CAPRISA
CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

Generating Knowledge - Impacting Health

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Antimicrobial Drugs Advisory Committee
FDA White Oak Campus
10903 New Hampshire Ave
Silver Spring, MD 20993-0002
USA

RE: FDA-2019-N-2779 for "Antimicrobial Drugs Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments.

On behalf of the Centre for the AIDS Programme of Research in South Africa (CAPRISA), I offer my support for the Supplemental New Drug Application (sNDA) submitted by Gilead Sciences for Descovy®, the fixed-dose combination of emtricitabine and tenofovir alafenamide (FTC/TAF), for the HIV pre-exposure prophylaxis (PrEP) indication including its use in cis-gendered women.

CAPRISA was established in 2002 with a programme grant award from the United States of America National Institutes of Health. It comprises a consortium of five partner institutions; University of KwaZulu-Natal, University of Cape Town, University of Western Cape, National Institute for Communicable Diseases, and Columbia University in New York. CAPRISA is a designated UNAIDS Collaborating Centre for HIV Prevention Research and undertakes research that contributes to understanding Clade C HIV pathogenesis, prevention of HIV in young women; monitoring of the evolving HIV epidemic and reducing deaths in HIV-TB co-infected patients.

I disclose the following interests: Coinventor of a patent (EP 2 579 871 B1) of tenofovir gel against HSV-1 and HSV-2 with Gilead Sciences, Co-Principal investigator of *the CAPRISA 018 trial: A phase I/II trial to assess the safety, acceptability, tolerability and pharmacokinetics of a sustained-release tenofovir alafenamide sub-dermal implant for HIV prevention in women,* in support of which Gilead Sciences has donated 200g of tenofovir alafenamide active pharmaceutical ingredient (API). In addition, Gilead Sciences has donated API for the two completed CAPRISA tenofovir microbicide gel trials, CAPRISA 004 and CAPRISA 008, where I was the Co-Principal Investigator and Principal Investigator respectively. I have no financial interests in Gilead Sciences.

I am a South African infectious diseases epidemiologist and have studied the evolving HIV epidemic in South Africa for over 30 years which has enabled me to garner a nuanced understanding of transmission dynamics in this context. A unique feature of the HIV epidemic in sub-Saharan Africa (SSA), is that adolescent girls and young women (15-24 years) acquire HIV 5–7 years earlier compared to their male peers and are up to four times more likely to be infected. Each week there are approximately 7000 new infections in young women in sub-Saharan Africa. The vulnerability of young women is as a result of a complex interplay of biological, behavioural and structural factors. Despite the increased burden and vulnerability for HIV infection in young African women, they have few options to reduce their risk of acquiring HIV that do not require male co-operation.

There is an urgent need for new, safe and accessible prevention options for use in young African women especially in the vulnerable period in their lives between 15-24 years. Adherence to daily, oral formulations of tenofovir/emtricitabine and monthly dapivirine rings have proven to be challenging for young women in some settings and access to new more potent drugs and formulations that are less user dependent is urgently needed. One such option is FTC/TAF (Descovy®) - a potent and safer alternative to Truvada® (FTC/TDF).

Noting that the primary clinical trials of Descovy® for its prophylactic indication excluded women and adolescents who would benefit most from this technology, we will continue our advocacy efforts with Gilead, and other pharmaceutical companies to include all key and priority populations including adolescents and young women early in the clinical research and development pathway so that they also benefit from new technologies as they become available with minimal delays. While efficacy data of FTC/TAF from randomized controlled trials in young women in Africa would be ideal, it is unavailable. Given the similarity between Truvada® and Descovy® viz., both are prodrugs that are metabolised to the active tenofovir diphosphate (TFV-DP) we are able to compare the two drugs for safety and efficacy using the extensive PrEP data available for Truvada®.

In the absence of clinical trial PrEP efficacy data of Descovy® in women, on balance, the combination of safety data of FTC/TAF from treatment trials that included women; comparable Descovy® and Truvada® non-human primate efficacy data with vaginal exposure; and protective drug level data in women provide evidence in support of the prophylactic use of Descovy® in cis-women. Due to its potency, smaller drug load, longer intracellular half-life and lower systemic circulation of the parent drug tenofovir (TFV), FTC/TAF offers an improved systemic safety profile.

Specifically:

i. The safety of Descovy® in women can be extrapolated from its use in treatment trials. FTC/TAF is prescribed as part of combined antiretroviral treatment of HIV-1 in men and women. Safety data from these treatment trials in women shows that relative to TDF, TAF users have a lower risk for deleterious renal and bone mineral density adverse events. These safety benefits of TAF in HIV-1 infected women is unlikely to be different in HIV negative women where the same dose and frequency of dosing is being proposed (1).

ii. Non-human primate (NHP) challenge studies offer initial insights on efficacy of FTC/TAF compared to FTC/TDF. Massud et.al, (2), demonstrated that use of oral administration of FTC/TAF (n=6), 24h before and 2h after each weekly vaginal exposure to SHIV162p3 challenge provided 91% protection in pigtail macaques for up to 15 weeks compared to controls. This efficacy of FTC/TAF is comparable to NHP data from PrEP evaluation of FTC/TDF.

iii. One of the major challenges in HIV prevention is obtaining adequate levels of drug in the female genital tract, i.e. the site of exposure, that can protect against sexually acquired incident HIV infection. CONRAD 137 (3) provides data from a study of 75 women; who received FTC 200mg/TAF 25mg (n=24), FTC 200mg/TAF 10mg (n=26) and the remainder FTC 200mg/TDF 300mg (n=25). Compared to those exposed to FTC/TDF, those exposed to FTC/TAF had four-fold higher TFV-DP concentration in PBMCs and importantly a Cmax of 144021 fmol/g in cervicovaginal tissues within 4 hours of dosing. Notably, there were fewer gastrointestinal adverse effects and lower circulating TFV levels for FTC/TAF group. This study was also able to demonstrate protection from HIV in an ex-vivo tissue infectivity model in a subset of women. A mean concentration of 40 fmol/10^6 cells for TFV -DP was detected after a single dose - this is approximately 3 times higher than what was needed for protection (90% reduction in HIV risk) from the iPrEX study.

Taken together these data provide evidence for the safety, efficacy and adequacy of protective drug levels from oral FTC/TAF (Descovy®) for preventing HIV in cis-women while additionally offering a superior safety profile compared to FTC/TDF.

Lastly, the inclusion of Descovy® in the medicines patent pool, will enable rapid access at affordable prices for women in Africa and other developing countries within a relatively short space of time following licensure for PrEP use in the USA.

Based on this body of evidence and the urgent need for offering young women more choices for reducing their risk of acquiring HIV, especially in sub-Saharan Africa, CAPRISA is supportive of this sNDA and the registration of FTC/TAF for its PrEP indication in cis-women.

Sincerely

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