



August 6, 2018

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
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*RE: Docket Number, FDA-2019-N-2779: Supplemental new drug application (sNDA) 208215, TAF/FTC for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection among individuals who are HIV-negative and at risk for HIV. Antimicrobial Drugs Advisory Committee Meeting, August 7, 2019*

To the Antimicrobial Drugs Advisory Committee and FDA:

Thank you for the opportunity to provide information to the Committee and to FDA regarding the sNDA for pre-exposure prophylaxis (PrEP) with TAF/FTC (*Descovy*).

AVAC is a non-profit organization founded in 1995 that uses education, policy analysis, advocacy and a network of global collaborations to accelerate the ethical development and global delivery of HIV prevention options as part of a comprehensive response to the pandemic. AVAC has worked on oral PrEP advocacy, policy and programs for 15 years.

We take no money from any pharmaceutical companies, including Gilead Sciences, Inc., the company submitting this sNDA. I should note, however, that I did serve, without compensation, on the DISCOVER trial's Independent Data Monitoring Committee (IDMC).

### ***1. F/TAF for PrEP for men and transgender women who have sex with men***

The available data presented in the application do, in our opinion, support approval of TAF/FTC as an additional, non-inferior, safe and effective daily oral PrEP option among men and transgender women who have sex with men. While the DISCOVER trial had very few HIV infections, the data do support the non-inferiority of F/TAF compared to F/TDF for this population.

Unfortunately, the DISCOVER trial did not enroll a diverse trial population, especially individuals who continue to fall out of current PrEP programs in the US and who are among those most at risk. It will be critical that access programs ensure oral PrEP (with both F/TAF and F/TDF) reaches those people who need it most, especially younger African-American and Latinx men and transgender women who have sex with men. But this should not delay regulatory approval of F/TAF for men and transgender women who have sex with men generally; the data presented support the safety and efficacy of F/TAF for PrEP for men and transgender women who have sex with men

Accelerating the ethical development and global delivery of HIV prevention options as part of a comprehensive, integrated and sustained response to the epidemic

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In addition, while more data from DISCOVER has been accrued and presented, including at the IAS 2019 conference last month, it remains too limited a data set to conclude that F/TAF is clinically safer or more effective than F/TDF for PrEP. Noninferiority of F/TAF to F/TDF is clearly demonstrated; that was the question the trial sought to address, and, in our opinion, did.

It is essential, therefore, that the PrEP indication for F/TAF for PrEP clearly state this new PrEP form is not inferior to F/TDF. Any claims of superiority of F/TAF are an overstatement of the data and, more importantly, will cause enormous confusion among both users and providers of PrEP. An indication that claims superiority could actually cause actual harm as potential F/TDF users delay initiation until F/TAF is later available for reasons of cost or coverage, and/or current F/TDF users might abandon PrEP use until they could access what would be marketed unfairly as “better PrEP”. All labeling and marketing materials should clearly state these as equivalent daily oral PrEP options.

## ***2. F/TAF for PrEP for cisgender women***

It is extremely unfortunate that similar safety and efficacy data for F/TAF for PrEP were not collected in an efficacy trial for cisgender women. The benefit of multiple trials in different populations was clear when a previous FDA Advisory Committee reviewed the data for F/TDF for PrEP in 2012. The data from the multiple clinical trials was consistent: HIV uninfected men and women who took daily TDF/FTC, as prescribed, along with the counseling and standard prevention they already use, and who are at risk of exposure to HIV-1 through sexual contact, and perceive themselves to be at risk, reduced their likelihood of infection substantially and to a much greater degree than if they had relied on counseling and standard prevention alone.

But, if the F/TAF for PrEP label is **not** extended to include cisgender women, there will be multi-year delays and denial of access of this additional form of oral PrEP that may be a good option for some.

The extrapolation of safety and pharmacokinetic data as presented by Gilead in this sNDA raises important questions about which drug concentrations matter most, systemic or local mucosal tissue. The systemic PK data in the sNDA do, in general, support an initial broader indication of F/TAF for PrEP for cisgender women, even as the local tissue concentrations seem less clear in this regard.

Given this application is limited to systemic drug exposure to support a PrEP indication in cisgender women, we believe this indication should also be approved but subject to specific post-marketing surveillance, Phase 4 studies and a robust Risk Evaluation and Mitigation Strategy (REMS). And these plans should also include other populations (e.g., adolescents and transgender men) that were also not part of the DISCOVER trial.

The Advisory Committee and the FDA should require Gilead to develop and implement a clear post-marketing research agenda and REMS that will provide clear evidence of safety

and **effectiveness** among cisgender women within the first 12-24 months of introduction of F/TAF for PrEP. The emphasis above on public health effectiveness is critical as we know from earlier oral PrEP trials that efficacy in this population can have wide confidence intervals. In addition, recent data about lipid and weight-gain side effects of TAF compared to TDF, especially in women and individuals of African descent, make strict post-marketing surveillance critical.

As part of this initial 24-month window, AVAC urges the FDA to consider the most efficient process for gaining additional data in women, including robust pharmacokinetic data, beyond the CONRAD A15-137 study, to monitor safety and potential effectiveness.

In particular, our own work along with many other groups has identified pill size as a particular barrier to oral PrEP uptake and ongoing use, especially amongst women. The smaller pill size of F/TAF could be an important factor in increasing effective oral PrEP use in this population, that has lagged far behind MSM. This issue should also be prioritized in post-marketing surveillance and the REMS.

Given the fundamental need for additional prevention options for cisgender women, AVAC believes the insufficient process for collecting data in Gilead's product development plan for F/TAF thus far could be major setback in HIV prevention. We urge the FDA to hold product developers to a higher standard in drug development plans that will gain sufficient data across a range of populations in a timely and efficient manner, and in advance of regulatory submissions.

### ***3. Education, Prescriber Information and Supportive Requirements***

As the FDA considers the informational and educational requirements for PrEP prescribers and users of F/TAF, we also urge clear guidelines and requirements of what is, and is not, known about F/TAF for PrEP. Given that behavioral, cultural and situational contexts around sexual risks may vary tremendously among PrEP users, and especially since F/TAF was studied in a very limited population and demographic, the FDA should include knowledgeable and representative public participation in FDA-required wording, format and content of educational/informational materials and programs to support safe use and adherence as a feature of post-marketing requirements. Furthermore, we request that the Committee and FDA include community input from representatives of the men and women who have and are most likely to be prescribed PrEP in the processes designed to negotiate the content and breadth of educational materials, and not engage in such negotiations solely between the manufacturer and FDA. In addition, the FDA should require that Gilead study and resolve issues of their marketing and physician/health worker engagement on the issues of equitable uptake of knowledge and access, including price factors.

### ***4. Conclusions***

For the reasons described above, we strongly encourage the Advisory Committee to recommend, and the FDA to approve, the supplemental indication for daily oral PrEP with F/TAF for adult men and women at risk of sexually acquired HIV-1 infection – with the

appropriate requirements for labeling, post-marketing surveillance and REMS as described above, and as per the FDA's own updated guidance on REMS and access posted earlier this year. The time for additional HIV prevention options, for all people at risk, is now, and oral PrEP is one of the most promising additions for prevention.

We also urge the Committee to consider the consequences should it vote *against* the broad indication of F/TAF for PrEP. F/TAF and F/TDF are available off-label today to anyone who is able to obtain a prescription. Health providers and potential PrEP users need accurate information – and an FDA-approved label, clear post-marketing surveillance requirements, and accurate, evidence-based health education and marketing materials that should be required as part of FDA approval of this application, are the best ways to ensure safe and effective use of PrEP of both combinations.

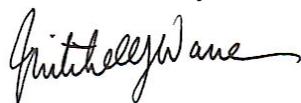
In addition, the consequences of non-approval are unnecessary delays in filling critical data gaps that affect domestic and global health at a crucial juncture of ending this epidemic. Political commitment must be translated into action and impact, and the FDA has an opportunity and obligation to act.

This is a unique situation, given that TAF is closely related to TDF, and not an entirely new product. Approving oral F/TAF for PrEP on the limited data is warranted in this case, but should not be the standard by which additional, novel PrEP options are tested and approved. Robust data across a range of populations at risk of infection must continue to be the standard, so that product development and regulatory approval can lead more seamlessly to acceptance, uptake and adherence by all populations who can – and should – benefit from innovation.

Oral PrEP, together with other prevention strategies, could help to significantly reduce HIV infections and could be a life-saving intervention for some men and women. Multiple clinical trials have clearly shown that tenofovir-based PrEP is safe and effective when used as prescribed. We all must now act on the scientific evidence and translate them into practice, universal access and impact.

We appreciate your consideration of these comments. Please do feel free to let me know if you have any questions.

Yours sincerely,

A handwritten signature in black ink, appearing to read "Mitchell Warren". The signature is fluid and cursive, with a long horizontal stroke at the end.

Mitchell Warren  
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