15 November 2011
EMA/802793/2011
Committee for Medicinal Products for Human Use (CHMP)

Concept Paper on the update of guidance on the clinical development of medicinal products for the treatment of HIV

Agreed by Infectious Diseases Working Party	September 2011
Adoption by CHMP for release for consultation	20 October 2011
End of consultation (deadline for comments)	31 January 2012

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Keywords	*HIV, Antiretroviral, Drug development, Guidance*

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1. Introduction

Over 20 antiretroviral agents (ARTs), belonging to several classes, have been approved in the European Union. Recent years have seen the licensure of new agents with better tolerability, more convenient dose regimens and activity against viruses resistant to multiple ARTs. Thus, the majority of patients can achieve the therapeutic goal of suppression of plasma viral load below the limits of quantification of presently used assays. Yet there are still a few patients that do not achieve sustained viral suppression, due to reasons such as extensive viral resistance to ARTs or inability to tolerate certain agents or combinations of agents to which their virus remains susceptible.

2. Problem statement

The present EMA guidance was adopted in 2008. The main circumstance prompting the need for updated guidelines is the changing landscape of HIV treatment following the licensing of new treatment options for treatment experienced patients since 2007 (e.g. darunavir, etravirine, maraviroc and raltegravir). The introduction of new ARTs has greatly enhanced the likelihood that treatment-experienced patients can achieve sustained viral suppression. As a result, the pool of treatment experienced patients failing on their present regimens has considerably decreased. New ARTs are still needed for patients infected with virus that shows extensive resistance to ARTs or who cannot tolerate certain agents or combinations of agents to which their virus remains susceptible. The existing guidance does not provide a feasible regulatory path for the clinical development of such agents.

Until recently, the paradigm guiding the pivotal studies of abovementioned agents in treatment experienced patients has been superiority trials comparing an optimized background treatment regimen (OBT) + placebo vs. OBT + the investigational agent. The pivotal studies included patients infected with HIV with a range of calculated phenotypic or genotypic sensitivity scores (PSS/GSS). The current guideline effectively states that studies that evaluate agents in the treatment experienced population should compare test agent and placebo in patients with viruses having an OBT PSS/GSS score of 2. This approach avoids the possibility that those with scores of 0 or 1 might be exposed to functional monotherapy and also addresses the fact that superior virological efficacy with the investigational agent might not be demonstrable in case of a PSS/GSS >2. The conduct of non-inferiority studies as an alternative is mentioned as a possibility for certain circumstances in the current guideline, but the specific issues that would be relevant to such an approach are not considered.

There are several other matters that will need to be addressed in conjunction with the main reason for updating the current guidance. For example, the conduct and interpretation of non-inferiority studies in treatment experienced patients and non-comparative studies in patients with multi-class resistant viruses require reliable prediction tools and clear nomenclature for classifying OBT activity. There is also a need to consider what could be the post-marketing requirements for monitoring of drug resistance if initial approval were to be based on relatively short term, non-comparative trials.

3. Discussion (on the problem statement)

With regard to the primary reason for updating current guidance, since it is now difficult to recruit treatment-experienced patients who are failing on their regimen, and also as it may now not be possible to demonstrate superiority of viral efficacy for a new agent + OBT vs. OBT alone in an unselected treatment experienced population, a re-consideration of the regulatory pathway is needed.

However, changing the current paradigm will raise several difficult issues. For example, if it was considered that demonstration of non-inferiority of a regimen containing the test agent vs. an appropriate comparative regimen could support approval there will be a critical need to identify an appropriate non-inferiority margin. This requires knowledge of the effect size of the active control drug over placebo when added to the OBT, but such data may not be available or the available data may not be conclusive.

In addition, present guidance recognizes the problem of conducting comparative trials in patients with little support from the OBT (leading to putative "functional monotherapy" which may result in drug resistance). However, the assumption is that a non-comparative study in which all patients receive the test agent would be supported by a program of one or two superiority studies in less extensively resistant treatment experienced patients, which are likely no longer feasible undertakings for reasons described above.

4. Recommendation

The Infectious Disease Working Party recommends a revision of the extant guidelines on the Clinical evaluation of medicinal products for the treatment of HIV infection.

Particular issues for the revision of the guideline would include:

- *Non-inferiority studies in treatment experienced patients*. To address the possible design of such studies and data required to support the selection of rational non-inferiority margins.
- *Trial design in patients with multiple drug resistance* (e.g., PSS/GSS <2). To consider study designs to evaluate new agents in patients for whom it is not possible to construct a viable regimen from only licensed therapies. In particular, to take into consideration the need to minimize the risk of selection for drug resistance due to functional monotherapy and insufficient sum regimen potency.
- *The prediction of OBT activity and the nomenclature for its description*. There is a need to consider the possibility of an improved system of prediction and nomenclature of activity of a given OBT to account for its expected activity beyond merely quantifying the "number of active drugs" (as per GSS/PSS as commonly used).

5. Proposed timetable

A first draft guideline is to be released for consultation not later than Q1 2012.

6. Resource requirements for preparation

Preparation of this Guideline will involve the IDWP and the anti-viral SAG.

7. Impact assessment (anticipated)

It is anticipated that updated guidance will facilitate the development of new ARTs, especially those suitable for patients infected with virus that cannot be adequately treated using currently licensed agents.