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Reflection paper on the non-clinical and clinical development for oral and topical HIV pre-exposure prophylaxis (PrEP)

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Reflection paper on the non-clinical and clinical development for oral and topical HIV pre-exposure prophylaxis (PrEP)

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1. Introduction

Worldwide millions of new HIV infections occur each year. Besides the ongoing efforts to develop preventive vaccines, current developments in the field of HIV chemoprophylaxis (oral and topical) offer an additional tool to existing standard preventive measures which mainly rely on promotion of condom use, to control the epidemic.

After decades of research, *positive* results from studies in PrEP are emerging that call for the elaboration of a formal EU position on the main aspects of the future benefit/risk assessment of products developed in PrEP. Given that positive findings available so far are related to the use of agents with antiretroviral activity, this paper will focus on these. However, several aspects may also apply to other topical preparations, the so-called microbicides.

This reflection paper follows the public consultation by the EMA, in February 2011, of a concept paper on regulatory guidance for the non-clinical and clinical development of medicinal products for HIV prevention including oral and topical PrEP and a subsequent workshop on 8 July 2011 involving invited academics, representatives from WHO, African Institutional body and patients' associations.

The purpose of this reflection paper is to highlight regulatory aspects regarding the preclinical and clinical development of PrEP, so that applicants are prepared to address these issues in their future applications.

It is foreseen that this reflection paper will be updated in accordance with further clinical experience gained in the field. In the future a guideline may be developed.

It is acknowledged that different populations at risk could be targeted by oral and topical PrEP in different epidemiological contexts, ranging from particular groups at high risk of infection to the general population in areas with high HIV prevalence. Still, both oral and topical PrEP approaches are being considered in this document as they will in part raise similar regulatory issues.

2. Particular issues on the non-clinical development

2.1. Safety

In principal, the requirements for non-clinical data will depend on whether the active agent is developed *de novo* for use in PrEP or is already approved for the systemic treatment of HIV infection and provided in a new presentation for clinical use in PrEP

For oral PrEP: For products developed for use in PrEP only, the standard non-clinical programme for products with a systemic pharmacological action will apply.

For topical PrEP: Besides the standard requirements for non-clinical testing of topical agents (cf. CPMP/SWP/2145/00 Guideline on non-clinical local tolerance testing of medicinal products) the need for additional tests that assess the local tolerance (e.g. on vaginal, penile and rectal mucosa, on the vaginal microbial flora and in light of the pH of the formulation) will need to be considered carefully. Condom compatibility testing will be required. Local carcinogenicity will have to be specifically assessed.

The need for other non-clinical safety pharmacology studies will depend on factors such as the extent of systemic absorption of the drug and, if it is already approved for systemic use, a comparison of the plasma concentrations that are achieved with the different methods of administration.

2.2. Pharmacokinetics/-dynamics

Animal models and *in-vitro* tests (e.g. in cervicovaginal or rectal tissue specimens) may be poor predictors of clinical efficacy. However, they can serve as proof of concept and may be used in the initial dose-finding process.

There should be a full *in-vitro* characterization of the mechanism of action and the antiviral activity of the agent (including activity against HIV-1 strains and viral genotypes and HIV-2, as well as an assessment of the risk of selection of resistance.

3. Particular issues concerning the clinical development

3.1. Pharmacology

For topical PrEP: The clinical pharmacology programme should include an evaluation of any effects on condom function due to the agent and/or the formulation intended for PrEP in healthy volunteers (so-called "condom functionality testing"). These studies should preferably be conducted with the formulation/presentation intended for commercialisation. Drug-drug interaction studies should be performed with other locally applied medicinal products (e.g. anti-fungals agents). Consideration should be given to studying the possibility of an interaction with other vaginally applied products, such as tampons.

3.2. Efficacy and Safety

- ***Study design***

There is no single design for pivotal PrEP trials that can be considered optimal to fully assess the benefit-risk relationship that might apply to routine use of the PrEP intervention.

A double-blind randomised study in which the test agent or placebo is added to standard preventive measures plus condom use, risk counselling with regular HIV testing is considered a study design that would be able to generate reliable information on the efficacy of the PrEP intervention.

For avoiding bias due to differential sexual behaviour a placebo-control is required. Differential dropout rates due to knowledge of study arm can only be avoided by a double–blind design. These design features are considered to be essential to support the overall validity of the study results.

However, an important caveat of a placebo-controlled study is that risk compensation - i.e. the potential adjustment of people's behaviour in response to the perceived reduction in risk - will *not* be detectable (see also section "risk compensation" below).

PK sampling (systemically/topically) at least in a subgroup of participants is recommended. Sampling should also be conducted in all subjects who seroconvert when they present at the first study visit after laboratory confirmation of seroconversion.

Daily versus intermittent administration of PrEP

The suitability of daily or intermittent PrEP usage strategies will depend on factors such as risk behaviours, social and cultural settings as well as the geographic location. Both types of use may have a place in PrEP and preferably both should be explored. While daily and intermittent use of PrEP may be associated with differences in efficacy, adherence rates and long term safety. Comparative data on the two modes of use are presently not available. Therefore, it is not possible to extrapolate results from a study of one mode of use to the other..

- ***Endpoints***

Primary endpoint

Studies are expected to be event-driven. The sample size should be determined from the estimated incidence of seroconversion in the absence of any PrEP intervention and the anticipated difference between placebo and PrEP. The duration of the study should be at least two years to enable collection of data from long term exposure but it would be acceptable that the primary analysis is based on data at one year.

The primary efficacy variable is HIV-1 (and/or HIV-2) infection status (measured by seroconversion) at the end of the PrEP intervention, analysed by a time-to-event analysis. This should include appropriate follow-up investigations to account for the diagnostic window between HIV acquisition also towards the end of the PrEP intervention and test positivity and thus to enable detection of all HIV infections occurring during the PrEP intervention. Percent reduction in the HIV incidence rate (i.e. 100 x [1 – (active product HIV infection rate / corresponding placebo HIV infection rate)]) is recognized as the most appropriate primary efficacy measure, expressed as hazard ratio/relative risk.

The primary analysis population should be the all-randomised (ITT) population. Secondary (sensitivity) analyses should be conducted in other pre-defined populations (e.g. according to level of adherence to PrEP intervention). Any discrepancies that are observed between the general conclusions that may be drawn from the primary and sensitivity analyses will require discussion that takes into account the possible need for further studies.

Deviation from the general rule of duplication of the results would need to be justified, and efforts should be made for collecting additional data with the tested PrEP that could reinforce the robustness of the efficacy demonstration.

Ultimately, the acceptability of the actual magnitude of the benefit of treatment that is observed will have to be assessed in light of the safety profile and, hence, the overall benefit-risk relationship. It is not possible to pre-define a minimum level of efficacy that could be viewed as sufficient for approval.

Modelling that is based on the data obtained from the pivotal clinical trials can help to predict the effect size in other settings compared to those that applied during the studies (e.g. HIV incidence, PrEP uptake or adherence to standard prevention measures) and could be taken into account when assessing the benefit-risk relationship.

Secondary endpoints

It is recommended that secondary endpoints include:

- Pre-defined safety endpoints
- Pregnancy rates
- Rates of Sexually Transmitted Infections
- Analyses of any viruses obtained from HIV seroconverters for genotypic/phenotypic drug resistance.

Subgroup analyses

In a multi-component intervention (PrEP on top of standard prevention), confidence in the effect size of the PrEP should be derived from subgroup analyses. For example, to explore efficacy according to age, estimated adherence to the tested PrEP (see below), condom adherence, sexual activity, STI-co-infections (notably HSV-2), countries and educational background.

Study duration / drug exposure

As mentioned above, in addition to the recommendations regarding the extent of population exposure to assess the clinical safety of a drug intended for long-term use (Population Exposure: The Extent of Population Exposure to Assess Clinical Safety - CPMP/ICH/375/95 (ICH E1 guideline)), it is recommended that studies should be of at least two years' duration. This may provide at least preliminary data on longer-term adherence and detection of usage fatigue.

- ***Adherence evaluation***

Currently, measures to evaluate adherence to PrEP include data collection on subjects' self reporting (interview, questionnaire, diary), pill/applicator counts and monitoring of drug concentrations (e.g. in plasma, tissue or vaginal fluid). All of these methods have limitations. Therefore, it is recommended that several different datasets are collected to provide estimates of adherence to PrEP during clinical trials and that the results are evaluated for consistency. Sponsors are encouraged to explore and develop new measures/processes to evaluate and to increase adherence within the studies.

Given the high protective efficacy of condoms when adequately used, it is anticipated that any demonstrable benefit of PrEP in studies will mainly be driven by events where condoms are not used adequately. Information about adherence to standard prevention (notably condom use) is of interest for obtaining a complete picture of the effects of the PrEP strategy.

- ***Populations***

Underlying risk for HIV-acquisition:

Possible populations for inclusion in studies of oral and topical (genital and rectal) PrEP include specific high-risk populations, such as MSM (oral and rectal PrEP) or sex workers, as well as any sexually active men and women in countries with high HIV prevalence.

When injection drug use (IDU) is the major risk factor for HIV acquisition it is not clear whether a PrEP intervention in addition to other risk reduction measures (e.g. supply of sterile needles, drug substitution programmes) would result in a measurable benefit in the clinical study setting in which there is regular risk counselling and close monitoring of adherence to routine prevention.

For serodifferent couples, treatment as prevention measure (i.e. use of antiretroviral drugs by the HIV-infected partner irrespective of the individual's need for therapy) on top of standard prevention has been shown to reduce secondary transmission by 96% (study HPTN-052), and therefore PrEP seems unlikely to be of additional benefit.

Age:

Age groups that are at highest risk of acquiring HIV infection will be included in the pivotal studies. For legal reasons this will often refer to adults (i.e subjects at least 18 years of age).

Whenever feasible, additional information should be obtained during the clinical development programme in the following groups:

- sexually active adolescents: Even though this group is at particular risk of HIV acquisition, enrolment in clinical trials for PrEP raise difficulties (e.g. obtaining parental consent, collecting information on sexual activity). If possible data on safety, acceptability and PK should be collected to support a conclusion regarding similar efficacy and safety of the PrEP intervention as compared to adults.

- For topical PrEP: In women over 45 years of age it is recommended that safety and PK data should be obtained due to the potential for peri-/postmenopausal changes in the vaginal mucosa and flora.

Extrapolation:

Extrapolation of efficacy data obtained in the population studied in the pivotal trials to other populations and/or modes of use is not acceptable as follows:

- For topical PrEP: Rectal and vaginal mucosae have different properties with respect to drug absorption/distribution. Therefore, the efficacy that is observed with applications to one cannot be extrapolated to the other (i.e. in the context of of efficacy of a PrEP intervention used in subjects engaging in vaginal or in anal intercourse).
- For oral PrEP: the concentrations that are achieved locally in the rectal or vaginal mucosa following oral administration of PrEP may differ. For example, the unabsorbed fraction of an agent that is not substantially metabolised within the gut could lead to higher local concentrations of antiviral activity within the rectum compared to concentrations achieved in the vagina.

  The efficacy that is achieved by an oral PrEP against HIV acquisition during sexual encounters cannot predict efficacy transmission via contaminated needles.

Indications for use in these different circumstances must be supported by specific efficacy data. Efficacy demonstrated in other circumstances could be viewed as supportive to some extent.

Outside of an Article 58 procedure, the relevance and applicability of the study results for the EU population would have to be justified (Ethnic factors in the acceptability of foreign clinical data - CPMP/ICH/289/95 (ICH E5) Guideline and CHMP reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU-population, EMEA/CHMP/EWP/692702/2008). The justification should take into account the possibility that the magnitude of the benefit of the PrEP intervention could be effected to some considerable extent by access to different modes of prevention (including post-exposure prophylaxis, treatment as prevention) that may vary by region/country. This, in turn, has implications for the overall benefit-risk relationship.

4. Post- authorisation issues

- ***Resistance***

The clinical development programme is unlikely to derive adequate reassurance on the impact of failing PrEP (HIV acquisition under PrEP) on the response to antiretroviral treatment *(given the few seroconversions in PrEP clinical trials, conditions of HIV testing and adherence in clinical trials likely to differ from the future real-life setting*).

It is therefore considered critical that the application includes measures to adequately assess this matter in the Risk Management Plan (RMP).

- ***Risk compensation***

In clinical trials of PrEP, a measure of relative risk reduction as well as of absolute risk reduction will be obtained. Whereas the former may be considered intrinsic to the PrEP strategy, the latter will be greatly dependent on extrinsic factors, such as the underlying risk of the studied population (e.g., frequency and nature of HIV exposure, condom use, etc), and may be impacted by behavioural changes caused by the use of PrEP. As for other interventions, the absolute benefit of a PrEP strategy will hence strongly depend on the setting of its use. Therefore, the regulatory assessment would by necessity largely be limited to an evaluation of its relative risk reduction as shown in the pivotal

studies, in relation to its safety profile. Relative Risk reduction may be useful for extrapolation, but absolute risk reduction may be more important in determining risk benefit.

The absolute benefit of a PrEP strategy needs to be evaluated at the level of the individual user and at the public health level. The behavioural impact of PrEP on risk compensation and condom replacement cannot be assessed in pre-licensure placebo-controlled trials.

Therefore, it is mandatory that the Marketing Authorisation Application contains a Risk Management Plan that adequately covers the public health impact of the PrEP intervention.

- ***Long term follow up***

As mentioned above, risk compensation and resistance are critical aspects to be followed and to be taken into account in the RMP. Other aspects that need to be followed up include HIV seroconversion rates, adherence and safety. The duration of monitoring of these issues after approval should depend upon the available data and the level of reassurance obtained.

- ***Implementation***

The implementation of HIV PrEP is under the responsibility of the relevant National Authorities and therefore this important issue is not addressed in this document.

One of the critical aspects for the implementation of PrEP is HIV testing. HIV testing should be performed before starting and at frequent intervals to identify early HIV infected patients and to avoid development of resistance.

HIV PrEP should be part of an integrated prevention plan and this plan should be looked and followed at the community level. Communities are different and present specific behaviours; therefore at implementation there should be a close follow-up taking into account the specificities of the different communities.

5. Conclusion

PrEP is recognized as a potentially valuable tool as part of an integrated approach for reducing the individual's risk of HIV acquisition and for combating the HIV epidemic. Based on the current knowledge and the regulatory experience gained so far, this reflection paper provides some recommendations for the pre-licensure non-clinical and clinical development of antiretrovirally as PrEP interventions. Critical aspects regarding the actual benefit that could be associated with the routine use of a PrEP intervention (e.g. risk compensation and viral drug resistance) can not be assessed until a product is in routine use. Therefore, the Risk Management Plan will be important in the evaluation of future marketing authorisation applications in oral and topical PrEP.

The EMA/CHMP is following the scientific developments in this area and giving scientific advice as requested. Following consultations that culminated in this reflection paper the agency is prepared to evaluate future marketing authorisation applications for PrEP.