European Medicines Agency

London, 20 November 2008
Doc. Ref. EMEA/CPMP/EWP/633/02
Revision 2

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

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

DRAFT AGREED BY THE EFFICACY WORKING PARTY	September 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	18 October 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 April 2008
AGREED BY EFFICACY WORKING PARTY	15 October 2008
ADOPTION BY CHMP	20 November 2008
DATE FOR COMING INTO EFFECT	01 June 2009

This guideline replaces guideline EMEA/CPMP/EWP/633/02 Rev. 1

KEYWORDS	*Human immunodeficiency virus, HIV infection, acquired immune-deficiency syndrome (AIDS), anti-retroviral therapy, EMEA, CHMP, Guideline*

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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

TABLE OF CONTENTS

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 HIV 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, this 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 CHMP scientific advice is recommended in these cases and also when agents belonging to new classes of anti-retrovirals 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.
- Clarification regarding the requirements for marketing authorisation for the use in treatment naïve patients.
- 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)

In this document "ART" refers to combination therapy with anti-retroviral medicinal products. Due to the inherent high rate of mutational resistance to ART in HIV, the use of sub-optimal regimens (i.e. constituting a potentially inadequate genetic barrier to development of resistance) during clinical studies should be avoided as far as is possible.

1.1 Patients to be studied

In order to minimise bias, efficacy studies are expected to be randomised and, whenever possible, double-blinded. It is recognised, however, that specific and prevalent side effects or insurmountable practical problems may make effective blinding impossible. In these cases, CHMP scientific advice should be considered in advance to commencement of pivotal studies. In any case, results of monitoring that is utilized in routine clinical management of patients, including CD4+ T cell counts, viral load, and HIV drug-resistance, should be accessible to the treating physician and to the patient during the conduct of clinical studies.

Throughout this document "treatment naïve" refer to patients not only naïve to treatment, but also without drug-related mutations in the major viral population as assessed with standard genotypic assays (see 1.2.4).

Provided that the properties of the experimental agent appear suitable, it is expected that safety and efficacy will be evaluated in patients who are treatment-naïve and in those who are treatment-experienced, including those with multiclass failure who are unlikely to regain virological control with licensed anti-retrovirals (i.e. heavily pre-treated patients). The clinical development programme should include sufficient numbers of women, individuals from ethnic minorities, patients infected with non-B subtypes and patients co-infected with HBV and/or HCV to allow generalised conclusions on safety and efficacy. These data should be accumulated as early as possible during the drug development programme, preferably in time to provide input into the design of confirmatory studies.

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

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 subjects with renal insufficiency, or hepatic impairment due to non-viral causes, is recommended.

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. The CDC criteria of 1993, excluding CD4 T-cell count as a defining event, are still considered applicable. For agents with potentially immunosuppressive properties, e.g. CCR5 antagonists, special attention to ADCs is warranted.

1.2.2 Viral load

The proportion of subjects that achieves and maintains undetectable plasma HIV-RNA (i.e. < 50 copies/ml) is the preferred primary efficacy endpoint for studies in treatment naïve as well as treatment experienced populations.

Alternative primary endpoints are possible if specifically justified. Secondary endpoints may include time averaged change from baseline and time to failure, e.g. as defined by TLOVR (see Definitions). The use of validated and sensitive assays for plasma HIV RNA that meet current standards is essential. The assay used must be able to accurately quantify HIV RNA from various (including rare) subtypes of HIV-1.

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 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. Due to the as yet immature status of this field, CHMP 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. 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 and discussed with the European regulators well in advance of a possible approval.

Throughout the document "treatment naïve" refers to patients naïve to treatment, and without drug-related mutations in the major viral population (as assessed with standard genotypic assays). Primary mutations according to the IAS-USA list of mutations (i.e. bold typed mutations in the most updated version at the time of enrolment into the study) are suitable to refer to as a definition of such mutations. Although single such mutations might have a very low impact on study outcomes, they indicate prior exposure of the virus to anti-retrovirals, including a risk of more mutations in minor reservoirs.

Before and after initial licensure, the clinical development programme should aim to identify resistance-associated mutations for the test agent. 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.

The resistance pattern should be documented at baseline and at least at time of virological failure. In treatment naïve patients all resistance selected in failing patients should be reported, both for the new agent and for the rest of the regimen. Genotypic and, if appropriate, phenotypic sensitivity scores (GSS and PSS) should be appropriately defined and reported in studies enrolling treatment-experienced patients, and are necessary in the design of studies with OBT. Outcome should be assessed and presented according to GSS and/or PSS at baseline. 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. Nevertheless, hidden resistant quasi-species at baseline may occur (e.g. due to primary acquisition of resistant virus or impact of prior ART) and may affect the response to treatment.

There is an inherent risk that the use of a new agent for the treatment of HIV may affect the possibility of successfully using other agents within the same class, due to resistance following virological failure with the new agent. Therefore *in vitro* studies of cross-resistance should be performed on HIV isolated after virological failure on regimens containing the new agent.

Studies investigating replicative capacity ("viral fitness") are also encouraged.

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 agent should be studied in relation to viral subtypes and where relevant with regard to co-receptor usage. Reasons for differential activity, e.g. in relation to viral subtypes should be investigated, but may be reported post approval if justified.

1.2.6 Pharmacogenomics

Genetic host factors may influence the metabolism of drugs, and the risk for adverse reactions. Pharmacogenomic studies should be considered in cases where the metabolic pathway indicates that plasma exposure may be strongly influenced by genetic variations, when large observed differences in plasma exposure require exploration, and when specific and clinically important side effects are observed.

1.2.7 Safety

In addition to the usual reporting of safety data, high quality data on long-term safety is of critical 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 seem relevant to a new agent based on class-experience, mechanistic reasoning and/or early clinical findings should be long-term monitored using appropriate methods. For example, metabolic side effects including cardiovascular complications and lipodystrophy should be followed for PIs and NRTIs, long-term effects on autoimmune diseases, infections and malignancies should be

followed for CCR5 inhibitors, etc. 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 validated 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.

2. SCOPE

The scope of this document is to provide guidance regarding 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 anti-retrovirals from different pharmacological classes makes it harder to obtain a precise estimate of the long term activity of the experimental agent.

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 (in their current version) on the conduct of clinical development.

- Dose-Response information to Support Drug Registration – CPMP/ICH/378/95 (ICH E4)
- Statistical Principles for Clinical Trials – CPMP/ICH/363/96 (ICH E9)
- Choice of Control Group in Clinical Trials – CPMP/ICH/364/96 (ICH E10)
- 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)
- Guideline on carcinogenicity Evaluation of Medicinal Products for the Treatment of HIV Infection EMEA/CHMP/SWP/194898/2006
- Pharmacokinetic studies in man – CHMP/EWP/147013/04
- Investigation of drug interactions – CPMP/EWP/560/95
- 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
- Fixed Combination Medicinal Products CPMP/EWP/240/95
- 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 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

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 agents 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, including 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 agents could be antagonistic, combination studies should be performed.

The potential for a new agent to be active against viruses other than HIV should be investigated in laboratory studies. In particular, activity against hepatitits B and C viruses (HBV and HCV) should be assessed (see also section 4.3.3). If potentially useful activity is detected against other viruses likely to co-infect subjects with HIV, an appropriate programme of investigations (including the potential of the new agent to select for drug resistance) should be instituted.

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 be performed in healthy, HIV-negative volunteers. The pharmacokinetics of anti-retrovirals may also be different 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 needed to properly characterise the pharmacokinetics of the new agent.

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, and genetic variations in metabolic capacity) should be evaluated. This should normally be done prior to the initiation of confirmatory studies.

For agents undergoing intracellular activation, such as nucleoside reverse transcriptase inhibitors (NRTI), the pharmacodynamics is governed by the intracellular pharmacokinetics of the activated agent. Sources of variability in the concentrations of the activated agent, such as drug-drug interactions, should be investigated as appropriate. Although there is still no established relationship between intracellular concentrations of activated agents and their safety/efficacy, these studies might be helpful should any unexpected findings arise during clinical studies or in routine clinical care. Preliminary data of some activated agents indicate that sex might be a factor of importance for the intracellular activation of the NRTIs. The new agent should be investigated respectively.

The intracellular concentrations of some agents may be affected by polymorphism and drug-drug interactions at transporter protein level. Well-documented intracellular pharmacokinetics might be helpful in the bridging between different dose-regimens or formulations. Drug concentrations should also be determined in viral sanctuaries such as cerebrospinal fluid.

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 patients. The limited predictive value of *in vitro* data for efficacy *in vivo* is, however, recognized.

The relationship between drug exposure and efficacy as well as safety should also be explored in confirmatory studies, e.g. by means of population pharmacokinetics. An understanding of these relations is a prerequisite for assessing the relevance of alterations in drug exposure, e.g. due to impaired hepatic function or drug-drug interactions.

For some agents, for instance those that have a complex interaction profile, therapeutic drug monitoring might be necessary for the safe and efficacious use in clinical practice. For such agents, target levels should be identified during drug development.

Fixed dose combination medicinal products

Fixed dose combinations (FDC) have been developed aiming at improving adherence by reducing pill burden. The need for specific clinical data will depend on the nature of the combination.

If the FDC is developed to be used in the place of a well-documented combination of two or three individual single-drug formulations, references supporting the favourable benefit-risk of the free combination should be submitted. Bioequivalence between the FDC product and the free combination of anti-retroviral agents should be demonstrated in studies conducted in the fasting and/or fed state .

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 will usually be needed if the benefit-risk of the selected combination of agents is considered insufficiently documented as a free combination. The necessary extent of clinical data must be considered on a case-by-case basis.

If the FDC includes a new anti-retroviral agent 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 should be addressed, e.g. different proportions of individual components may become necessary for different age and weight groups.

Drug-drug interactions

Due to the pharmacokinetic properties of many anti-retroviral agents, there is major potential for clinically relevant drug-drug interactions. Interaction studies should be mechanistically based, taking drug metabolising enzymes as well as transporter proteins into account. If appropriate, the possibility of interactions involving intracellular phosphorylation and/or intracellular concentrations should be considered.

For an agent 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 should provide a justification for the selection of agents for study in specific drug-drug interaction studies that take into account:

- potential effects of other medicinal agents on the new anti-retroviral agent
- potential effects of the new anti-retroviral agent on other medicinal agents

For each drug (or class of drugs) considered to be of major importance to patients with HIV, the potential for important drug-drug interactions should be evaluated on the basis of available preclinical and clinical data, and it should be concluded whether no interaction is expected, an interaction is expected or an interaction cannot be excluded. The clinical drug-drug interaction programme should reflect the conclusions drawn.

It is not expected that all drug-drug interaction studies considered appropriate have been performed before initial licensure. However, in designing the programme, priority should be given to studies of co-administration with other drugs for the treatment of HIV and for the treatment of concomitant infections (e.g. HCV, HBV, invasive fungal and bacterial infections including mycobacterial diseases), hormonal contraceptives, drugs for the treatment of metabolic abnormalities such as hyperlipidaemia, gastro-oesophageal reflux, and therapies used in the management of substance abuse. Within these areas, 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.

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

4.1.3 Exploratory studies in HIV-infected individuals

Monotherapy studies

Monotherapy studies are needed to characterise the relationship between dose, plasma concentrations of the new agent and anti-retroviral activity. The results should influence the selection of regimens for further study. 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 new agent is added to regimens on which patients are failing so constituting "functional monotherapy" (also refer to section 4.2.3).

A new agent belonging to a new class should be studied in treatment naïve subjects, while a new agent within an existing class should be studied in both treatment naïve patients and in patients with virus harbouring HIV with various degrees of resistance to agents in the class.

When studying the activity in patients harbouring resistant virus (i.e. agent of existing class), a minimum of 8 weeks of stable ART prior to initiation of functional monotherapy is needed to obtain interpretable results. In such patients the relationship between short-term, anti-retroviral activity *in vivo* and different degrees of reduced susceptibility *in vitro* should be explored, both during initial and subsequent studies of functional monotherapy (section 4.2.3).

Monotherapy studies should be of as brief duration as possible. The anticipated genetic barrier to resistance (based on *in vitro* and other available data) should be considered in the design (particularly the duration) of these studies. The sample size should be the minimum needed to meet the objectives of the study. Selection criteria based on HIV-RNA and CD4+ T-cell count should be designed to minimise any risks to participants. For some agents (e.g. some entry inhibitors) it might be informative to conduct studies in healthy volunteers, in order to define doses/dose-intervals and the drug exposure necessary for target saturation. These studies are no substitute for studies in patients, but may reduce the risk of exposing patients to suboptimal doses.

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 *in vitro* susceptibility. 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 new agent with an active comparator.

The possible need for a loading dose and, in case of auto-induction of metabolism, 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 might be of importance to optimise benefit/risk ratio, 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 subsequent studies.

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

Combination studies

In order to explore tolerability and activity of the experimental agent 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 product.

The general guidance provided with respect to inclusion criteria, combination regimens, failure criteria, etc. as outlined in section 4.2 applies here, too. Depending on the type of agent and the intent of the developmental programme, combination studies may be performed in either treatment naïve patients or experienced patients or both. Such studies can run in parallel.

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 agent in suboptimal way, e.g. 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 according to current treatment 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 CD4+ T-cell counts.

Treatment experienced patients

The design of these studies should take into account the fact that, for the most part, at least two active agents (i.e. predicted to be active against an individual's HIV based on genotypic and phenotypic data) are considered necessary to achieve the desired and stable virological response. For an experimental agent with an expected low genetic barrier to resistance, two rather than one active anti-retroviral would be needed in the background regimen.

A short period of add-on functional monotherapy, prior to optimisation of the background therapy, may be feasible (see "Monotherapy studies" in section 4.1.3), and should be considered for new agents of existing class, to increase the amount of data on short term activity in relation to baseline resistance.

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 new agent and a relevant authorised medicinal product. This may be accomplished by "add-on" or "substitution" studies. In substitution studies one (or rarely more) agent(s) in an established regimen that will serve as control regimen is substituted with the new agent, while, in add-on studies, the experimental agent, or an active comparator is added to an optimised background regimen. "Substitution" and "add-on" may be used in order to compare agents within a pharmacological class, but also in a comparison between classes. Placebo-controlled, add-on studies are superiority studies and 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 double-blind conditions. In most cases, however, it is sufficient to blind the study with respect to the new agent and its head-to-head comparator.

Adherence to therapy is of vital importance for treatment outcome. Major efforts to encourage and document compliance should be made. As a minimum, pill counts and questioning regarding compliance should be performed. Since poor adherence tends to obscure differences in efficacy, it may render the results of non-inferiority trials non-interpretable.

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.

Switching patients who experience virological failure on comparative regimens to the experimental agent is commonly undertaken, especially in placebo-controlled add-on studies. This should be taken into account in the planning of safety data reporting. Adverse event rates should be expressed per time periods and per patient-year of exposure.

As a general rule, the appropriate study duration should be defined by the need to obtain robust safety data and convincing efficacy results. In most circumstances, non-inferiority results need a longer time to mature. 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.

Stratification should be considered for the most important prognostic factors, such as baseline viral load, CD4+ T-cell count and, if applicable, resistance-associated mutations. This is particularly important when studies are conducted in heterogeneous populations. The study sample size should be large enough to 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. Possible differences between reference studies and the actual study have to be taken into account, especially regarding 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 the possibility to detect relevant differences between the active comparator and the experimental agent if there were any. This has implications for the number of putatively active agents allowed in the OBT, and should be thoroughly discussed and justified in the study protocol.

For superiority studies, the most suitable primary analysis is generally in an ITT population including all randomised patients, 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 of patient categories are given, with recommendations concerning the design of clinical studies in the respective groups. It is understood that the practical applicability of these definitions and recommendations may be unclear, and that their relevance may change over time, e.g., due to rapid advances in the field. If this guideline is found conceptually difficult to apply, CHMP 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 treatment guidelines. If other approaches are planned, a CHMP scientific advice is highly recommended to precede such studies.

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

These studies are normally designed as substitution studies. The choice of comparative agent should facilitate a double-blind study design by taking into account issues such as pharmacokinetic interactions, pill burden (compliance), and adverse reactions. In order to show non-inferiority in terms of virological efficacy, a study period of at least one year is needed. It is, however, recommended that these trials should be designed to provide long term safety and efficacy data, i.e. at least for two years. The proportion of patients with plasma HIV-RNA below the limit of quantification (currently < 50 copies/ml) at 48 weeks (or a later time point) is the appropriate primary endpoint in these studies, but time to treatment failure should be provided as secondary endpoint.

Patients with resistance in major viral population at screening should not be regarded as treatment naïve and should not be included in these studies (see section 1.2.4). 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

While 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 virologically suppressed patients are also of considerable clinical interest. The most commonly used study design involves the substitution of the novel agent for one or more drugs 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 ill-tolerated pill burden (e.g. due to double dummy technique), it is debatable whether the merits of blinding outweigh the likely loss of compliance. If an open label design is chosen, it is of special importance that conservative efficacy analyses which do not favour the experimental arm are applied. For instance, all criteria for withdrawal 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., last observation carried forward (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 will have been on an effective ART regimen prior to baseline, large, long-term studies (usually around 2 years) are needed. If improved safety is the rationale behind the experimental regimen, an adequate measure of safety should be defined in the protocol as a key secondary endpoint.

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 new agent belongs to an authorised class of agents, 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 new agents belonging to a novel class of agents 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 agents in the OBT must be thoroughly justified as this may impair the possibility to detect differences between study arms. A brief period of active comparator controlled, functional monotherapy prior to optimising background therapy should 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). In most cases, viral load below the limit of quantification, e.g. at 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 the institution of a "roll-over" protocol to follow at the time of failure, if appropriate. If a non-inferiority margin can be scientifically justified and non-inferiority is a reasonable clinical objective, such studies are acceptable. In such cases 48 week data are generally sufficient. 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 suitable licensed agents based on sensitivity scores and treatment history. 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. 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, CHMP scientific advice is recommended.

Potential clinical development scenarios and study designs include :

Scenario A

If there are convincing data regarding the magnitude of the treatment effect and the 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 of the agent as well as long-term safety under well-controlled conditions. Additional studies should be conducted in the following target populations:

1. *Patients with 1 remaining licensed therapeutic option to be used in the OBT.*

   These studies should either be single-armed, or could include arms with different doses of the investigational agent.

   For a new agent from an existing class of drugs, short-term, functional monotherapy studies followed by optimization of OBT (with remaining therapeutic option) should be undertaken. The initial phase of functional monotherapy is important in order to assess the consequences of a wide spectrum of mutations on the anti-viral activity during therapy with the selected dose regimen in an adequate number of patients.

   For an agent belonging to a new class of drugs, functional monotherapy is not likely to be relevant to be studied in this population. However, to verify safety and in part efficacy, add-on treatment (including optimized background) should still be performed in this patient population.

2. *Patients with 2 remaining licensed therapeutic options to be used in the OBT.*

   In such patients a placebo-controlled, add-on superiority 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 endpoints.

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

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 or in a companion study in which they receive the novel agent plus OBT (which in some circumstances might include another experimental agent, see also below in scenario B). 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 expanded access programmes.

Scenario B

The developmental scenario includes an organised co-development program for 2 separate investigational agents, and hence possibly involving two companies.

Before embarking on such studies, the potential for pharmacokinetic and pharmacodynamic interactions to occur between the two investigational agents should have been explored.

Ideally, at least one study should directly compare the efficacy of each agent plus OBT with the combination plus OBT, in patients with virus that is still susceptible to one or two licensed agents. However, if there are already substantial data for each of the agents when administered to such patients it may sometimes be justifiable to only evaluate the combination.

4.3 Studies in special patient populations

4.3.1 Studies in children

The development of acceptable and palatable pharmaceutical formulations with suitable strengths for children is normally expected to take place early. Dose selection is often based on results from pharmacokinetic studies, where doses for different age groups are selected to produce blood levels similar to those observed in adults.

Drug clearance and bioavailability 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. For an agent only intended for treatment experienced patients, studies in the very young might not be relevant.

Provided that reliable pharmacokinetic data support robust dose recommendations, 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 available clinical and non-clinical data, studies of a “new” agent 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 agents, seemingly relevant changes in drug exposure have been reported during pregnancy. Joint efforts undertaken by companies and research groups to collect data on systemic exposure during and after pregnancy are therefore encouraged. Due to putative changes in protein binding, the unbound fraction should be assessed whenever relevant and feasible.

As the use of a new agent during pregnancy is partly inevitable, the applicants should commit to provide reliable follow-up data of children exposed to anti-retroviral agents, *in-uteri* (e.g. for potentially delayed development and carcinogenic potential) at least until a reasonably founded benefit risk assessment is achievable. This should be addressed in the Risk Management Plan. 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 sites, large proportion of HIV-infected individuals.

Therefore efficacy against HIV should be documented in these patients, and sufficient numbers should be exposed to the new agent, in order to document its safety over medium to long-term follow-up periods.

When the new anti-retroviral agent also shows activity in non-clinical studies against HBV or other viruses that may co-exist in HIV-infected individuals, the potential for a clinically important effect when the agent is used in an ART regimen should be assessed during clinical studies. The risk of selecting for resistance to the new anti-retroviral agent in the co-infecting virus, and the potential for cross-resistance to agents commonly used to treat that virus should be evaluated. However, if non-clinical data suggest that the risk of resistance in one or more potentially co-infecting viruses is very high, the new anti-retroviral agent should probably not be evaluated in such patients.

If the applicant intends to develop the new anti-retroviral agent as a possible treatment for a co-infecting virus, it becomes essential to determine whether the dose regimen that is to be used for ART may also be effective against the other virus. Since the clinical development may be rather complex the applicant is strongly advised to seek CHMP scientific advice.

Tuberculosis is frequently seen in HIV patients, and is the most common AIDS-defining event in some regions. Before initiating studies, particularly in regions with a high TB prevalence, it is crucial that relevant drug-drug-interactions studies have been performed, to allow for adequate use of TB agents in patients in need of TB therapy during the study.

4.3.4 HIV-2 infection

Patients in need of treatment and infected with HIV-2 presently have few alternatives. If *in vitro* findings indicate that the experimental agent show promising activity against HIV-2, clinical studies in this population are highly encouraged.

4.4 Requirements for marketing authorisation

This section is meant to provide guidance with respect to authorisation criteria.

For *ART naïve patients* extensive efficacy and safety data, derived from studies encompassing different regimens, should normally be provided. Convincingly demonstrated non-inferior benefit – risk at 48 weeks versus a well recognized reference product may serve as a basis for approval, with data after prolonged follow up to be provided post approval. Longer term data may, however, be required pre-approval due to safety concerns identified in clinical or non-clinical studies. The database should permit a qualified comparative safety analysis.
At the time of approval, comprehensive data on secondary virological failure (i.e. relapsing patients), and 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 48 weeks duration (see

section 4.2.3). Post approval commitments may encompass safety follow-up and resistance profiles, as appropriate.

An indication for use in *ART experienced patients with few remaining therapeutic options* should be supported by at least 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 agent 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 Characterisitcs

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 5.1.

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 rather 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, unless otherwise justified.

DEFINITIONS

GLOSSARY AND ABBREVIATIONS

ADC	AIDS-defining condition
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
ART	Anti-retroviral therapy¸ currently consisting of at least 3 different agents (frequently from 2 different substance classes)
ART-experienced	Patients treated with ART for more than a very short period of time
EAP	Expanded access programme
EPAR	European Public Assessment Report
FDC	Fixed dose combination
GSS	Genotypic sensitivity score
HAART	Highly Active Anti-retroviral Therapy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Heavily pre-treated	Patients with multiclass failure who are unlikely to regain virological control with licensed anti-retrovirals
HIV	Human immunodeficiency virus
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
PI	Protease inhibitor
Primary virological failure	Adequate suppression of viral load not achieved with ART
PSS	Phenotypic sensitivity score
Secondary virological failure	Rising viral load during ART after a period of adequate suppression
SPC	Summary of Product Characteristics
TLOVR	Time to loss of viral response: Intent to treat analysis that examines time to failure as the earliest time when death, discontinuation of study drug, loss to follow-up, introduction of new anti-retroviral drug (unless changed for reasons of toxicity or intolerance), or confirmed HIV RNA > 400 copies/ml following undetectable viral load occurred.
Treatment experienced	Patients with previous treatment failure and with documented resistance
Treatment naïve	Patients not previously treated with ART, and infected with wild type (WT) HIV-1 or HIV-2 (NB: WT defined as the absence of primary mutations according to updated version of IAS-USA list of mutations).

ANNEX A

Presentation of pharmacokinetic interaction data in the SPC

These recommendations refer to anti-retroviral agents with high propensity for pharmacokinetic interactions. The principles guiding data presentation should take the following into account:

- The SPC is a tool to be used by the clinicians. For compounds with complex interaction potential, the most user-friendly way to present data is by therapeutic areas.
- The aim should be to provide clear recommendations as regards use/non-use and, for drugs of major importance, which dose to be used.
- If major interactions with a specific compound have been identified, there may be alternatives within the same therapeutic area without this interaction propensity. Therefore, absence of PK interactions is informative and should be provided for therapeutic areas where (potentially) problematic interactions have been identified.
- For some agents (e.g. substrates of CYP3A), the number of possible combinations of interacting agents might be high in clinical practice. For such agents therapeutic drug monitoring (TDM) might be useful. Information as regards target concentrations may be put forward in sections 5.2 and/or 4.2, depending on the robustness of data and foreseen need for TDM in clinical practice.

The table below may be used as a template to structure information as regards PK interactions in the SPC.

Drugs by Therapeutic Area	**Interaction** **Geometric mean change (%)**	**Recommendations concerning co-administration**
If a class of drugs is not affected, this is stated with a general comment. For compounds given with and without ritonavir-boosting, information should be clearly separated. **Example ("HIV agent Y") :**	Changes in relevant PK-parameters presented with arrows (↑↓↔) and as geometric mean change (%). Negative findings are of interest – particularly within a therapeutic area where interactions are found for some agents and not for others. "No interaction" then to be stated. The mechanism behind the interaction should be stated if known, otherwise "mechanism unknown "should be stated.	A clinically useful recommendation to be given in this box.
INFECTION *Anti-fungals* **Agent A**	**Agent** Y AUC ↑ 35 % **Agent** Y Cmin ↑ 55 % **Agent** A ↔ (CYP3A inhibition)	No dose adjustment necessary.

HYPERLIPIDAEMIA *HMG CoA reductase inhibitors* **Agent B** **Agent C**	Based on theoretical considerations Compound Y is expected to increase **Agent** B and C concentrations.	Combination contra-indicated due to an increased risk of myopathy, including rhabdomyolysis
Agent D	**Agent** D AUC ↑ X-fold Metabolite AUC ↓ Y% **Agent** Y ↔ (CYP3A inhibition)	Combination not recommended
Agent E	Interaction not studied, but not expected based on mechanistic consideration	Preferred choice when coadministration with a HMG CoA reductase inhibitor is needed

In addition to the information given in section 4.5 (table above), more detailed information should be placed in the EPAR (scientific discussion).

Data that may be included in the EPAR (Scientific Discussion)

- Number of subjects
- Doses used
- Geometric mean effect expressed in % change
- Variability presented as range and/or quartiles of relevant exposure parameters (AUC, Cmax and Cmin) with and without interacting agent

ANNEX B

Template SPC section 5.1

The virological data and clinical study data that appear in section 5.1 of the SPC should be limited to the information that is most likely to be useful to the prescriber. Therefore this section should be short, readable and, as far as possible, should display the information in tabulated form.

Detailed virological and clinical efficacy data will be reported in the EPAR.

5.1 Pharmacodynamic properties

Mechanism of action: *Brief* description in text.

Antiviral activity *in vitro*: A brief paragraph should describe if active vs HIV-2 as well as HIV-1 and if similar activity seen vs all clades tested.

Resistance:

Antiviral activity according to genotypic/phenotypic resistance (new agent in licensed class):

The cut-offs of activity (not affected, decreased, resistance) as measured by change in HIV-RNA from baseline should be justified by the applicant.

Data should derive from short term functional monotherapy (see section 4.1.3 in main document). Alternatively for anti-retrovirals indicated for the treatment of experienced patients the table could be based on week 4 data, if available, from patients harbouring virus with a sensitivity score of 0. If key mutations exist they should be summarized in text, in addition to be shown in table.

When applicable, response by an additional international list of mutations (IAS-USA, Stanford, etc.) should be presented also in cases where the list defined by the applicant correlates somewhat better with the efficacy.

TABLE 1. Clinical cut off values for reduced activity of the applicant's agent by baseline genotype/phenotype based on short term functional monotherapy (x weeks).

	Activity not affected	**Decreased activity**	**Resistance**
Applicant's genotypic score[1] (no of mutations)	0-X	X-X	X+
Identified Key mutations [2] (of the applicant's agent)	0-X	X-X	X+
Additional list (version) [3] (no of mutations)	0-X	X-X	X+
Clinical cut-off Phenotype[*] (Fold change)	0-X	X-X	X+

[1] Codon change:
[2] Codon change:
[3] Codon change:
[*] assay:…specified

Clinical results

The data should be presented under separate heading for treatment naïve patients and treatment experienced patients.

The study designs should be *briefly* described.

Examples of tables to be included:

- Primary and most important secondary efficacy parameters; for primary, by subgroups.
- Virological outcomes by number of active agents in OBT (sensitivity score defined) and by any documented baseline resistance to agent. The sensitivity score of the individual patient should be based on the drugs actually included in the OBT. (This separate table concerns new agent, existing class). Outcome by phenotypic resistance, seldom used in clinical practice, should be described in the EPAR if not otherwise justified.

TABLE 2. Outcome at week X in pivotal studies.

Parameter	Test (N)	Control (N)
< 50 cps/mL, % (n)		
All patients		
With Baseline		
HIV-RNA > 100.000 cps/mL		
< 100.000 cps/mL		
CD4-count < 50		
50-100		
101-200		
201-350		
Sensitivity score		
<2		
≥2		
all		
> 1 log_{10} reduction in HIV-RNA, %		

TABLE 3a. Proportion (%) of patients with < 50 cps/mL at week X by genotypic sensitivity score in OBT and number of baseline mutations (applicant's mutation score [1]).

	Test				Control
		Number of baseline mutations			
Genotypic sensitivity score in OBT [*]	All	0-X	X-X	X+	
<2					
≥2					
all					

[*] [Sensitivity score: defined]
[1] Codon change:

TABLE 3b. Proportion (%) of patients with < 50 cps/mL at week X by genotypic sensitivity score in OBT and number of baseline mutations (alternative mutation score [1]).

	Applicant's agent				Control
		Number of baseline mutations			
Genotypic sensitivity score in OBT *	All	0-X	X-X	X+	
<2					
≥2					
all					

* [Sensitivity score: defined]
[1] Codon change:

The cut-offs of activity used in table 1 should be specifically reflected upon in relation to table 3.

The section should be updated at relevant intervals. Old studies considered to not to be relevant anymore should be deleted in the updates of the agent.

Template EPAR (Scientific Discussion)

The EPAR should present pharmacodynamic data in a similar way to that of section 5.1, but in greater detail. Tables are preferred to text format and only relevant information should be included. *In vitro* data (e.g. activity and resistance) is only briefly mentioned in section 5.1 and should be given in detail in the EPAR, preferably using the formats below.

Antiviral activity *in vitro*:

If an agent is highly protein-bound, a serum-adjusted EC_{90} should be reported. After examining the *in vitro* antiviral activity in the presence of human serum, e.g., at 5, 10, 20 and 40 percent, an EC_{90} value at 100 percent human serum can be estimated.

TABLE 1. Activity Against Laboratory and Clinical Isolate Wild-type Víruses

Parameters	**Median EC_{50} (nM)**	**Range (nM)**	**Median EC_{90} (nM)**	**Range (nM)**
Laboratory Virus [a]				
HXB2 (n=)				
BaL (n=)				
IIIB (n=)				
Serum Shift Data				
50% Human Serum (n=)				
Clinical Isolates				
Subtype A (n=)[c]				
Subtype AE (n=) [c]				
Subtype B (n=) [c]				
Subtype C (n=) [c]				
Subtype D (n=) [c]				
Subtype F (n=) [c]				
Subtype G (n=) [c]				
Subtype H (n=) [c]				
HIV-1 group O/N (n=)[c]				
HIV-2 (n=) [d]				
CXCR4-utilizing (n=)[e]				
CCR5-utilizing (n=)[e]				
a. cell line assay clinical isolate detail				

Footnotes should include type of assay – single cycle, multi cycle, etc.

***In vitro* resistance:**

a) *in vitro* selection of resistance from WT HIV-1 virus:

Assay used for phenotypic resistance testing and type of cell lines used should be specified. Fold change (or other relevant parameter, for example maximal % inhibition) according to accumulating resistance should be presented.

TABLE 2. Mutations selected *in vitro* in cell line systems [1], in the presence of the applicant's agent

Parameter	**Mutations at codons**		
	a, b, c	d, e, f	etc
Appearance (number of passages)	X	Y	etc
IC 50 Fold Change [2] versus BL			

[1] cell line(s) used specified. [2] phenotypic assay: specified

b) cross-resistance *in vitro*:

Detailed analyses of *in vitro* resistance to clinical isolates resistant (= clinical failure) to other agents of same drug class.

TABLE 3a. Cross-resistance of clinical isolates resistant (clinical failure) to other drugs (same class)

Parameter	Drug 1	Drug 2	Drug 3	Drug 4
N:o of isolates tested				
Subtypes tested				
Fold Change Drug 1-4 , range vs WT. *				
Fold Change applicant's agent, range vs WT*				

* assay:…specified

Detailed analyses of *in vitro* cross resistance to other drugs same drug class of clinical isolates of patients who failed therapy with the applicant's agent. Data on patients failing class first time and those having failed class prior to treatment with the applicant's agent should be presented in separate tables and clearly indicated in text/table headings.

TABLE 3b. Cross-resistance of clinical isolates to other drugs (same class) resistant (clinical failure) to the applicant's agent.

Parameter	Drug 1	Drug 2	Drug 3	Drug 4
N:o of isolates tested				
Subtypes tested				
Fold Change applicant's agent after failure, range vs WT*				
Fold Change Drug 1-4 , range vs WT. *				

* assay:…specified

***In vivo* resistance:**

In addition to the tables presented in section 5.1, the following tables should be constructed as appropriate to the clinical study database and should be updated regularly (e.g. yearly):

TABLE 4a. *De novo* mutations in treatment naive patients failing therapy with (dose regimen)

Frequency	**Codons**
>20%	
10-20%	

TABLE 4b. *De novo* mutations in treatment experienced patients failing therapy with (dose regimen)

Frequency	**Codons**
>20%	
10-20%	

These tables should be followed by a short description or if possible tabulation of any correlation observed between specific mutations and change in phenotypic sensitivity.