perhaps in a population infected with organisms resistant to multiple licensed agents. In addition, it remains possible that a new regimen containing more than one new agent could be superior to standard of care, consisting of regimens that are tailored to the susceptibility of the individual patient's organism. Other development scenarios not addressed in this guideline can be envisaged and should be discussed with EU Competent Authorities.

There are recognised difficulties in diagnosing pulmonary tuberculosis in children, especially in those aged less than 5 years in whom extrapulmonary disease occurs more often and the clinical presentation and radiological findings may differ from those in older children and adults. Nevertheless, an extrapolation of efficacy data in adults to paediatric age groups is considered to be possible

provided that appropriate age-specific dose regimens can be established using 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

Pulmonary disease caused by *Mycobacterium tuberculosis* is currently treated with combination therapy for many months. Factors that influence the choice of regimen and the duration of therapy include (among others) 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.

Simpler and shorter treatment regimens and agents with less potential for drug interactions and better tolerability are needed for the management of pulmonary disease due to *M. tuberculosis*, regardless of its susceptibility pattern. There is a particular need for short and simple regimens that are effective against *M. tuberculosis* that is rifampicin-resistant, multi-drug-resistant or extensively drug resistant.

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 pulmonary 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 anti-tuberculosis agents.

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.

2. Scope

This addendum covers the evaluation of new agents for the treatment of pulmonary disease due to *Mycobacterium tuberculosis*, defined as disease affecting the lung parenchyma.

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. The guidance is relevant whether a new agent is to be developed as a standalone formulation for co-administration with other new or licensed agents 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 extra-pulmonary disease, latent infection, post-exposure prophylaxis or the management of disseminated Bacillus Calmette Guerin after immunisation.

Existing CHMP guidance should be consulted regarding the evaluation of in-vitro antibacterial activity, pharmacokinetics, pharmacokinetic-pharmacodynamic relationship and safety of test agents or regimens. Detailed guidance on these issues is not provided in this guideline..

As always, not all possible clinical development scenarios can be anticipated or addressed in guidelines. Sponsors considering other approaches should reflect on the elements of this guideline that are applicable to their plans and should discuss their proposed clinical development programmes with EU Competent Authorities.

3. Legal basis and relevant guidelines

This guideline must 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 the following and the guidelines that are listed in them:

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

ICH topic E7 Studies in Support of Special Populations: Geriatrics. Questions and Answers (July 2010)- EMA/CHMP/ICH/604661/2009

4. Microbiological data

4.1. In vitro activity

For each new anti-tuberculosis 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.

4.2 Efficacy in nonclinical models

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 anti-tuberculosis 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.

Animal models, including immunocompetent and immunodeficient models, may 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. The range of parameters measured in in-vivo efficacy studies should be selected and defined based on the scientific literature.

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 different methodologies, or on rapid diagnostic tests applied to appropriate specimens obtained at screening visits (see section 6). If rapid diagnostic tests are to be used to detect *M. tuberculosis*, with or without detection of specific drug resistance, they should be specified in the protocol and used at all trial sites or testing should be conducted at central laboratories using screening visit specimens.

Recognising the global nature of clinical development programmes and ongoing developments in the field, rapid diagnostic tests applied to sputa or other specimens from the respiratory tract 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. The potential impact of the characteristics of the test used on the patient population enrolled should be discussed (e.g. the possibility that the test used could result in exclusion of patients with low bacterial burdens).

Currently it remains important to attempt to culture *M. tuberculosis* from appropriate baseline specimens in order to confirm organism identity and to assess susceptibility at least to the agents included in trial regimens. In future it may be acceptable to replace culture as well as current susceptibility testing methods with alternative non-culture-based (e.g. genomic) methods.

Primary culture may occur in accredited local laboratories or in designated central laboratories with appropriate expertise. It is recommended that primary culture should employ an appropriate selective liquid medium. If a solid culture medium is also used, 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 viable organisms during and post-therapy

Culture-based methods

The same culture method(s) selected for confirmation of *M. tuberculosis* at baseline should be applied to the isolation of organisms in post-baseline specimens. It is recommended that an appropriate selective liquid medium is used. If the sponsor chooses to use an additional culture medium, a positive result obtained using any method may be used for the primary analysis of efficacy.

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 the sputum 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 ability of the selected methodology for sample processing and culture to detect low numbers of viable organisms should be assessed.

Non-culture-based methods

A negative result obtained using a sensitive PCR method to detect *M. tuberculosis* may be useful but a positive result is not since it could represent only non-viable bacteria. Sponsors may consider using recently developed non-culture-based methods that can detect live organisms in specimens instead of, or in addition to, culture-based methods.

Contaminated cultures

Protocols should explain the procedures to be put in place in case of a contaminated culture either with a non-mycobacterial organism or with an organism belonging to a mycobacterial species other than *M. tuberculosis*. If contamination is evident soon after specimen collection and processing, a fresh specimen should be obtained if this is possible. Non-culture-based methods may also be used to assist in determining whether live *M. tuberculosis* is still present (see above).

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

Patient eligibility should be based on both clinical (signs, symptoms and imaging) and laboratory evidence of active pulmonary tuberculosis. Section 9 considers additional issues regarding enrolment of HIV-infected individuals and paediatric patients.

Laboratory evidence (see section 4.3)

Patients may be enrolled based on prior documentation of active pulmonary tuberculosis at local or reference laboratories and/or the results of rapid diagnostic tests applied to appropriate specimens obtained at the screening visit. Rapid tests used to determine eligibility may include detection of resistance to specific anti-tuberculosis agents. Whilst it is recommended that patients are not enrolled solely on the basis of a positive smear accompanied by clinical signs and symptoms, having a positive smear may correlate with having a relatively high bacterial load and consideration could be given to stratification according to smear status. In addition, or alternatively, if a semi-quantitative or quantitative rapid test becomes available, consideration could be given to stratification of patients according to the result.

Clinical evidence

Protocols should specify the clinical and imaging investigations required to characterise the extent of pulmonary tuberculosis (e.g. number of lobes affected and presence of cavitation).

7. Assessment of efficacy

7.1 General considerations for trial design and analysis

It is recommended that clinical trials should employ directly observed treatment (DOT).

Although a double-blind and double-dummy design is preferred, especially for pivotal studies, it is acknowledged that this may not always be a practical option due to the need to co-administer multiple agents, some of which may be given by injection. In addition, to address some strategies, the regimen content may need to be tailored to the susceptibility of the individual patient's organism. Moreover, if rifampicin is included only in some of the treatment 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.
- 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. The protocol should specify the appropriate duration of safety follow-up after the last dose administered to patients who are withdrawn from the trial and referred to routine local treatment services.

- Handling of results of on-treatment and post-treatment culture-based and/or non-culture-based methods for detecting viable organisms. The protocol must adequately justify the method(s) from which results will be used for the primary analysis. Depending on the range of tests and the criteria for including results in the primary analysis, adequate sensitivity and/or secondary analyses should be planned.
- Handling of patients with single positive results in the primary analysis when some prior and all sequential specimens are negative. The protocol should also clarify whether or not a positive result should prompt an additional visit to collect another specimen, depending on the trial visit schedule and the timing of the positive finding.
- Handling of visits at which no satisfactory respiratory tract specimen can be obtained despite the use of measures taken to induce sputum production. The protocol should specify how the lack of a laboratory result at these visits will be counted in the primary analysis and in sensitivity and/or secondary analyses.
- Handling of contaminated cultures obtained at one or more visits in the primary analysis, with or without the results of a non-culture-based test.

7.2 Efficacy endpoints

Sponsors should always justify the primary and secondary endpoints selected for each trial and should apply definitions in accordance with the trial objectives and scientific literature. This section considers some examples of the endpoints that may be designated primary or secondary in any one trial and how they may be defined. Additional endpoints and alternative definitions for endpoints that reflect recent advances in the field may be added to or replace the examples below.

- 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. Section 7.3.3 considers the duration of post-therapy follow-up and the use of sustained SCC up to a specific time elapsed from randomisation as the primary endpoint in dose/regimen-finding and pivotal trials.

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 when using a specified culture medium. 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

For the purposes of evaluating the efficacy of a regimen within a clinical trial 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.

- Primary treatment failure

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

- 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 the case should be counted as a relapse in the primary analysis of efficacy. In trials that include planned follow-up to determine post-treatment relapse rates it is recommended that sponsors explore the data collected on all protocol-defined endpoints at each trial visit for any correlation there may be with relapse.

- Deaths

In the primary analysis the usual approach should be to count all deaths as unfavourable outcomes. Depending on where a trial is conducted and other features of the patient population, there may be some circumstances in which sponsors could justify that the primary analysis excludes deaths that are due to traumatic events, such as road traffic accidents and assaults. If deaths due to trauma are excluded from the primary analysis there must be a sensitivity analysis planned in which all deaths are counted as unfavourable outcomes.

- 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 of duration that takes into account the perceived risk of selecting for resistance is usually recommended at least for agents that show a rapid bactericidal effect *in vitro.* For example, EBA could be evaluated over a range of doses of a new agent 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 of similar design 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.

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 be useful to conduct one or more multiple-arm trials over defined periods (e.g. 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. 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 anticipated to be curative (if this duration was not already completed) 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 (i.e. in an adaptive clinical trial design) then the analysis of final outcomes in patients who are switched should be 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

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 compared to currently recommended standard of care in patients infected with organisms that are susceptible to all agents in the fixed regimen. 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 parenteral administration is required for one or more agents).

For test regimens suitable for patients with many remaining treatment options:

One approach would be to randomise patients infected with organisms susceptible to all agents in the test regimen to receive the test regimen or the recommended standard regimen for organisms treatable with first-line therapies. Patients could also be randomised to different durations of the test regimen. The primary analysis would aim to demonstrate non-inferiority between the test regimen group(s) and the standard of care group. A positive result should support an indication for the FDC or for the individual new agent(s) in the regimen for the treatment of pulmonary tuberculosis using the shortest duration of the test regimen that is shown to be non-inferior to standard of care.

It is possible that patients infected with organisms susceptible to all agents in the test regimen but not eligible for treatment with a first line regimen could have more advanced lung disease or other host factors impairing their response to treatment, possibly leading to need for a longer duration of treatment. To investigate this possibility, one approach would be to enrol an additional arm consisting of such patients to receive a fixed duration of the test regimen or to randomise them to different durations of the test regimen. The outcomes in these patients could be compared with those observed in the primary analysis to investigate whether an alternative duration of treatment should be considered or recommended.

For test regimens unsuitable for patients with many remaining treatment options:

In this case one possible approach would be to randomise patients infected with organisms resistant to a range of licensed agents but susceptible to the test regimen to receive one or more durations of the test regimen or standard of care regimens tailored to individual organism susceptibilities. Another approach may be to use a single widely-recommended standard of care regimen if it is possible to identify one that is expected to be suitable for the vast majority of eligible patients. In each of the possible trial designs described, 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 unfavourable bacteriologic and clinical outcomes (i.e. counting all patients who fail to achieve sustained SCC, relapses and deaths as having an unfavourable outcome). An initial approval may be based on such an analysis. Identifying a margin for concluding non-inferior efficacy is not straightforward. CHMP guidance should be consulted and proposals should be discussed with EU Competent Authorities.

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

Sponsors may wish to evaluate whether inclusion of one or more new agent(s) to which the individual patient's organism is susceptible in regimens that are tailored to the susceptibility of the individual patient's organism allows for a shortening of the duration of treatment. The efficacy of the 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. 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

It is unlikely that a new regimen of standard or shortened duration 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 testing for

superiority. In addition, it could be pre-defined that secondary endpoints are explored for evidence of superiority (e.g. based on time to SCC).

The likelihood that superiority can be demonstrated for a single new agent compared to placebo when each is added to tailored background regimens appears to be low and 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. Meanwhile, it cannot be ruled out that a new regimen (of standard or shorter duration) containing one or more very active new agent(s) could provide superior efficacy to regimens that can be assembled based on the susceptibility of individual patients' organisms or to external controls.

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. In this specific setting in trials in patients with very few remaining treatment options, 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). 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 all or almost all of 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

Patients with extrapulmonary disease

Patients with pulmonary disease due to *M. tuberculosis* who also have certain types of well-documented extra-pulmonary disease may be considered eligible for enrolment into clinical trials if they otherwise meet the inclusion criteria and if pharmacokinetic data for the test regimen suggest that it could be an adequate treatment. If such patients are enrolled, it is recommended that there is stratification 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).

Paediatric populations

The presentation and treatment of pulmonary tuberculosis is similar in adults and paediatric patients aged from approximately 10 years so that an extrapolation of safety and efficacy data obtained from adults is acceptable. Sponsors may also consider including adolescent patients with tuberculosis in trials conducted in adults.

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 this age group.

There are recognised difficulties in diagnosing pulmonary tuberculosis in children aged less than 5 years in whom extrapulmonary disease occurs more often and the clinical presentation and radiological findings may differ from those in older children and adults. Nevertheless, an extrapolation of efficacy data in adults to paediatric age groups is considered to be possible provided that appropriate age-specific dose regimens can be established using pharmacokinetic data obtained in children with tuberculosis and the safety profile is shown to be acceptable. The diagnosis of tuberculosis in these children should be based on age-specific criteria recommended by internationally-recognised expert bodies.

Sponsors may also consider establishing post-authorisation registries for collecting data on treatment outcomes from paediatric patients.

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 new regimens in adequately treated HIV-infected 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 the same 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 relapse rates in HIV-infected patients.

The assessment of safety of an individual anti-tuberculosis agent or test regimen in HIV-infected patients with tuberculosis is complicated by the number of concomitant medications and the potential for an extensive range of drug-drug-interactions to occur, 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.

10. 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 (https://www.theunion.org/)