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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)**

**DRAFT**

# GUIDELINE ON THE CLINICAL DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF HIV INFECTION

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**GUIDELINE ON THE CLINICAL DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF HIV INFECTION**

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## EXECUTIVE SUMMARY

This document is meant to provide guidance on the clinical development of medicinal products for the treatment of HIV infection including requirements for authorisation and wording of the Summary of Products Characteristics.

The need to protect patients' interest and the limitations as regards the design of clinical studies that follow from this are fully acknowledged. Thus, along with this document, note must be taken of updated, scientifically well-founded and generally acknowledged treatment guidelines.

Primary HIV infection, or pre/post-exposure prophylaxis are not covered. Also, due to the as yet limited regulatory experience with immune-based therapies (IBT) including vaccines, the guideline mainly focuses on the clinical evaluation of direct-acting anti-retroviral substances.

This document is meant for guidance only, but deviations should be justified and European regulatory scientific advice is recommended in these cases and also when compounds belonging to new classes of ART are under development.

This revision includes changes mainly with respect to:

- Study design in treatment experienced patients in order to minimise the risk of functional monotherapy.
- Recommendations regarding the selection of drug-drug interaction studies to be conducted before and after initial licensure.
- Recommendations for the presentation of drug-drug interaction data in section 4.5 and the virological and clinical study data in section 5.1 of the Summary of Product Characteristics.

## 1. INTRODUCTION (background)

Due to the inherent high mutation rate in HIV, the combined use of at least three active medicinal products is currently considered essential. In the following, "ART" refers to this combined use of medicinal products. Any use of sub-optimal therapy during drug development should be minimised as far as is possible.

In order to minimise bias, efficacy studies are expected to be randomised and, whenever possible, double-blind. It is recognised, however, that specific and prevalent side effects or insurmountable practical problems may make effective blinding impossible. In these cases, regulatory scientific advice should be considered in advance to commencement of pivotal studies.

However, blinding with respect to information that is used in the routine management of patients, such as viral load, CD4+ T-cell count, or drug resistance pattern is not expected.

### *1.1 Patients to be studied*

The CHMP acknowledges the need for new active compounds for patients with few or no remaining treatment options. Therefore, for novel compounds with antiviral activity against HIV that is resistant to many licensed therapies the CHMP strongly encourages sponsors to co-operate in order to make it possible to conduct informative and ethically acceptable trials early in the clinical development programme.

Provided that the properties of the experimental agent appear suitable, it is expected that safety and efficacy would be evaluated in patients who are treatment-naïve and in those who are treatment-experienced, including heavily pre-treated patients. The numbers of women, individuals from ethnic minorities and patients co-infected with HBV and/or HCV should be sufficient to allow generalised conclusions on safety and efficacy. These data should be accumulated early during drug development to provide input into the design of confirmatory studies.

When safety has been reasonably established in adults and promising efficacy data are available, a paediatric investigational plan should be developed in accordance with the Paediatric Rule.

As for other medicinal products, pharmacokinetic studies should be conducted as appropriate in patients with impaired renal or hepatic function and prospective gathering of safety data in patients with renal insufficiency, or hepatic impairment due to non-viral causes, is recommended.

Until such time as proper safety and efficacy data are made available in these groups of patients, the Summary of Product Characteristics would carry statements regarding any such deficiencies.

### *1.2 Measures of treatment outcome and supplementary investigations*

Since the introduction of Highly Active Anti-retroviral Therapy (HAART = ART in this document), viral load and CD4+ T-cell counts have been generally accepted as surrogate markers for efficacy in studies with anti-retroviral agents. For the evaluation of alternative treatment strategies over the very long term, and for treatment modalities that would not primarily be expected to modify the viral load, such as some IBT, clinical events remain the most relevant outcome measure.

#### *1.2.1 Clinical events*

Although the assessment of efficacy according to clinical events would be expected only in specific situations as mentioned above, the occurrence of HIV-related clinical events, including AIDS-defining conditions (ADCs), should always be detailed in clinical study reports. For compounds with potentially immunosuppressive properties, for example CCR5 antagonists, special attention to ADCs is warranted.

#### *1.2.2 Viral load*

For most efficacy studies, HIV RNA is an appropriate measure of efficacy. Therefore the use of validated and sensitive assays that meet current standards is essential. Currently a cut-off of 50 copies/ml is considered acceptable. In order to define the relationship between viral kinetics and sustained viral response, it is recommended that the dynamics of the early viral response are carefully documented, not only in dose-finding studies, but also in confirmatory (sub-) studies.

Undetectable HIV RNA is the preferred primary efficacy end-point for both treatment naïve and treatment experienced patients. This can be supplemented with secondary end points, including time averaged change from baseline and time to loss of virological response. Alternative primary endpoints are possible if specifically justified.

Depending on the study population and the geographical location of the study sites, the need for an assay that is able to quantify HIV RNA from various (including rare) subtypes of HIV-1 and HIV-2 should be addressed.

#### *1.2.3 Immune function*

Effects on the CD4+ T-cell count should always be documented. The correlation between changes in CD4+ T-cell count and viral load should be explored for populations and individuals as appropriate, and any unexpected findings should be further investigated and discussed. Therefore outcome (virological response and immune recovery) by baseline CD4 strata should always be presented. In heavily pre-treated patients with very low CD4+ T-cell count, improved immune function is of crucial importance. In these patients, CD4+ T-cell response is often a late event. This should be considered in the design of studies in enrolling these patients.

A shift in viral tropism may occur in patients treated with co-receptor inhibitors. The long-term consequences of such a shift may not be obvious at time of treatment failure. Therefore, long-term follow-up might be needed to specifically address treatment outcome with subsequent therapies.

If specific claims are to be made for an effect on immune function, such as for IBT, a much more detailed assessment of the functionality of the immune system is expected. This may include studies of the impact of the therapy on the immune response to conventional vaccines, effects on specific subpopulations of T-cells such as recent thymic emigrants, functionality assays and in the case of co-infection, putative effects on the co-infecting agent (CMV, HBV, etc). Due to the as yet immature status of this field, regulatory scientific advice is recommended regarding the design of these studies.

#### *1.2.4 Viral resistance*

The importance of viral resistance/reduced susceptibility makes the investigation of genotypic and phenotypic resistance an essential element of drug development. The choice of assays and assay conditions should be justified. It is recommended that the resistance pattern should be documented at

baseline and at least at the time of virological failure. It is recognised, however, that hidden resistant quasi-species at baseline may influence study outcome. Therefore the likelihood of primary acquisition of resistant virus, or impact of any prior ART, should be taken into account.

Characterisation of the co-receptor usage with validated genotypic and/or phenotypic methods at baseline and follow-up is of particular interest for some entry inhibitors where an apparent shift in, for example, co-receptor usage may lead to selective outgrowth of species present at baseline, or evolution through mutations.

The use of a new compound for the treatment of HIV may affect the possibility of successfully using other products after virological failure on the new compound. Essentially this refers to compounds within the same class of drugs such as PI, N(N)RTI or entry inhibitors. This may be regarded as an inherent property of the new drug. Therefore in-vitro studies of cross-resistance should be performed on HIV isolated after virological failure on the new compound.

Before and after initial licensure, the clinical development programme should aim to identify resistance-associated mutations and appropriate breakpoints to be applied to in-vitro susceptibility test results. Studies investigating replicative capacity ("viral fitness") are also encouraged. Resistance data collected during long-term follow-up of clinical studies and patients treated in Expanded Access Programme (EAP) should normally be provided as yearly updates.

If new assays are used during clinical studies and are needed to identify suitable patients for treatment and/or to monitor treatment effects (e.g. assays for viral tropism), the availability of these assays or validated alternatives outside of the clinical study setting should be addressed.

Genotypic or phenotypic sensitivity scores (GSS or PSS) should be reported in studies enrolling treatment-experienced patients and are necessary in the design of studies with optimised background therapy (OBT). When assessing outcome according to GSS and/or PSS, the score for the OBT selected for the individual patient should be compared with virological responses. Whenever applicable, it is expected that genotypic resistance testing is used. The algorithm for interpretation of genotypic resistance data and cut-off values for phenotypic resistance should be defined in advance and justified.

A separate template for how to present resistance data for inclusion in section 5.1 of the SPC and the European Public Assessment Report (EPAR) is provided in Annex B.

### *1.2.5 Viral subtypes/viral tropism*

The anti-retroviral activity of the novel compound should be studied in relation to viral subtypes and where relevant as regards co-receptor usage. Differential activity, e.g. in relation to viral subtypes should be mechanistically investigated, but may be reported post approval if justified.

### *1.2.6 Pharmacogenetics and immunogenetics*

Genetic host factors influence the natural course of HIV disease and apparently contribute to differences in the response to ART. Therefore genetic evaluation might elucidate the reasons for inter-individual differences in pharmacokinetics, idiosyncratic adverse reactions, and anti-viral activity.

### *1.2.7 Safety*

In addition to the usual reporting of safety data, high quality data on long-term safety is of crucial importance. The conduct of long-term post-marketing studies is therefore considered essential, as well as the participation in, or sponsoring of pharmaco-epidemiological studies.

Safety issues that would seem to be relevant to a novel compound based on class-experience, mechanistic reasoning and/or early clinical findings should be specifically followed long-term. For example, lipodystrophy should be followed for PIs and NRTIs, long-term effects on autoimmune diseases, infections and malignancies should be followed for CCR5 inhibitors. In the case of potentially severe but rare side effects, specific HIV cohort studies may be needed and should be addressed in the Risk Management Plan.

In addition, any adverse events that might be predicted by preclinical findings should be sought and followed with special care.

Potential differences related to sex or ethnicity should always be explored. The use of justified Quality of Life instruments in long-term, controlled and preferably double-blind studies may provide important additional information on the benefit – risk profile, given the impact of poor tolerability on compliance and psychosocial well-being.

Boosted protease inhibitors (PI) regimens may result in higher drug exposures than those previously studied in non-boosted regimens. Consideration should therefore be given to the possible need for additional safety pharmacology and/or toxicology studies. Also, specific studies may be required in cases where studies with the non-boosted PI revealed specific safety concerns (e.g. QTc prolongation).

## 2. SCOPE

The scope of this document is to provide guidance as regards drug development for the treatment of patients infected with HIV. It is foreseen that Ethics Committees and National Authorities may object to long term studies *de facto* conducted as functional monotherapy studies. This guideline recognises these restrictions, fully acknowledging that this and the availability of a large number of licensed drugs from different pharmacological classes makes it harder to obtain a precise estimate of the long term activity of the experimental compound.

## 3. LEGAL BASIS

This guideline has to be read in conjunction with the introduction and general principles (4) and parts I and II of the Annex I to Directive 2001/83/EC as amended. Applicants should also refer to other relevant European and ICH guidelines on the conduct of clinical trials, including those on:

- Dose-Response information to Support Drug Registration – CPMP/ICH/378/95 (ICH E4)
- Choice of Control Group in Clinical Trials – CPMP/ICH/364/96 (ICH E10)
- Statistical Principles for Clinical Trials – CPMP/ICH/363/96 (ICH E9)
- Choice of a Non-Inferiority Margin - CPMP/EWP/2158/99
- Adjustment for Baseline covariate – CPMP/EWP/2863/99
- Missing data – CPMP/EWP/177/99
- Extent of Population Exposure to Assess Clinical Safety – CPMP/ICH/375/95 (ICH E1A)
- Pharmacokinetic studies in man – CHMP/EWP/147013/04
- Investigation of drug interactions – CPMP/EWP/560/95
- Fixed Combination Medicinal Products CPMP/EWP/240/95
- Reporting the Results of Population Pharmacokinetic Analyses CHMP/EWP/185990/06
- Clinical investigation of medicinal products in the paediatric population – CPMP/ICH/2711/99 (ICH11)
- Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population CHMP/EWP/147013/04
- Reflection Paper on the Regulatory Guidance for the Use of Health-Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products CPMP/EWP/139391/04
- Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances pursuant to Article 14(8) of Regulation (EC) No 726/2004 (EMEA/357981/2005)
- Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No. 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 EMEA/509951/2006
- The Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council

## 4. MAIN GUIDELINE TEXT

### *4.1 HUMAN PHARMACOLOGY*

#### *4.1.1 In vitro pharmacodynamics*

Head to head comparative in-vitro studies with relevant anti-retroviral compounds must be performed whenever possible. It is recommended that these studies include experiments to determine the effects of protein binding on anti-retroviral activity, and that cell lines include peripheral blood mononuclear cells (PBMC). The novel agent should be tested against HIV-1 (including different clades) and HIV-2, in a wide range of clinical isolates and recombinant viruses that express various resistance-associated mutations. Whenever there is a suspicion based on theoretical considerations or "class experience" that a certain combination of compounds could be antagonistic, combination studies should be performed.

#### *4.1.2 Pharmacokinetics*

In order to reduce the risks associated with sub-optimal therapy in the HIV-infected individual, the initial pharmacokinetic studies should normally be performed in healthy, HIV-negative volunteers. If there are concerns regarding safety, however, it may not be appropriate to perform studies in HIV-negative healthy subjects. Some pharmacokinetic data can therefore only be obtained as part of exploratory treatment studies in HIV-infected persons. The pharmacokinetic behaviour may also be altered in HIV-infected patients with advanced disease. A mixed study programme of healthy volunteers and HIV-infected individuals in different stages of the disease is therefore normally needed to properly characterise the pharmacokinetics of the novel compound.

**General aspects**

The pharmacokinetic properties, including possible time-dependency (*e.g.* auto-induction) must be thoroughly characterised. Possible sources of variability (*e.g.* food interactions, drug-drug interactions, age, sex, ethnicity, effects of hepatic and renal impairment, genetic variations in metabolic capacity) should be evaluated. This should normally be done prior to the initiation of confirmatory studies.

For compounds undergoing intracellular activation, *e.g.* nucleoside reverse transcriptase inhibitors (NRTI), the pharmacodynamics are governed by the intracellular pharmacokinetics of the activated compound and sources of variability in the concentrations of the activated compound, such as drug-drug interactions, should be investigated. Preliminary data indicate that sex might be a factor of importance and higher levels of the activated compound have been reported in women. This should therefore be investigated, e.g. in phase 1 dose-comparative trials.

The intracellular concentrations of some compounds may be affected by polymorphism and drug-drug interactions at transporter protein level. Exploratory studies addressing these issues are therefore encouraged and, where relevant, studies documenting intracellular drug levels over the dosing interval. Well-documented intracellular pharmacokinetics might be helpful in the bridging between different dose-regimens or formulations. It is also recommended that drug concentrations are determined in viral sanctuaries such as cerebro-spinal fluid and genital secretions.

Data derived from pharmacokinetic studies conducted in HIV-negative volunteers may be used in order to identify dosages and schedules that are likely to be effective and tolerable in HIV-infected individuals. The constraints regarding the prediction of concentration-related activity *in vivo* from in-vitro data are, however, recognised. Ideally, it should be demonstrated that achievable and tolerable concentrations *in vivo* are several-fold higher than protein adjusted IC50/IC90 values for the full dose interval.

The relationship between drug exposure and safety and efficacy should be explored also in confirmatory studies, *e.g.* by means of population pharmacokinetics. An understanding of these relations is a prerequisite to be able to assess the relevance of changed drug exposure, *e.g.* due to impaired hepatic function, or changed variability in the population.

For some compounds, such as those showing a complex interaction profile, therapeutic drug monitoring might become necessary for the safe and efficacious use in clinical practice. For such compounds, target levels should be identified during drug development.

## Fixed dose combination medicinal products

In order to reduce pill burden, fixed dose combinations (FDC) have been developed. The need for clinical data will depend on the nature of the combination.

If the FDC is developed to be used instead of a well-documented "free" combination, references supporting the favourable benefit-risk of the free combination for a specific indication should be submitted. Bioequivalence between the FDC product and the free combination of anti-retroviral compounds should be demonstrated in studies conducted in the fasting and/or fed state (Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98).

In cases where a new posology is foreseen for the FDC product, clinical efficacy/safety studies are needed, but bridging PK/PD data may reduce these requirements. Further efficacy and safety data would usually be needed if the benefit-risk of the selected combination of compounds is considered insufficiently documented as a free combination. The extent of clinical data needed would have to be considered on a case-by-case basis.

If the FDC includes a new anti-retroviral compound or a new “booster”, this should be reflected, as appropriate, in all parts of the development programme and a justification is expected if the new agent is intended for marketing as a FDC only.

While the benefits of a FDC might be of particular relevance in children, special considerations are warranted as regards age/weight related differences in clearance or bioavailability of the individual components of the combination. The need for suitable tablet strengths for the intended target population (different proportions of individual components may become necessary) should be addressed.

## Drug-drug interactions

Due to the pharmacokinetic properties of many anti-retroviral compounds there is major potential for clinically relevant drug-drug interactions. Interaction studies should be mechanistically based, taking into account also transporter proteins, as well as the evaluation of any consequences for intracellular phosphorylation and/or intracellular concentrations as appropriate. If the mechanisms governing, *e.g.* a low oral bioavailability, have not been elucidated, however, exploratory interaction studies with commonly co-administered compounds may be needed.

For a compound with an extensive interaction potential, the selection of specific drugs for clinical interaction studies should reflect the anticipated need for co-administration in clinical practice. The applicant is therefore expected to discuss the range of clinical studies that are actually conducted in this light. This discussion should include:

- potential effects of other medicinal products on the new anti-HIV agent
- potential effects of the new anti-HIV agent on other medicinal products

For each drug (or class of drugs) considered to be of most relevance to patients with HIV, it should be concluded whether no interaction is expected, an interaction is expected or an interaction cannot be excluded and the clinical drug-drug interaction programme should reflect the conclusions drawn.

Before initial licensure it is not necessarily expected that all the drug-drug interaction studies considered to be appropriate for a novel agent would have been performed. However, in designing the programme priority should be given to studies of co-administration with other drugs for the treatment of HIV and those for the treatment of concomitant infections (e.g. HCV, HBV, invasive fungal infections and bacterial infections including mycobacterial diseases), metabolic abnormalities such as hyperlipidaemia, gastro-oesophageal reflux and therapies used in the management of substance abuse. Within these areas, essential drugs without reasonable therapeutic alternatives and a potential for interaction should be prioritised for study. The initial dossier should include a plan for completion of the interaction study programme.

For essential drugs, interaction studies should aim to provide sufficient data to support recommendations for adjustment of dose and/or dose-interval as necessary.

Information regarding interaction potential together with recommendations regarding combined use should be included in the SPC. For a compound with an extensive interaction potential, information on lack of interaction is useful and should be included at least for essential drugs (see Annex A).

### *4.1.3 Exploratory studies in HIV infected individuals*

**Monotherapy studies**

Monotherapy studies are needed to characterise the relationship between anti-retroviral activity and dose/dose-interval/plasma concentration. Such studies may be conducted over a very brief period in:

- Treatment-naïve subjects without need for combination therapy in the near future.
- Treatment experienced patients on a failing regimen. That is, the novel agent is added to regimens on which patients are failing so constituting "functional monotherapy" (also refer to section 4.2.3).

Monotherapy studies should be as short as possible in duration. The anticipated rate of development of resistance during monotherapy should be considered in the design of these studies.

Similarly, the number of patients should be the minimum needed to meet the objectives of the study. The patient selection criteria should include cut-offs applied to viral load and CD4+ T-cell counts that will not jeopardise the safety of participating patients.

The primary aim of these studies is to provide reliable data on short-term anti-retroviral activity of the new compound and, thus, to provide the best possible basis for the designs of further exploratory and confirmatory studies. Due to the risk of resistance development, these studies should be designed to maximise the information gained from any individual study and study participant so that a minimum number of patients are exposed to single agent therapy. These studies should, nevertheless, be designed to minimise the risk that suboptimal doses are further investigated in confirmatory studies. Data derived from these studies may also provide important bridging PK/PD documentation, *e.g.* if new formulations are to be developed in the future.

For some compounds, e.g. some entry inhibitors, it might be informative to conduct studies in healthy volunteers in order to define doses/dose-intervals and exposure compatible with target saturation. These studies are no substitute for studies in patients, but may reduce the risk of exposing patients to doses that are too low.

Interpretation of study data is made easier if patients infected with viral strains that show reduced sensitivity to the experimental agent are excluded, and if enrolment is restricted according to viral load limits. If the novel agent belongs to an existing class of ARTs and efficacy/safety studies in class-experienced patients are planned, then the relationship between short-term, anti-retroviral activity *in vivo* and different degrees of reduced susceptibility *in vitro* should normally be explored.

Early and repeated determinations of viral load and drug concentrations are recommended and PK/PD modelling may be a useful tool for dose selection. Appropriate modelling might also provide information on pharmacokinetic markers of importance for efficacy in relation to virus with different degrees of reduced susceptibility *in vitro*. If a range of doses is found to be active and well tolerated, additional short-term, comparative studies of monotherapy may be warranted. These should be randomised studies that compare various doses of the experimental drug with an active comparator.

The possible need for a loading dose and, in case of auto-induction, the need for dose adjustment over time should be considered. If available PK/PD data and/or data related to the pharmacological class indicate that a parameter, *e.g.*, $C_{min}$ might be critical for anti-retroviral activity, the degree of and reasons for inter- and intra-individual variability in this parameter should be specifically investigated.

If pharmacokinetic and pharmacodynamic data altogether indicate that therapeutic drug monitoring would be of importance to optimise benefit/risk, *e.g.*, in subgroups of patients with increased variability (including variability due to PK interactions), or in patients infected with virus with reduced susceptibility, this should be considered in the design of confirmatory studies.

Prior to the initiation of medium or long term combination studies it is expected that all reasonable measures have been undertaken to define mono-therapy doses and dose-intervals with relevant and well defined anti-retroviral activity.

**Combination studies**

In order to explore tolerability and activity of the experimental compound in combination with other anti-retrovirals, further studies prior to the initiation of confirmatory studies may be indicated. These studies may include those with dose-comparative aims as well as a head to head comparison with a relevant reference compound.

The general guidance provided with respect to inclusion criteria, combination regimens, failure criteria, etc. as outlined in section 4.2 applies.

Treatment naïve patients

Due to the importance of first-line therapy, it is of special relevance that appropriate anti-retroviral activity has been documented and that the use of the experimental compound in suboptimal dose, dose intervals, or combinations has been excluded with reasonable certainty prior to the initiation of studies in these patients. Treatment naïve patients in need of immediate therapy under current guidelines *i.e.* those with CD4+ T-cell count below about 200 or symptomatic patients should be included in exploratory studies only if there is a scientific rationale and if data are available from patients with higher T-cell counts.

Treatment experienced patients

The design of these studies should take into account the fact that at least two active compounds are considered necessary to achieve a significant and stable anti-retroviral response. However, a period of short-term add-on functional monotherapy, prior to optimisation of the background therapy, is usually feasible (see “Monotherapy studies” in section 4.1.3).

The dose regimens of the novel agent that are studied should not include any regimen that seem unlikely to be efficacious based on PK/PD predictions. These precautions should reduce the risk of selecting for HIV resistant to the novel agent.

## *4.2 CONFIRMATORY STUDIES*

### *4.2.1 General considerations*

The most commonly used designs in confirmatory studies aim at a head-to-head comparison between the novel agent and a relevant authorised medicinal product. This may be accomplished by “add-on” or “substitution” studies. In substitution studies one (or rarely more) compound(s) in an established regimen that will serve as control regimen is substituted with the experimental agent, while, in add-on studies, the experimental agent, an active comparator, or placebo is added to an optimised background regimen. “Substitution” and “add-on” may be used in order to compare products within a pharmacological class, but also in a comparison between classes. Placebo-controlled, add-on studies are typically conducted only in patients with no available treatment options other than OBT. Whatever the design and treatment regimen, every effort should be made to conduct these studies under effectively double blind conditions. In most cases, however, it is sufficient to blind the study with respect to the experimental agent and its head-to-head comparator.

Adherence to therapy is of vital importance for treatment outcome and major efforts to encourage and document compliance should be undertaken. As poor compliance tends to bias the results towards “no difference”, non-inferiority results may become non-interpretable in case of poor adherence.

Virological failure, whether primary or secondary, should be clearly defined in the protocol and should be in accordance with clinical guidelines of relevance for the study population. These criteria should also take into account the need to minimise the number of withdrawals due to patient wish derived from efficacy concerns prior to study endpoint. It is therefore of importance to establish justifiable criteria in the protocol that are adhered to throughout the study. If superiority for the experimental arm is convincingly shown at a medium-term, pre-planned analysis in a study designed to run long-term, *e.g.*, for safety reasons, this may lead to a need to revise failure criteria in order to protect the rights of the study subjects. In a study conducted in treatment naïve patients, for example, and depending on the magnitude of the observed difference in efficacy, it may be appropriate to unblind treatment assignment for all individuals with measurable viral load. An independent data

monitoring committee should therefore be in operation. Every effort should be made to identify the reason(s) for virological failure in individual patients.

As a general rule, the appropriate study duration should be defined by the need to obtain robust safety data and convincing efficacy results and here non-inferiority results normally need longer time to mature. Long-term safety is a major concern which until now frequently has not been appropriately addressed in registration files. It is fully recognised that new pharmacological classes of agents may not be associated with severe long-term adverse events, however, this has to be shown. In the following and when a specific duration of clinical studies is recommended, this refers in principle to the last patient being on study for this period of time.

Especially if studies are conducted in heterogeneous populations, stratification should be considered for the most important prognostic factors. The sample size of the studies should allow for the conduct of meaningful exploratory subgroup analyses with respect to other factors that potentially affect outcome such as sex and ethnicity.

In order to establish a non-inferiority margin, the activity of the active comparator in the control regimen has to be defined in the population of interest and the acceptance limits have to be justified directly or indirectly in terms of study data and clinical relevance (Choice of Non-Inferiority Margin, CHMP/EWP/2158/99). Possible differences between reference studies and the actual study have to be taken into account, especially as regards viral load at baseline, prior therapies and disease status. In active comparator controlled, add-on studies to OBT, it is of major importance to consider assay sensitivity, i.e. the possibility to detect relevant differences between the active comparator and the experimental agent, if there were one. This has implications as regards number of putatively active compounds allowed in the OBT and should be thoroughly discussed and justified in the study protocol.

For superiority studies, the most suitable primary analysis is normally that in an ITT population defined as all treated patients and with all indeterminate outcomes and withdrawals designated as failures. There are, however, no ideal way to handle those with indeterminate outcome and withdrawals. Also for superiority studies, sensitivity analyses exploring alternative ways of handling these data may be appropriate. Outcomes in patients who meet the criteria for the “per protocol” population are also important when evaluating consistency between populations and analyses.

Especially in studies conducted in populations where a high withdrawal rate is expected and in the case of non-inferiority trials, further “sensitivity analyses” should be undertaken and should be defined in the protocol. If the study cannot be conducted under double-blind conditions, very conservative analyses should be employed in order to minimise the impact of possible bias related to withdrawal from therapy.

These studies should be designed and analysed with the aim to explain variability in efficacy and safety and to provide guidance to physicians and patients. This may include the use of pharmacogenomics, population PK, analyses related to predefined subgroups of patients, etc. as appropriate and based on the results from exploratory studies and prior confirmatory studies.

In the following, provisional definitions are given as regards groups of patients to be studied and recommendations with respect to the design of clinical studies. It is understood that some of these definitions and recommendations may prove hard to employ in practice, *e.g.*, due to the dynamics of the field. If this Guideline is found conceptually difficult to apply, regulatory scientific advice is recommended.

### *4.2.2 Studies in ART naïve patients*

Patients included in clinical trials should fulfil criteria that indicate a need to commence ART, as defined by recognised clinical guidelines.

The comparative regimen should be chosen from among those that are “strongly recommended” for the initial therapy of established HIV infection and virological failure criteria should comply with clinical guidelines.

These studies are normally designed as substitution studies and the comparative agent should be chosen so as to facilitate double-blinding, taking into account pharmacokinetic interactions, pill burden (compliance), adverse effects, etc.

In order to show non-inferiority in terms of virological efficacy, a study period of at least one year is needed for compounds assumed to be equally effective. It remains mandatory, however, that these studies are designed to provide long-term safety data (96 weeks), preferably under double-blind conditions (see section 4.2.1).

The percentage of patients with HIV viral load below the limit of quantification (currently < 50 copies/ml) at 48 weeks (or a later time point) is an appropriate primary endpoint in these studies. Viral responses according to alternative criteria and time-averaged differences may be secondary measures of efficacy.

Patients infected with resistant virus should not be regarded as treatment naïve and included in these studies. Nevertheless, search for mutations that may have already been present at baseline should be undertaken in patients with virological failure.

Due to the importance of safety and tolerability, it is advisable to use patient withdrawal due to other reasons than virological failure as an important outcome measure. For simplified maintenance regimens, see "Patient responding to their current regimen" in section 4.2.3.

### *4.2.3 Studies in ART experienced patients*

**Patients responding to their current regimen**

Most studies in ART experienced patients are conducted in patients with evidence of virological failure on their current regimen. Studies of maintenance therapy with simplified and/or possibly better tolerated regimens in patients with HIV-RNA below the limit of detection after induction therapy is, however, an area of current clinical interest. The most commonly used study design involves the substitution of one or more drugs with the novel agent within an existing regimen that will serve as a control regimen.

These studies should normally be double-blinded with respect to treatment assignment, but may be open label as regards common elements in the two regimens. If the conduct under double blind conditions results in an unavoidable and hard to accept pill burden (double dummy, etc.), it is debatable whether the merits of blinding outweigh the likely loss in compliance. If an open label design is chosen, it is of special importance that conservative efficacy analyses not favouring the experimental arm are applied. All criteria for withdrawal, for example, have to be strictly defined and justified in the protocol. Withdrawal from the control arm in accordance with pre-specified criteria may then be regarded as treatment failure, while in case of withdrawal due to "patient wish", etc. LOCF may be used for imputation of missing data with respect to viral load. In the experimental arm, however, all withdrawals may be regarded as failures in conservative sensitivity analyses.

Time to virological failure as defined in current management guidelines is an acceptable primary endpoint. As all patients should show adequate viral response at baseline, and as the experimental regimen is not assumed to be more potent, more than 48 weeks of follow-up are expected to be needed to properly assess long-term efficacy. If improved safety is the rationale behind the experimental regimen, an adequate measure of safety should be defined in the protocol as a co-primary end point. Normally it is expected that the duration of the study as determined by efficacy considerations is sufficient also from a safety perspective.

**Patients with various remaining treatment options at time of treatment failure**

The decision when and how to change an apparently failing regimen is not straightforward and it is recommended that eligibility is defined in accordance with up-to-date guidelines on patient management.

Treatment history in combination with resistance testing should be used to characterise the individual patient's suitability for inclusion in the studies.

There are several possible designs, but all eligible patients should be well suited for treatment with the selected comparator regimen(s) according to current patient management recommendations. If the

novel agent belongs to an authorised class of compounds, the simplest design is to select patients naïve to this class for a randomised comparison with an agent of the same class on top of OBT (”add-on”) or within a justified standard regimen (“substitution”). This approach is also applicable in the case of experimental drugs belonging to a novel class of compounds for a head-to-head comparison with an established agent from a class to which the patients are treatment naïve. For add-on, active comparator-controlled studies on top of OBT, a sensitivity score (usually GSS) requirement of ≥ 2 for the OBT (together with treatment history) is considered appropriate. The use of more than 2 likely active compounds in the OBT must be thoroughly justified from the perspective of assay sensitivity. A brief period of active comparator controlled, functional monotherapy prior to optimising background therapy may be considered (see “Combination studies” in section 4.1.3).

The treatment goal in clinical practice is to achieve a viral load below the limit of quantification (currently HIV-RNA < 50 copies/ml) and the proportion of patients that achieve this degree of viral suppression should always be reported. In most cases, viral load below the limit of quantification at, e.g. 48 weeks, is also an appropriate primary endpoint. Primary and secondary “virological failure” criteria should be defined in relation to the expected activity of the comparative regimen and updated clinical treatment guidelines. For superiority trials, the primary efficacy analysis may be performed at 24 weeks, but the trial duration should be at least 48 weeks (see section 4.2.1), with or without institution of a "roll-over" protocol to follow at the time of failure, if appropriate, or at week 48. If a non-inferiority margin can be scientifically justified and non-inferiority is a reasonable clinical objective, such studies are acceptable, but, in most cases, a longer duration of therapy is needed to obtain mature efficacy data. A low “lost to follow up" rate is essential and sensitivity analyses are expected.

**Patients with few or no remaining licensed therapeutic options at time of treatment failure**

This section refers to patients with no more than 2 likely active and possible to use licensed compounds based on sensitivity scores and treatment history. Here drug development constitutes a challenge. In the interest of the patient, prolonged functional monotherapy must be avoided and, for the same reasons, the duration of dual active therapy should be minimised. Taking this into account, potential study designs include:

1. If there are convincing data as regards the magnitude of the treatment effect and durability of response from comparative studies conducted in less heavily pre-treated patients, this may form the main basis for a submission. The rationale being that data derived from such studies delineates the efficacy potential for the compound as well as long-term safety under well-controlled conditions.

   For a novel compound from an existing class of drugs, short-term, functional monotherapy studies in the target population should be undertaken in order to assess the consequences of a wide spectrum of mutations on the anti-viral activity.

   For a compound belonging to a new class of drugs, functional monotherapy may provide reassurance as regards the anti-viral activity in the target population.

   Functional monotherapy should be followed by add-on treatment in patients likely to benefit from the experimental compound, with an OBT including at least one likely active compound.

2. For patients for whom it is possible to include two likely active licensed compounds in OBT, a placebo-controlled, add-on study is an option. Time to virological response (i.e. usually defined as HIV RNA < 50 copies/ml) or sustained response at a pre-defined time point could be acceptable primary end points.

   After completion of the comparative phase, all patients may enter a long-term follow-up study in which they receive the experimental compound.

   After screening for inclusion, there will be patients detected who are ineligible for randomisation because they have less than two likely active licensed drugs available for use in OBT. These patients could be included in a parallel arm of the study in which they receive the novel agent plus OBT (which in some circumstances might include another experimental compound). Such patients should be followed in the same manner as those in the randomised arms of the study with the primary aim to provide safety data. An assessment of the new agent in this manner is considered to be preferable to inclusion of these patients only in extended access programs.

3. In an organised co-development program, factorial design may be used to document the efficacy and safety of two experimental compounds.

A minimum of 8 weeks of stable ART prior to initiation of functional monotherapy is needed to obtain interpretable results. The proper duration of functional monotherapy should be defined in relation to what is already known about the specific compound and the class of compounds.

To enable the use of two experimental compounds, putative pharmacokinetic interactions should have been investigated if mechanistically warranted.

If there are no specific safety or efficacy concerns, a submission based on 24-week study data is considered acceptable.

Prior to the initiation of a development programme in this target population, EU regulatory advice is recommended.

## *4.3 STUDIES IN SPECIAL PATIENT POPULATIONS*

### *4.3.1 Studies in children*

The development of acceptable and palatable pharmaceutical formulation with suitable strengths for children is normally expected to take place early. Dose selection is often based on results from pharmacokinetic studies, where dose in different age groups are selected to produce blood levels similar to those observed in adults (Pharmacokinetics in children, CPMP/EWP/968/02).

Drug clearance and also absorption may differ considerably between age groups due to organ maturation, etc. Hence, a sufficient number of children ranging from the very young to adolescents should be enrolled in pharmacokinetic studies to enable adequate dose recommendations. In many cases dose per weight band (e.g. 10 mg for a child between 10 and 20 kg) is an unambiguous way to express dose recommendations (CHMP/EWP/147013/04).

Provided that reliable pharmacokinetic data allow for robust dose recommendations to be made an extrapolation of efficacy data obtained in adults to children may be accepted. However, at least non-comparative data in children on the safety and efficacy of the proposed dose regimens over appropriate time-spans should be provided. Due to high viral loads in the youngest children, viral response data in these patients are of particular interest. Trials should take into account maternal treatment histories and viral susceptibility patterns and, as necessary, should reflect the considerations for patient management as outlined in section 4.2.3.

The provision of adequate data in children is especially important should large inter-individual pharmacokinetic variability be observed in the paediatric population. Also, additional drug-drug interaction studies may be considered necessary, at least as post-marketing commitments, and population pharmacokinetic studies should be considered.

Prior to the initiation of therapy, it is of major importance for adherence that child and family are well informed and emotionally “ready for therapy”. Further counselling and support should be provided during therapy and adherence monitored.

Long-term post-marketing and pharmaco-epidemiological studies are encouraged.

### *4.3.2 Studies in pregnant women*

The need to further optimise anti-retroviral therapy in pregnant women is fully recognised, balancing the risk of sub-optimal therapy, viral resistance and vertical viral transmission against foetal toxicity and long-term consequences for the child. Prospective and well-designed studies are therefore needed. Based on mature and promising clinical and non-clinical data, studies of a “new” compound may, thus, be warranted and are encouraged. For most medicinal products, however, data to make this judgement are not available until some years after approval.

For some compounds, seemingly relevant changes in drug exposure have been reported during pregnancy. Joint efforts undertaken by companies and research groups to collect data on exposure during and after pregnancy are therefore encouraged, e.g. from experienced laboratories analysing drug exposure. Due to changes in protein binding, the unbound fraction should be assessed whenever relevant and feasible.

As the use of new compounds during pregnancy is partly inevitable, the applicants should commit to provide reliable follow-up data of children exposed *in-utero* to anti-retroviral compounds at least until a reasonably founded benefit risk assessment is achievable. This should include long-term follow-up as far as possible as regards potential delayed development and carcinogenic effects. This should be addressed in the Risk Management Programme. As appropriate, this may also include the active support of Anti-retroviral Pregnancy Registries.

#### *4.3.3 Studies in co-infected patients*

Patients who are co-infected with HIV and HCV and/or HBV constitute an important, and in some study sites, large proportion of HIV-infected individuals.

Therefore safety and efficacy against HIV should be documented in these patients and sufficient numbers should be exposed to the experimental agent so as to document safety of ART over medium to long-term follow-up periods.

When the novel anti-retroviral agent also shows activity against HBV or other viruses that may co-exist in HIV-infected individuals, it is important that any activity on these other viruses is documented during ART. Whether or not the applicant intends to formally study the experimental agent in separate studies in patients who are infected with these other viruses, it is vital to determine whether the dose regimen that is to be used for ART may be effective against these viruses. Viral loads of co-infecting viruses should therefore be monitored so as to assess any potential for the selection of drug-resistant mutants. These data cannot be used to assess the efficacy of the novel compound against these co-infecting viruses, but the information is of importance in order to provide prescribers with guidance as to the safe use of the drug in co-infected patients.

### ***4.4 REQUIREMENTS FOR MARKETING AUTHORISATION***

This section is meant to provide guidance as regards authorisation criteria.

For ART naïve patients, extensive efficacy and safety data, normally derived from studies encompassing different regimens, should be provided.

If superior anti-retroviral efficacy has been demonstrated, one-year safety data are normally considered acceptable if there are no specific concerns and if the number of patients treated for one year is sufficient for a reliable comparative safety analysis. A commitment to provide 2-year safety data post-approval, derived from extension phases of pivotal studies is expected.

Otherwise, study data confirming acceptable benefit/risk after about 24 months of therapy should be available at the time of marketing authorisation. The database should make possible a qualified comparative safety analysis.

At the time of approval, comprehensive data on secondary virological failure (i.e. relapsing patients), resistance patterns may not be available. These issues should be covered by post approval commitments.

An indication for use in ART experienced patients with several remaining treatment options should be supported by efficacy and safety data derived from studies of at least 12 months duration (see section 4.2.3). Post approval commitments may encompass safety follow-up, resistance profiles, as appropriate.

An indication for use in ART experienced patients with few remaining therapeutic options should be supported by 24-week data derived from studies conducted as outlined in section 4.2.3.

Whether it is possible or not to obtain a non-restricted indication without conclusive study data in relation to all groups of patients detailed above has to be judged on a case by case basis. If safety and efficacy are well documented in treatment naïve and ART experienced patients and the clinical activity of the compound has been documented in relation to a broad range of clinical viral isolates, a non-restricted indication may be appropriate. Each case must be supported by a comprehensive justification from the Applicant.

## *4.5 INFORMATION IN THE SUMMARY OF PRODUCT CHARACTERISTICS*

At the time of approval of a new anti-retroviral product the benefit/risk has normally not been demonstrated in the full spectrum of HIV infection. This should be reflected in section 4.1 of the SPC, with a reference to section 5.1. For example, “X is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV infected, anti-retroviral experienced adults (see section 5.1)”.

If the experience is restricted to a subgroup of patients, e.g. patients with a viral load below 100,000 copies/ml, this should also be clearly stated.

When the documentation covers the full spectrum of HIV infection, a general indication should be used "X is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV infected adults, adolescents, and/or children above X years of age” (as appropriate)

If comprehensive clinical efficacy data have not been provided at the time of authorisation the limitations of the data should be clearly outlined in section 4.2.1.

Sections 4.5, 5.1 and 5.2 of the SPC (see Appendix A and B) should not mirror the cumulative growth of experience, but should focus on the most relevant information, *i.e.* information becoming less relevant should be deleted when new data are incorporated. In general, the information should be as concise as possible. Resistance data should be up-dated on a yearly basis if not otherwise justified.

## **DEFINITIONS**

GLOSSARY AND ABBREVIATIONS

| | |
|---|---|
| Advanced disease (= AIDS) | Patients diagnosed with any condition meeting the 1993 CDC definition of AIDS (excluding CD4+ T-cell count <200), whether treated with ART or not |
| AIDS | Acquired immune-deficiency syndrome |
| ADC | AIDS defining condition |
| ART | Anti-retroviral therapy¸ currently consisting of at least 3 different compounds (frequently from 2 different substance classes) |
| ART-experienced | Patients treated with ART for more than a very short period of time |
| EAP | Extended access programme |
| FDC | Fixed dose combination |
| HAART | Highly Active Anti-retroviral Therapy = ART |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| Heavily pre-treated | Patients harbouring multi-resistant virus and with few or no remaining treatment options |
| IBT | Immune based therapies |
| MAA | Marketing authorisation application |
| NNRTI | Non-nucleoside reverse transcriptase inhibitor |
| NRTI | Nucleoside reverse transcriptase inhibitor |
| OBT | Optimised background therapy |
| PBMC | Peripheral blood mononuclear cells |
| Primary virological failure | Adequate suppression of viral load not achieved with ART |
| PI | Protease inhibitor |
| Secondary virological failure | Rising viral load during ART after a period of adequate suppression |
| Treatment naïve | HIV infected patients previously not treated with ART and being infected with wild type HIV-1 or HIV-2 |

## REFERENCES (scientific and/or legal)

Note: See http://publications.eu.int/code/en/en-250304.htm for guidance on referencing published information and http://publications.eu.int/code/en/en-130102.htm for guidance on referencing EU texts. References to related guidelines should also be included.