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Guideline on the clinical development of medicinal products for the treatment of HIV infection

Draft

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

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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 provides guidance on the clinical development of direct-acting antiretrovirals for the treatment of HIV infection.

In contrast with the approach taken in EMEA/CPMP/EWP/633/02 Rev2 this revision defines trial populations according to documented viral resistance rather than treatment histories. In this guidance document, the term *treatment naïve* refers to patients who have not previously received antiretroviral therapy, and who are infected with HIV without mutations conferring drug resistance in their major viral populations, as determined by standard genotypic assays (i.e. virus that is predicted to be fully susceptible). The term *treatment experienced* is not used in this revision since it does not adequately define a patient population that is harbouring drug-resistant viruses. Instead, the focus is on the evaluation of the in-vitro and in-vivo activity of a new agent against HIV, including virus with demonstrated resistance that is relevant to the class to which the new agent belongs.

In EMEA/CPMP/EWP/633/02 Rev 2 it was recommended that placebo-controlled studies with a statistical superiority design and with virological endpoints at 24-48 weeks should be performed in patients who were failing on their treatment regimen in order to obtain an indication for use in "treatment experienced" patients. However, due to the introduction of numerous new antiretroviral agents in recent years, and to the general use of pharmacoenhancement ("ritonavir-boosting") when protease inhibitors are part of the treatment regimen, the development of extensive resistance *de novo* is now rare in patients who are treated with optimised regimens in the EU. As a result, placebo-controlled superiority designs are no longer feasible and non-inferiority trials in such populations are fraught with methodological problems.

Therefore for all new agents, it is proposed that data on safety and efficacy are generated in randomised double-blind controlled trials in treatment naïve patients. For first agents of a new class and in the absence of any known cross resistance to the new class, such data might suffice for an indication encompassing all HIV-infected patients. Additional data would be required to support the use of new agents of existing classes in patients infected with virus with resistance to other members of the class to which the new agent belongs. In this setting data should be generated from one or more studies that include a short initial period during which patients continue their failing regimen with or without addition of the new agent (which may itself be given at different dose regimens) followed by a longer period during which all patients are treated with the new agent (at one or more dose regimens) in association with an optimised background regimen.

Development programmes for new agents that are not suitable for study in treatment-naïve patients (e.g. injectable agents) would need to be discussed on a case by case basis.

In line with this approach it is recommended that the antiviral activity, specificity and capacity for selection of resistant variants initially be characterised *in vitro*, and that all viral isolates from patients failing therapy be characterised genotypically as well as phenotypically if not previously investigated. This revision recommends that drug-drug interaction studies that seem to be the most crucial for the safe and effective use of a new agent are performed prior to marketing authorisation.

Suggestions for how the data generated in the clinical program should be reflected in the SmPC follow at the end of the guideline.

1. Legal basis and relevant guidelines

This guideline has to be read in conjunction with the introduction and general principles and parts I and II of the Annex I to Directive 2001/83/EC as 2003/63/EC of 25 June 2003 amending Directive

2001/83/EC Applicants should also refer to other relevant European and ICH guidelines (in their current version) on the conduct of clinical development.

- Choice of a Non-Inferiority Margin - CPMP/EWP/2158/99
- Pharmacokinetic studies in man – CHMP/EWP/147013/04
- Investigation of drug interactions – CPMP/EWP/560/95
- Use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products - EMA/CHMP/37646/2009
- Evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function - CPMP/EWP/2339/02
- Evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function - CPMP/EWP/225/02
- 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
- Guideline of the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation data EMEA/CHMP/3133666/2005.

2. Pharmacodynamics and pharmacokinetics

2.1. In-vitro virological studies

2.1.1. Initial laboratory evaluations

The in-vitro investigation of a new agent for the treatment of HIV should, as a minimum, include the following:

1. Characterization of the mechanism of action of the new agent
2. Determination of the antiviral activity in cell culture, including the determination of EC50/90 against HIV-1 and HIV-2 and against a relevant range of HIV subtypes, laboratory strains and clinical isolates. It is recommended that cell lines include peripheral blood mononuclear cells (PBMCs).
3. Determination of the impact of protein binding on EC50/90.
4. Determination of the cytotoxicity and of the therapeutic index of the drug against the same cell line in which antiviral activity is determined.
5. Assessment of the in-vitro selection of resistant variants and characterisation of their phenotypic and genotypic properties. Selection experiments should be performed with a range of drug concentrations in relation to the EC50, to characterize the concentration-dependency of the selection of resistant variants.

6. Characterization of the activity of the new agent against viruses (which may include laboratory derived recombinants) harbouring a range of resistance associated mutations (RAMs). Studies should adequately describe the potential for cross-resistance between the new agent and licensed antiretroviral agents.

7. Studies of the potential for additive/synergistic or antagonistic effects to occur when the new agent is co-administered with other antiretroviral agents.

8. Studies of the activity of the new drug against other viruses (e.g. in particular Hepatitis B and C viruses). If activity that might exert selective pressure against such viruses is detected, this should prompt further investigations to evaluate the potential for this to occur when using the agent to treat HIV in co-infected patients.

9. If the new agent requires intracellular modification to form the active moiety (e.g. serial phosphorylation as for NRTIs) it is important to assess the possible effects of co-incubation with other drugs that may compete for the activation pathway resulting in modification of antiviral activity. The results of such studies may be particularly helpful should any unexpected findings arise when using certain regimens during clinical studies or in routine clinical care.

2.1.2. Evaluation of resistance in isolates obtained during the clinical programme

Throughout the clinical programme it is expected that baseline isolates and all isolates obtained from those who fail treatment (as defined per protocol) that are present in sufficient quantities should be subjected to phenotypic and genotypic investigations. The IAS-USA list of mutations is a suitable reference (https://www.iasusa.org//sites/default/files/tam/19-4-156.pdf). Although single such mutations at baseline might have a very low impact on the virological response to treatment, their presence may indicate prior exposure of the virus to antiretroviral agents and enhance the risk of emergence of more resistant variants.

The choice of assays and assay conditions should be justified. Since phenotypic assays are hardly used in clinical practice, the focus should be on generating genotypic data. Phenotypic analysis should be performed, however, on clinical samples from patients failing without previously characterised genotypic changes. The results should be reflected in the SmPC and the correlation between genotype and any relevant phenotypic resistance should be described. For genotypic assays population sequencing of the major viral population remains the recommended approach. Monitoring of changes in minority variants using next generation sequencing techniques may be useful within the drug development program but is presently not applicable for clinical practice. In development of CCR5-inhibitors the use of genotypic assays in combination with software algorithms in clinical studies is now accepted, in line with European expert consensus (1)

If new assays are used in clinical trials and are needed to identify patients suitable for treatment and/or to monitor treatment effects, the availability of these assays or validated alternatives outside of the clinical study setting should be addressed and discussed with EU Regulators well in advance of a MAA.

All genotypic changes that emerge during treatment should be assumed to be associated with the selection of resistant variants, unless otherwise proven through phenotypic analysis. In all studies the documentation of emergent resistance against the new agent and against the other components of the regimen should be tabulated.

When evaluating the short term viral response in patients infected with multiple drug resistant viruses

the use of clonal or next generation sequencing techniques with frequent sampling should be considered. The results may add to the understanding of viral dynamics and may be useful when assessing any correlation there may be between results in the early, comparative phase of the study and the subsequent prospective observational phase. These techniques are evolving very quickly; hence, a standard method for use cannot be recommended. Therefore, even when the protocol includes use of a recently developed sequencing method it is recommended that samples should be collected during clinical studies so that retrospective analysis using future technological advances is possible.

2.2. In-vivo pharmacokinetics

The pharmacokinetic study programme should follow the relevant guidelines (Pharmacokinetic studies in man – CHMP/EWP/147013/04). 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. Studies of pharmacokinetics in patients with hepatic and renal impairment should usually be performed prior to approval, and should be conducted in accordance with the principles described in the relevant CHMP guidelines (CPMP/EWP/2339/02 and CPMP/EWP/225/02).

The determination of drug concentrations in cerebrospinal fluid and genital secretions should be considered, though the impact on therapeutic (or prophylactic) decisions is presently unclear.

2.3. Drug-drug interactions

Due to the requisite for treatment of HIV with combination regimens and the high likelihood that patients will be taking a range of other medications there is a major potential for clinically relevant drug-drug interactions to occur. In addition, many types of antiretroviral agents have a considerable potential to be involved in DDIs (as perpetrator and/or as victim), which complicates the assembly of HIV regimens and the management of concomitant medical conditions. Therefore it is essential that existing CHMP guidance is consulted (Investigation of drug interactions CPMP/EWP/560/95 Rev 1) and that sufficient investigations are conducted in the initial pre-approval period to support the co-administrations anticipated in the clinical studies and in clinical practice.

It is not expected that all the drug-drug interaction studies considered to be appropriate or at least desirable will have been performed at the time of initial licensure. In the initial development programme it is recommended that priority should be given to DDI studies 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 drugs used in the management of substance dependence. Within these areas, drugs without reasonable therapeutic alternatives and with a potential for interaction should be prioritized for study. The initial dossier should include a plan for completion of the interaction study programme.

2.4. PK/PD considerations

Data derived from the initial studies in healthy subjects may be used for the preliminary selection of doses and regimens likely to be effective and tolerable in HIV-infected patients. For example, plasma levels may be compared to protein binding adjusted EC50/95 values for target viruses, to justify target pharmacokinetic indices and the range of doses to be tried in patients with HIV infection.

It is essential that the relationship between drug exposure and safety and efficacy parameters is adequately explored based on data obtained from clinical studies in HIV-infected subjects. Therefore

adequate PK sampling should be planned including intensive sampling in subsets of patients. Factors that may impact on drug exposures should be explored by means of population PK analyses. The results of PK/PD analyses should be taken into account when assessing the potential clinical relevance of any alterations in drug exposures that are observed in studies in subjects with hepatic or renal insufficiency and in DDI studies.

3. Clinical efficacy

3.1. General considerations for development programmes

The range of licensed antiretroviral agents commonly allows construction of fully active (generally 3-active drugs with or without a pharmacokinetic enhancer) combination regimens even in patients that have repeatedly failed prior therapy or do not tolerate specific agents. Thus, therapeutic failure is becoming increasingly less frequent and is usually due to poor adherence rather than to insufficient inherent activity of the regimen.

As a result, it is no longer generally thought feasible to demonstrate superiority in studies in which patients who are failing their current regimen are randomised to receive a new agent or placebo added to optimised background regimens. In addition, the efficacy of the optimised background regimens is such that a non-inferiority study design might not provide adequate assay sensitivity. Furthermore, recruitment has been difficult during recent attempts to conduct non-inferiority studies in treatment experienced patients with existing treatment options, especially when there are protocol-specified limitations to the background regimen.

As discussed in more detail in section 3.3, there is a need to reconsider the content of clinical development programmes according to the properties of each new agent. To summarise:

For a *new agent of a new class* randomised controlled double-blind studies in patients with fully drug susceptible HIV (referred to as treatment-naïve patients for the purposes of the following text, although it is acknowledged that drug-resistant virus may be acquired through transmission) might suffice to support use in HIV-infected subjects regardless of prior treatment history and presence of RAMs relevant for agents of other classes.

For a *new agent of an existing class* it is also proposed that randomised controlled double-blind studies are conducted in treatment naïve patients to provide the basic evidence that the selected dose regimen is suitably efficacious and has an acceptable safety profile when compared with appropriate widely-recommended regimens. This could suffice if a claim is to be made only for use in class-naïve patients. However, an endorsement for use in patients infected with virus that is resistant to some or all of the other agents that are in the same class as the new agent would require additional clinical evidence of efficacy.

The following sections provide further details of efficacy endpoints and the clinical study designs that are suggested in each of these scenarios.

Finally, it is possible that a drug of an existing or new class might be developed only for patients with extensively drug resistant virus (e.g. this could apply for agents that would not be suitable for use in other patient populations due to an injectable route of administration or need for a complex dosing regimen, or perhaps due to safety considerations). Specific recommendations for development of such agents are not included below and it is recommended that each case is discussed with EU Regulators to identify suitable development strategies.

Section 5 of this guidance provides examples of how the final indications resulting from these programmes could be worded as well as issues for other sections of the SmPC.

3.2. Efficacy endpoints

3.2.1. Virological endpoints

The suppression of HIV replication is an established surrogate endpoint for clinical benefit, maintained immune status and durability of the virological response by preventing the selection of resistant variants. It is expected that plasma HIV-RNA be quantified using a validated real-time PCR method. The use of a validated and sensitive assay for plasma HIV RNA that meets current standards is essential.

In early dose-finding studies using short-term monotherapy, and when studying short term addition of a new agent to a failing regimen in patients harbouring virus with resistance relevant to the class to which the new agent belongs (see below), the mean change from baseline in HIV-RNA would be the primary end point.

In all other clinical studies the proportion of subjects that achieves and maintains suppression of the plasma viral load to below the limit of quantification (<LLOQ of the HIV-RNA assay used) is the preferred primary efficacy outcome measure. Detectable low level viraemia (i.e. above the LLOQ for the assays with the lowest LLOQ in clinical use, but below a previously applied cut-off such as 50 or 400 copies/mL) could indicate real differences in antiviral potency between regimens. Since future comparative trials are expected to be of non-inferiority designs, the most sensitive virological endpoint possible (i.e. < LLOQ of a suitable assay) should be used.

The use of the FDA snapshot algorithm with missing, switch or discontinuation = failure, is considered appropriate (2), but should be complemented with a secondary Time to Loss of Virological Response TLOVR analysis based on a confirmatory measure of viral load.

In addition to the proportion of patients reaching the <LLOQ endpoint the proportions with viral loads falling into pre-defined strata (e.g. 20-49, 50-99, 100-199, 200-400 and > 400 copies/mL) should be tabulated.

There is presently no clinical consensus on when to switch treatment in case of persistence or re-appearance of detectable low level viraemia and such patients are managed on an individual basis. Therefore protocol-specified criteria that would be applied to serial viral load measurements to prompt a change in therapy may be based on viral loads above the LLOQ. The protocol defined criteria for changing therapy should be justified in relation to the known qualities of the study drugs (primarily the risk of selecting for resistance to one or more agents within the regimen) and to relevant clinical treatment guidelines.

Taking the considerations above into account, virological failure, whether primary or secondary, should be clearly defined in the protocol and the definition should be carefully justified based on the assay and the criteria that will be applied to trigger a switch in treatment.

3.2.2. Immunological endpoints

Effects on absolute CD4+ T-cell count, and the CD4 percentage, should always be documented, as well as response (virological response and immune recovery) by baseline CD4+ cell strata.

3.2.3. Clinical endpoints

The occurrence of HIV-related clinical events, including AIDS-defining conditions, should always be detailed in clinical study reports. The CDC criteria of 1993, excluding CD4+ T-cell count as an AIDS-defining event, should apply.

3.3. Dose finding studies

3.3.1. Monotherapy studies

Monotherapy studies in HIV infected patients should be performed in the initial stages of the clinical development programme, after appropriate virological investigations and pharmacokinetic investigations in healthy subjects (see sections 2.1.1. and 2.4.). The purpose is to characterize the relationship between dose, plasma concentration and the short term in-vivo antiretroviral activity of the new agent. The results should form the basis for the selection of doses for further study. Such "de facto" monotherapy studies, where the investigational agent is the only antiretroviral drug administered to HIV-infected patients, should only be performed in treatment naïve patients without advanced disease.

The duration of monotherapy should take into account the anticipated risk of selecting for resistance to the test agent and should be the minimum needed to meet the objectives of the study, normally 7-10 days. Early and repeated determinations of viral load and drug concentrations are recommended. PK/PD modelling may be a useful complementary tool for dose selection. Depending on these considerations, the monotherapy phase might need to be followed immediately by an active combination regimen to minimize the risk for selection of resistant virus when the new agent is stopped.

For agents targeting host receptors (e.g. some entry inhibitors) studies in healthy volunteers may also be of use to define the drug exposure necessary for target saturation.

3.3.2. Combination studies in treatment naive patients

Co-administration of the experimental agent when administered in combination with other antiretrovirals should be explored initially in smaller scale studies that characterise the efficacy and safety of one or more dose regimens of the new agent compared to that of a relevant reference product when each is administered in combination with other suitable agents. These studies should follow a sound analysis of the available virological and pharmacokinetic data to support dose regimen selection and should be of randomized double-blind design. The efficacy endpoint used for further decision-making in such studies is usually at 16-24 weeks, although it is recommended that the planned study duration is longer.

Patients with more pronounced immunosuppression (e.g., CD4+ cells < 200/µL) or symptomatic patients should be included in phase I/II studies only if there is a specific scientific rationale and if promising efficacy and safety data are already available from patients with higher CD4+ T-cell counts.

Combination studies should be performed in such a way that putatively relevant differences between doses in antiviral efficacy and the risk of selecting for resistance can be detected; i.e. the assumption that adding the new agent to the background regimen increases efficacy over and above the background alone should not be doubtful. As an example, dose ranging a new agent in treatment naive patients, in combination with tenofovir and a boosted PI, would likely not render the study capable of showing differences in efficacy between different doses of the new agent, given the usual study sizes. Such designs should be avoided.

3.3.3. Dose finding in patients with viral resistance relevant to the drug class to which the new agent belongs.

It may be that virus with resistance to other drugs in the same class as the new agent is likely to be susceptible to the new agent. Such resistant variants may have similar EC50/90 for the new agent as

has wild-type virus. It should be noted that in such cases, the barrier to resistance of the new agent might still be impacted by the resistance mutations conferring decreased susceptibility to other agents of the same class.

It may also be that EC50/90 is higher than wild-type, but it is expected that the new agent will still exert a clinically relevant antiviral effect provided that adequate drug exposure is achieved. In such a case, it is possible that higher doses or a different dose regimen (e.g. twice daily rather than once daily dosing) might be needed for patients whose virus has reduced susceptibility to the new agent, in order to reach the maximal efficacy.

For agents with a potential for use against virus resistant to other drugs of the same class, a satisfactory initial monotherapy study in the treatment-naïve should be followed by a dose finding study in patients infected with these types of viruses. For example, patients failing therapy after at least 8 weeks of stable ART and with documented viral resistance by population sequencing (i.e. in a major viral population) during the screening period could be randomized to one or several doses of the new agent or to placebo, each administered in conjunction with the failing regimen. Such studies should generally have a short term virological endpoint (e.g., after 7-14 days of therapy). Design considerations for such a study are largely similar to those discussed below in **section 3.4.3**.

3.4. Confirmatory studies

3.4.1. General considerations

Confirmatory studies should aim to document and explore the possible reasons for the variability in efficacy that is observed. To this end it is important that every effort should be made to identify the reasons for virological failure in individual patients.

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

Confirmatory studies should aim to enrol a representative sample of patients. In particular, sponsors should make all efforts to recruit a representative proportion of women, who have historically been under-represented in clinical trials.

3.4.2. Studies in treatment naive patients

For reasons explained in 3.1, it is anticipated that randomised controlled confirmatory studies will usually be conducted in treatment naïve patients. Patients should fulfil criteria that indicate a need to start antiretroviral therapy, according to recognized clinical treatment guidelines. The existing guidance regarding selection of an appropriate non-inferiority margin should be followed (CPMP/EWP/2158/99). It is recommended that any alternative approaches to study design and/or novel approaches to selection of an appropriate non-inferiority margin should be discussed in advance of study initiation with EU Regulators. Studies should generally be double-blinded. If the sponsor considers that the study cannot be conducted under double-blind conditions, this should be subject to regulatory scientific advice prior to starting the study.

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 estimated background regimen activity, viral subtype, sex and ethnicity. Patients should be stratification for the

most important prognostic factors and as a minimum by baseline viral load and CD4 count. Furthermore, as differences in antiviral efficacy may be apparent only in patients with a high baseline viral load, studies investigating the initiation of therapy in untreated patients should contain a sizable proportion of patients with a baseline viral load ≥ 100,000 copies/ml.

The study should generally employ randomisation of all patients to receive the new agent or another agent, each given in conjunction with the same other agents. If the sponsor wishes to compare the new agent with a reference agent, each against different backgrounds (e.g., tenofovir/emtricitabine and abacavir/lamivudine, respectively), it is recommended that the sponsor seeks regulatory scientific advice prior to study start; if this approach is considered reasonable, the background regimen should be a stratification factor. The comparator selected should enable a double-blind design, and should not cause inadvertent "unblinding", e.g., due to a characteristic adverse event profile.

The proportion of patients with virological suppression at 48 weeks is the appropriate primary endpoint. The total study duration is recommended to be at least two years, to provide long term safety and efficacy data. Important secondary efficacy endpoints include the proportion of patients counted as experiencing treatment failure due to lack of virological efficacy or virological failure, the proportion of patients with detectable or quantifiable viraemia below the defined cut-off for virological failure (if different from the assay LLOQ), as well as the proportion of patients with HIV that develops resistance to one or more antiretroviral agents.

3.4.3. Studies that include patients with viral resistance relevant to the drug class to which the new agent belongs

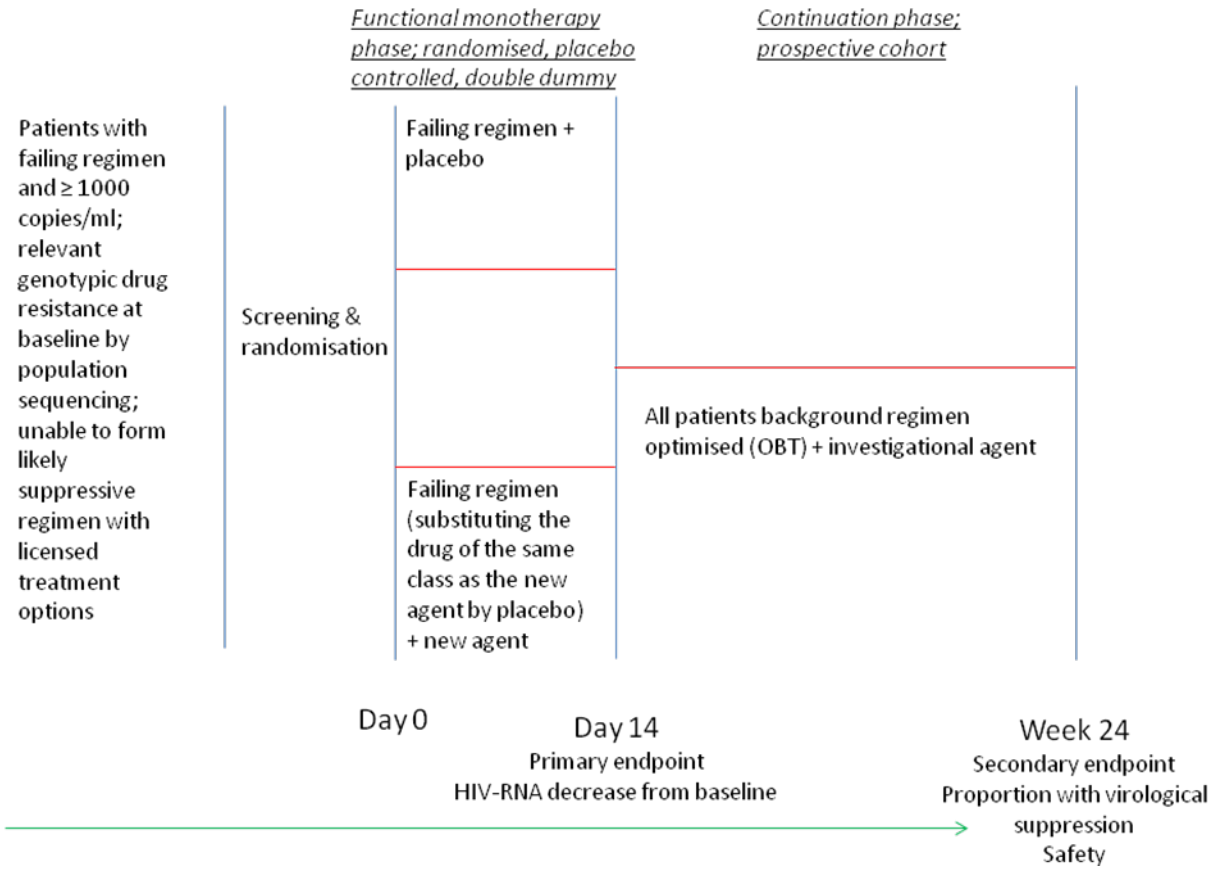
Clinical studies to evaluate the efficacy of a new agent of an existing class against viruses that show resistance against at least one agent in the same class (i.e. referred to as class resistance below) should follow on from a sound documentation of in-vitro activity and studies as described in section 3.3.

The first prerequisite for inclusion of a patient in a study as described below, is viral resistance relevant to other agents of the same class as the new agent in the major virus population (i.e. detectable by population sequencing at screening). The reason for this is that the primary efficacy variable follows short term "functional monotherapy", as outlined, and it is assumed that much of the detectable effect will be exerted on the dominant viral population. What constitutes resistance relevant to other drugs in the class needs to be justified on a case to case basis.

A second prerequisite is that such studies be conducted in patients that are in need of the new agent in order to create a likely suppressive regimen. The baseline viral load of patients should be at least 1000 copies/mL, to allow for population sequencing, and to ensure a reasonable dynamic range (down to the limit of quantitation of the method used for measurement of plasma HIV-RNA), to ascertain assay sensitivity of the trial. Sufficient representation of differing OBT activities and different levels of resistance to the test agent should be captured.

Patients to be included should be on a failing regimen that was unchanged for a minimum of 8 weeks. The failing regimen should include a relevant agent from the class that the new agent belongs to, and the study should be a double blind,, double dummy trial, as outlined below. Resistance to drugs in the class, of relevance for the intended use of the new agent, should be demonstrated by population sequencing at screening. If the latter is not feasible at all study sites for logistical reasons, prior documented resistance could be accepted as inclusion criteria. However, sampling for resistance would always have to be performed at baseline, and only those with relevant drug resistant variants present at this time point by population sequencing should be part of the primary efficacy analysis.

To assess efficacy without putting patients with limited remaining options at risk, the following study design is suggested:



A) **Short term "functional monotherapy"** (e.g. maximum 14 days)

In the following, the term "functional monotherapy" refers to the addition of a new agent to a failing regimen, without any change in the latter other than the withdrawal of an agent of the same class, for which the new agent is substituted. In accordance with common usage, it does not in a strict sense imply that the failing regimen entirely lacks residual antiviral activity. Moreover, it is acknowledged that a clinically relevant selection pressure favouring less fit, resistant variants, may be exerted by the continued use of agents in the failing regimen.

During this first study period patients are randomized to substitute the new agent for the old agent in class, or to continue with the latter, while otherwise not changing the failing regimen. This design would apply to drugs of the same class as an agent in the failing regimen, presumably competing for the same site of action. An exception to this are NRTIs, for which such a substitution would be relevant for drugs that are analogues of the same base as an agent in the failing regimen, or which, according to available clinical and in vitro data, select for the same resistance mutations indicating that co-treatment might not be rational.

The duration of this period of functional monotherapy could vary. The maximal allowable duration of this phase will be dictated by the known properties of the drug and risk of acquiring resistance with very short term exposure. In most cases 7-14 days is the recommended duration for the comparative short term monotherapy phase of the study. Given the very limited duration of this double blind phase the relatively high pill count caused by the double dummy design is not expected to impact adherence.

A staggered design, where patients initially randomised to placebo/reference substance + failing regimen for, e.g., two weeks, are subsequently treated with the test agent for a similar period of time prior to optimizing the background, should be considered. In this case, exposure to the test agent would be similar, provided that the time of the secondary (24 week) endpoint differed by two weeks between arms, in relation to study start.

The number of patients should be large enough, and the degree of resistance sufficiently variable, to certify that a comprehensive assessment of the activity by baseline resistance can be achieved. If supported by results previously obtained in vitro and in clinical studies, at least two doses of the new agent should be considered, provided that this can be justified on the basis of available pre-clinical and clinical safety data. This applies both for this period of functional monotherapy and for the study period that follows.

If two doses are compared, consideration should be given to:

- Primary stratification by baseline resistance (relevant to the class) defined by resistance pathways (based on the available understanding of the evolution of resistance to drugs in the relevant class) or by other relevant categories (e.g. expected lower-level, higher-level resistance to the new agent) as appropriate in the given case
- Secondary stratification by the predicted activity of a subsequent OBT

The primary end point of this period is the viral load reduction from baseline to end of monotherapy with the new agent, compared to that seen with placebo. A pre-specified level of viral decline considered clinically relevant should be justified by the sponsor, and should take into account the remaining activity of the drug in proportion to that seen in monotherapy studies in patients with wild-type virus. This phase of the study will likely be very similar in design to a phase II study in a similar population (see section 3.3.3); by virtue of being larger, however, it allows for the investigation of activity in a broader population, perhaps with a more diverse population in terms of viral resistance patterns; also, short term monotherapy response can be correlated to longer term effect in the continuation phase, within a more diverse population in terms of viral resistance as well as background regimen activity.

B) **Continuation phase; safety and durability of response**

After the first phase described above, all patients should get treatment with the new agent (if appropriate more than one dose) in conjunction with an individually optimised background regimen (i.e. in place of the prior failing regimen). The efficacy objective of this phase is to study response rates at 24 weeks (secondary efficacy endpoint) and on through 48 weeks, by degree of baseline resistance and activity of OBT. Furthermore, this phase is of importance for the safety assessment, and particularly so if a higher dose is used in this population, compared to the treatment naïve studies (see section 4). In such cases, at least 48 weeks of follow-up is mandated.

These analyses are non-primary end points, to be used to further understand the durability of the antiviral effect, and the need for support from co-treating agents. The longer term outcome achieved with test agent and OBT should be assessed and presented according to genotypic, and if appropriate phenotypic, sensitivity scores predicted, counted from start of optimized therapy. This analysis plan, including definitions for the sensitivity score, should be prospective, but the applicant should also submit the dataset to retrospective explorative analysis, in order to provide a maximal understanding of the parameters that are predictive of success, including the need for support from the background regimen of the new agent.

3.5. Fixed dose combination medicinal products

The specific guidelines for the development of FDC should be consulted (CPMP/EWP/240/95). If the FDC is to be used in the place of a well-documented combination of two or three individual single-drug formulations, the application may be based primarily on demonstrating bioequivalence between the FDC and the free combination of anti-retroviral agents in the fasting and/or fed state in accordance with the dosing conditions for individual agents.

In cases where a new posology is foreseen for the FDC it is recommended that the programme is discussed with EU Regulators to identify the degree to which the application may be supported by PK/PD data. If the FDC includes a new anti-retroviral agent and/or a new pharmacokinetic enhancer then a full clinical development programme will be required.

For FDCs intended for use in children, special considerations are warranted as regards age/weight related differences in clearance or bioavailability of the individual components of the combination and the need for sufficient dose forms to accommodate dose adjustment by weight.

3.6. Studies in special patient populations

3.6.1. Studies in children

The development of acceptable and palatable pharmaceutical formulations with suitable strengths for children is normally expected to take place early in drug development. In case FDC are developed for use in the paediatric population, it is expected that acceptability and palatability of these formulations is an integral part of the development. Dose selection is generally based on results from pharmacokinetic studies, where doses for different age groups are selected to produce plasma levels similar to those observed in adults. Relevant CHMP guidelines should be taken into account (Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population CHMP/EWP/147013/04; 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)).

Under certain circumstances, early dose studies could be performed in children with ongoing therapy and suppressed viral loads, by adding the new agent to the ongoing regimen. This approach could minimize the risk for resistance development prior to identifying an appropriate dose. However, this pre-supposes the documented absence of drug-drug interactions between the investigation agents and the agents used for treatment. Further, it is recognised that no PK/PD data are generated with such a study design; however, as stated below, an assumption underlying the recommendations for paediatric studies, is that the PK/PD relation for antiretrovirals is likely to be similar in children and adults, given the same level of viraemia.

Bioavailability and drug clearance may differ considerably between age groups and 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. If possible, the use of WHO weight bands should be considered.

A specific demonstration of antiviral efficacy in paediatric patients is not required. As it is assumed that the PK/PD relation for a direct acting antiviral is roughly similar regardless of the age of the patient, the efficacy of a dose that yields sufficiently similar exposure in children, compared to adults, would be inferred. The parameters that would be applied to conclude on similarity should be based on available data from the entire development programme, including PK and efficacy data in adults.

Therefore non-comparative data in children on the tolerability and safety of the proposed dose regimens as well as documentation of adherence should be generated over appropriate time-spans.

Data collected over 24 weeks would form a reasonable basis for the evaluation of a paediatric indication. Large inter-individual variability in pharmacokinetics is common for antiretrovirals, and particularly in children, making population PK an important objective of these studies.

The number of treatment naïve children is low in the EU, and mostly limited to the very young. Older children and adolescents are to a great extent suppressed on successful therapies and those failing in many cases do so for reasons of poor adherence, making them less suitable for clinical trials (and particularly where PK evaluation is crucial). Therefore, switch studies in suppressed children, if deemed feasible for the new agent with respect to the drug qualities, is one possible way forward. Such studies are not likely to include the youngest children. Dose suggestions for that group could be based on more limited PK data obtained during add-on to existing regimens, as suggested in first paragraph, in combination with modelling.

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

3.6.2. Studies in older patients

No specific studies are expected in older patients. However, as the lifespan of HIV-infected patients continues to increase it should become increasingly feasible to enrol representative numbers of older subjects in adult clinical trials. During the clinical development programme the potential impact of increasing age on pharmacokinetics should be adequately investigated. For example, drug elimination in light of the age-related decrease in renal function and the potentially higher risk of DDIs since the number and range of co-administered agents is likely to be greater in older subjects.

3.6.3. Studies in pregnant women

For some agents, potentially important changes in PK may occur during pregnancy. Therefore, the pharmacokinetics of new antiretrovirals during pregnancy should be studied if use during pregnancy is anticipated, with particular focus on changes in the second and third trimester. Comparisons both with pharmacokinetics post-pregnancy (same patients), as well as historical non-pregnant controls, are recommended. Due to putative changes in protein binding, the unbound fraction should be assessed whenever relevant and feasible.

Concerning the post-marketing monitoring of exposure and safety in pregnancy, see Guideline of the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation data EMEA/CHMP/3133666/2005.

3.6.4. Studies in patients co-infected with hepatitis B or -C

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. Hence, it is important that such patients are represented in adequate numbers in the pivotal studies, to confirm hepatic safety in patients with chronic hepatitis infections.

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 nonclinical 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 also as a possible treatment for a co-infecting virus, it is 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.

3.6.5. Tuberculosis co-infection

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.

3.6.6. HIV-2 infection

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

4. Clinical Safety

As for all other medicinal products, the size of the safety database that would be required before initial approval of an antiretroviral agent or before approval of additional indications and alternative dose regimens must always take into account the demonstrated and anticipated benefits and risks.

Generally safety data on 500-1000 patients treated for 48 weeks with the relevant dosing regimen have been available at the time of initial approval for use in treatment naïve populations. If a new agent has not been studied in the treatment naïve but appears to have benefit in patients with limited treatment options then a smaller safety database and a shorter duration of exposure may be acceptable, subject to the actual data that are available.

As discussed in section 3.3, it is possible that higher doses and/or a different dose regimen might be needed to maximally suppress virus that has reduced susceptibility to the new agent, compared to wild type virus. Such alternative regimens may have a different safety profile compared to regimens investigated for the treatment of patients with fully susceptible virus, but the number of patients that need to receive an alternative regimen in pre-licensure studies may be limited. In these situations there is a need to consider whether the potential safety issues associated with the alternative, higher dose-intensity regimen are of sufficient concern that sound data are required pre-licensure or whether data could be collected during a targeted post-licensure PASS. It is recommended that sponsors discuss with EU regulators on the extent of pre-licensure safety data are deemed to be necessary and how to generate the information.

In addition to the usual reporting of safety data during pre-licensure clinical trials the collection of longer-term safety data may be mandated (e.g. beyond the 48-96 weeks duration of studies) in post-marketing studies. These studies should especially focus on safety issues identified as being relevant to the new agent (e.g. based on class-experience, mechanistic reasoning and/or clinical findings).

5. Information in the Summary of the Product Characteristics

For the SmPC section 4.1. (therapeutic indication), a study program comprising studies only in treatment naive patients could support an indication as follows:

(Product name) is indicated, in combination with other antiretroviral medicinal products, for the treatment of adults infected with HIV-1 without present or past evidence of viral resistance to agents of the X class (see section 5.1.).

The X class is the class to which the new agent belongs.

If a study in treatment experienced patients has also been performed in accordance with the outline above, a wider indication could be supported:

(Product name) is indicated, in combination with other antiretroviral medicinal products, for the treatment of HIV-1 infected adults (see section 5.1.)

Sections 4.5 and 5.1 of the SPC are of particular importance for antiretrovirals, since these drugs are often very prone to interactions, and must be used in accordance to predicted drug susceptibility (resistance algorithms) in patients with resistance relevant to the class. Section 5.1. (and if relevant section 4.4.) should also include information pertaining to the likely need for support from co-treating agents, to guide the use of the drug in patients with drug resistance relevant to the new agent or to other antiretrovirals. This must be inferred from available evidence, including, e.g., treatment outcome data and data on the emergence of resistance in case of virological failure. Resistance data should be up-dated when appropriate, based on the emergence of new information.

6. References

1) European recommendations for the clinical use of HIV drug resistance testing: 2011 update, *AIDS rev* 2011

2) A Meta-analysis to Assess the FDA DAVP's TLOVR Algorithm in HIV Submissions Smith et al, *Drug Information Journal* 2011