EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

November 2010
EMA/759784/2010
Committee for Medicinal Products for Human Use

Reflection paper on the need for active control in therapeutic areas where use of placebo is deemed ethical and one or more established medicines are available

Draft

Adoption by CHMP for release for consultation	November 2010
End of consultation (deadline for comments)	31 March 2011

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

Keywords	*Active control, placebo control*

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1. Summary

Where feasible, three-arm trials including experimental medicine, placebo and active control represent a scientific gold-standard and there are multiple reasons to support their use in drug development. However, there are situations where such trials are not required by CHMP for a properly informed decision on benefit-risk.

It is the position of CHMP that, where ethical and feasible, a placebo control arm should be included in the pivotal trial(s) used to support marketing authorisation application. The need for an active control must be considered on a case-by-case basis. CHMP consider it to be particularly important for estimated benefits and risks to be contextualised through comparison to active control where:

- the experimental medicine might be associated with **safety** concerns which impact mortality or morbidity, markedly impair quality of life or cause active treatment to be discontinued or delayed leading to significant, long-term or irreversible harm.
- treatment with a medicine of inferior **efficacy** might conceivably lead to significant, long-term or irreversible harm for the patient.

In both scenarios, the comparison to active control will usually need to be 'direct' (i.e. within the same trial). There are few circumstances where an indirect comparison might be considered sufficiently reliable.

This paper should not be interpreted as describing criteria used by CHMP for making a benefit-risk decision. CHMP opinions are given on the basis of a benefit-risk balance in the context of a marketing authorisation application. This paper outlines a framework for the discussion and justification of the choice of control arms that is expected from an applicant in a marketing authorisation application.

2. Scope

This paper describes regulatory considerations, and expectations of applicants, in discussing the importance of a direct comparison to active control for a properly informed decision on benefit-risk. The scope of the paper is limited to those therapeutic areas where placebo is deemed ethical and one or more established medicines are available. The principles outlined are applicable to pivotal trials to establish efficacy and safety, for 'add-on' trials as well as trials without background treatment. CHMP has previously provided Position Statements on issues related to this topic (EMEA/17424/01 and EMEA/119319/04). This paper supplements these documents. The paper should be read in conjunction with relevant therapeutic area and methodological guidance documents.

The following are outside the scope of this paper:

- the role of comparisons to active control (direct or historical) in the benefit-risk decision
- therapeutic indications where use of placebo is unethical or where no established medicine is available
- recommendations for the design of clinical studies to support marketing authorisation applications for generic medicines and biosimilars
- certain orphan diseases / small populations, for which the number of patients that can reasonably be recruited in a sensible timeframe do not enable formal comparisons to more than one control
- medicines traditionally tested using external controls given the extremely large sample size, rarity of the clinical outcome and because the underlying response in the absence of treatment is well quantified

The paper is written in the context of an application for marketing authorisation, though the framework outlined also applies to a discussion of the need for active control during a scientific advice procedure, which remains the appropriate forum for discussions on specific development programmes.

3. Background

Following Directive 2004/27/EC of the European Parliament and of the Council and as described in EMEA/119319/04, it is not necessary for the benefit-risk profile of an experimental medicine to at least

as favourable as the benefit-risk profile of any or all established medicines in order to receive marketing authorisation. This is appropriate as frequently more than one treatment is required per indication (some medicines suit some people better than others) and clinical trials do not definitively capture all information on benefits and risks; knowledge accumulates during a product's lifecycle. It is important to recognise that the purpose of regulatory approval is not to determine clinical practice (over and above the act of issuing a particular license for a medicine) and there is no limit to the number of medicines that can be licensed for any given therapeutic indication providing the benefit-risk of each is favourable.

A proper contextualisation of the benefit-risk decision for an experimental medicine is beneficial for the promotion of public health through the rational use of medicines and through properly informed product labelling. Determining whether risks outweigh benefits, or vice versa, is not trivial and must consider the clinical context of the proposed therapeutic indication including the availability, the use and the safety and efficacy profiles of other medicines. Because effect sizes seen in clinical trials depend on multiple factors, including the therapeutic indication under study, the efficacy and safety variables measured, the precise patient population recruited and other experimental conditions under which the study is performed, accurately judging the levels of benefit and risk observed without contextualisation by at least a placebo control group and, in certain therapeutic indications, also by an active control group is difficult. One particular value of a comparison to active control is to contextualise efficacy and safety using a reference about which more information is known, not only from a historical clinical trial programme but also from clinical practice. Three-arm trials can be beneficial to the sponsor. For example, in indications where placebo-controlled, pivotal studies have a high failure rate (e.g. studies in depression) an active control arm can aid inference, helping to distinguish between a study failing because of inadequate efficacy associated with the experimental treatment and a study failing because of inadequate assay sensitivity, wherein the active control also fails to distinguish itself from placebo. In addition, if the magnitude of the effect observed with the experimental treatment is considered to be of borderline clinical importance, a demonstration that performance in the pivotal clinical trials is broadly similar to that of an established medicine, about which much more is known through use in clinical practice, can be reassuring.

Section 5.2.5.1 of Annex I to Directive 2001/83/EC states *"In general, clinical trials shall be done as 'controlled clinical trials' if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo."*

It is the position of CHMP that, where ethical and feasible, a placebo control arm should be included in the pivotal trial(s) used to support marketing authorisation application. Whilst a placebo control may sometimes not be suitable to address all study hypotheses (the complete evidence base for many regulatory decisions comprises evidence of short-term efficacy and safety, maintenance of efficacy and evidence of long-term safety) this should not rule out its use for other study hypotheses. For example, in a long-term trial, it may be feasible, ethical and scientifically beneficial, to include a short-term placebo arm or to include a placebo arm with an option for escape treatment, which may assist in the interpretation of some study hypotheses. One exception to this request to include a placebo is where the only aim of the active control trial is to demonstrate superior efficacy to an established medicine.

Comparisons to active control as well as to placebo control would be expected in certain therapeutic indications. Nevertheless, given the impact on the complexity, duration and cost of drug development, there will be circumstances where such trials should not be required by CHMP as a properly informed decision on benefit-risk can be made without such data. When an active comparator is required, the comparator selected would usually be the gold-standard, EU-licensed, product for the appropriate indication, following relevant CHMP guidelines and international treatment guidelines as appropriate. Of course, there exist more complex situations where it is necessary to use alternative strategies, for example investigator's best choice of therapy, medicines licensed by other regulatory agencies but not in the EU, or medicines for which use is clearly supported by medical literature. In some therapeutic areas, comparison to historical datasets is possible, in particular where estimated effect sizes for the experimental medicine are considerably more impressive than previously seen and the improved effects can be attributed to the experimental medicine rather than a change in the experimental conditions (e.g. improvements in diagnosis or background treatments over time). In other therapeutic areas, gauging and understanding the magnitude of benefit or risk from a clinical perspective is greatly facilitated by a direct comparison to an established medicine.

4. Discussion

Regulatory considerations for determining whether a direct comparison to active control is required for a properly informed decision on benefit-risk

ICH E10 describes the pros and cons of different controls arms. Some fundamental concepts determining the choice of control arm(s) are highlighted in Table I and Figure I of that document. In addition, therapy-area specific guidance on the design of trials in support of a marketing authorisation application is provided in the various CHMP guidelines and product-specific guidance can be obtained through CHMP Scientific Advice. The marketing authorisation application must include a discussion on the choice of control arms in the pivotal trial(s). In a therapeutic indication where placebo is deemed ethical, the absence of a placebo control would be controversial and would require detailed discussion.

Where feasible, three-arm trials including experimental medicine, placebo and active control are usually preferred to support marketing authorisation applications. Even in situations where estimates of efficacy and safety relative to placebo are sufficient for regulatory decisions on benefit-risk, the inclusion of an active control arm still offers potential advantages for sponsors, regulators and other stakeholders including medical practitioners and patients. The need for an active control must be considered on a case-by-case basis (see also flowchart in section 6). CHMP consider it to be particularly important for estimated benefits and risks to be contextualised through comparison to active control where:

- the experimental medicine might be associated with **safety** concerns which impact mortality or morbidity, markedly impair quality of life or cause active treatment to be discontinued or delayed leading to significant, long-term or irreversible harm.
- treatment with a medicine of inferior **efficacy** might conceivably lead to significant, long-term or irreversible harm for the patient.

In both scenarios, the comparison to active control will usually need to be 'direct' (i.e. within the same trial). There are few circumstances where an indirect comparison might be considered sufficiently reliable.

Whilst it may still be possible to estimate benefits and risks with only a placebo control in the scenarios described above, clinical trials are complex and without a direct comparison to active control it may not be possible to properly gauge and understand the magnitude of benefit or risk from a clinical perspective and hence to make a properly informed decision on benefit-risk. The difficulty for the drug developer is that these scenarios will not usually be readily identifiable in advance of conducting the confirmatory trial(s). Indeed, the true benefits of a comparison to active control may not be realised until data from the confirmatory trials are available. This represents a risk to the drug developer and gives rise to important decisions regarding the design of the pivotal trials. In particular, if either of the above scenarios is considered plausible it would represent a risk not to plan any comparison to active control as such data may be required by CHMP for a properly informed decision on benefit-risk.

Based on the arguments above, the regulatory position on the importance of an active control in the marketing authorisation application will consider the following aspects, which should be addressed by the applicant in the marketing authorisation application if no direct comparison to active control is available:

- Considering real-world intended use (which may differ to the conditions of a clinical trial, for example in terms of duration of treatment) what is the risk to the patient of significant or long term harm as a consequence of a treatment with inferior efficacy? In particular, it should be considered whether the disease is progressive or transient in nature, the severity of symptoms, whether later lines of more toxic therapy are avoided or delayed by successful treatment and whether patients in clinical practice are adequately monitored over time to determine response or lack of response prior to increased risk of significant or long term harm.
- Does the experimental medicine have an innocuous safety profile? Specifically, does the experimental medicine have a safety profile which is more adverse than other medicines licensed for the relevant indication? In this situation it is even more important that the magnitude of the treatment effects on both efficacy and safety are properly understood and contextualised. Are any patients irreversibly disadvantaged by adverse events from the experimental treatment or by discontinuation of experimental treatment due to adverse event? What are the consequences of any delays to administering other active treatments caused by toxicity of the experimental treatment and do other established medicines suffer from similar concerns?

- What proportion of patients is adequately treated with existing medicines? Are there reasons to consider that the new medicine will benefit a complementary group of patients to those benefitting from established medicines? In particular, a product with a different mechanism of action might be more likely to complement existing medicines and so enhance the therapeutic armamentarium than a product with the same mechanism of action as existing treatments.
- Whether the magnitude of the effect observed with the experimental treatment is considered to be borderline or unequivocally clinically important?
- How well the do the efficacy endpoints measured translate into clinical outcomes likely to be observed in practice? Some rating scales and other patient reported outcomes are primarily tools for use in clinical trials with limited direct relevance to the patient in clinical practice. For these it is particularly informative to contextualise the benefits observed through direct comparison to active control about which more is known because of (often extensive) use outside of the clinical trial setting. Similar arguments apply for subjective endpoints in open-label trials, or trials in which blinding is compromised in a significant proportion of patients.
- The validity of any potential comparison to a historical control (see below).

Between-trial (historical) comparisons

If a direct comparison to active control is not available from within the confirmatory trial programme a sponsor would need to put the observed effects into clinical context via historical comparisons of data from the confirmatory trials to trials of an appropriate reference treatment. Such comparisons are notoriously unreliable and might only be considered an adequate alternative to a direct comparison under the following conditions:

- based on a literature review, it can be substantiated that the historical trials selected are comprehensive and representative of the performance of the reference treatment.
- it can be substantiated that the historical trials have been planned, conducted and reported to high standards with methods of data collection, synthesis and analysis, for efficacy and for safety data, of the same standards as for the trials of the experimental agent.
- the trials are contemporary in that their design does not differ to an important degree from the design of the studies in the confirmatory development programme of the experimental medicine (considering, for example, the region of trial sites, characteristics of patient population, background standard of care / concomitant medication, endpoints, selection of control arm; the comparison is facilitated if placebo is the control arm in both trials).
- evidence from the trials of the experimental medicine is sufficiently impressive to outweigh any concerns over the likelihood of bias in the historical comparison.

There are numerous clinical indications for which new medicines have been developed and standards of clinical practice have changed such that a naïve comparison to the historical dataset would be uninformative. Data presentations in the marketing authorisation application should be accompanied by a balanced, qualitative critique on whether data from the two trials can be reliably compared, addressing issues which may compromise the comparison of the trials and a quantitative exploration on how differences in any important aspects of the trial design and conduct affect the comparison of the trials.

Objectives for trials including both placebo and active control

Two of the most common primary objectives for pivotal clinical trials are to demonstrate superiority to placebo control, or to demonstrate non-inferiority or equivalence to an active control.

For trials where it can be agreed (in line with a relevant CHMP guidance document or scientific advice) that an appropriate primary objective is to demonstrate non-inferiority or equivalence to an active treatment, the assay sensitivity of the trial and evidence (possibly 'indirect') of superiority to placebo must be established. Requirements for the demonstration of assay sensitivity are described in ICH E10. The most compelling evidence for assay sensitivity will be inclusion of a treatment arm against which superiority can be demonstrated, usually placebo, though differentiating between multiple doses of test and / or reference treatment can also suffice. Hence, a 3-arm, active and placebo controlled trial will often be required even where the primary objective is to demonstrate non-inferiority or equivalence to an active treatment. In this situation, the requirements to establish assay sensitivity are usually equivalent to the requirements to show superiority to placebo for the active treatments and thus the study should be planned with the additional objective of demonstrating superiority to placebo (as a

pre-cursor to the test for non-inferiority / equivalence). It may therefore be that the randomisation scheme is unbalanced to allocate fewer patients to placebo than to either active treatment.

For trials where it can be agreed that an appropriate primary objective is demonstration of superiority to placebo, objectives for comparison to active control can vary. Including a third arm of similar size (assuming 1:1 randomisation) would usually give sufficient power to demonstrate superiority of the active control compared to placebo, but would not necessarily give the statistical properties (in particular, statistical power) desirable for a formal comparison of non-inferiority, i.e. exclusion from the confidence interval for the estimated differences between groups of all differences of clinical importance. However, the absence of a formal demonstration of non-inferiority may not be critical in circumstances where primary evidence of efficacy is based on a comparison to placebo (i.e. where exclusion of clinically important inferiority to the control is not necessary to establish favourable benefit-risk). Instead it may be sufficient to plan to estimate relative efficacy to a certain precision. The selected precision and hence number of patients required will need to be justified. A starting point for discussion would be to examine the statistical properties of recruiting the same number of patients to the active control as are recruited on the test treatment (i.e. 1:1 randomisation). Where the primary rationale for including an active control is because of a serious adverse event associated with experimental treatment and / or potentially inferior safety compared to other available treatments, it may be necessary to estimate the relative frequency of the adverse event on each active treatment. In this case the precision with which the incidence rates are estimated should be justified and the study should be powered appropriately, in addition to considerations of statistical power for the primary efficacy objective.

5. References

EMEA/17424/01 – EMEA/CPMP Position Statement on the use of Placebo in Clinical Trials with regard to the Revised Declaration of Helsinki
(http://www.ahppi.org.uk/CMS/STORE//EU%20Directive/EU_placebo_files/ATTACHMENTS/EMEAposition.pdf)

EMEA/119319/04 - EU Standard of Medicinal Product Registration: Clinical Evaluation of Risk/Benefit - The role of Comparator Studies
(http://www.ema.europa.eu/docs/en_GB/document_library/Position_statement/2009/12/WC500017660.pdf)

Directive 2004/27/EC of the European Parliament and of the Council, (Official Journal L 136, 30/4/2004 p. 34 - 57)

Directive 2001/83/EC (Consolidated version: 05/10/2009)

ICH E10 Choice of Control Group and related issues in Clinical Trials
(http://www.ich.org/LOB/media/MEDIA486.pdf)

6. Flowchart

Step 1 - **Judge possibilities for choice of control**

Is placebo control ethical and feasible?

Is active control available?

Step 2 - **Judge therapeutic setting / potential for loss of chance**

Consider questions outlined in **Section 4**, e.g:

Is there a risk to the patient of significant or long term harm as a consequence of a treatment with inferior efficacy?

Is success of treatment monitored so that inadequate efficacy can be detected, and significant or long-term harm consequently avoided?

Step 3 - **Consider safety**

Consider questions outlined in **Section 4**, e.g:

Does the experimental medicine have a safety profile which is more adverse than other medicines licensed for the relevant indication?

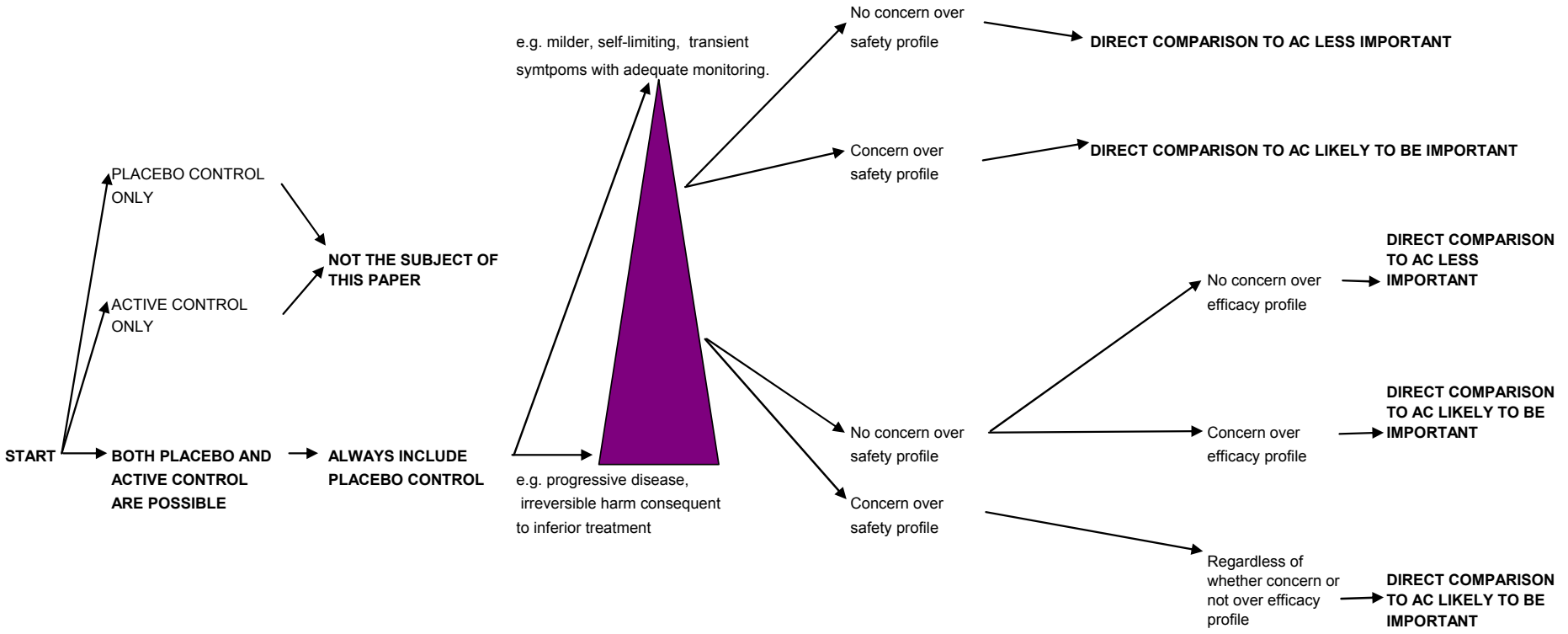
Is safety profile innocuous, mild, no suspiscion being inferior to established medicine?

What are the consequences of any delays to administering other active treatments caused by toxicity of the experimental treatment?

Step 4 - **Consider efficacy**

Consider questions outlined in **Section 4**, e.g:

Is there suspicion that efficacy is inferior to licensed active such that there is loss of chance to the patient?



KEY: HC - Historical control AC - Active control