VIA SUBMISSION AND HAND DELIVERY

U.S. Antimicrobial Drugs Advisory Committee

Re: *Docket No. FDA-2019-N-2779 for "Antimicrobial Drugs Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments"*

7 August 2019

Dear Committee Members:

We submit this testimony in regard to the supplemental new drug application No. 208-215 ("sNDA") for DESCOVY (tenofovir alafenamide fumarate \ emtricitabine, commonly referred to as "TAF\FTC") for an HIV-1 pre-exposure prophylaxis ("PrEP") indication.

While we are committed to universally ensuring access to state-of-the-art HIV prevention modalities, we are troubled by the conduct of the applicant, Gilead Sciences, Inc. ("Gilead") in their efforts to develop, market, and promote this technology. Furthermore, the complete lack of conclusive safety and efficacy data for this technology for some of the populations most impacted by the HIV epidemic is alarming.

We believe that it is imperative that both this committee and the FDA consider these concerns when making decisions regarding this sNDA.

Specifically:

1. **The study population of the DISCOVER clinical trial does not reflect the makeup of communities most vulnerable to HIV. Furthermore, there is *no* efficacy data for DESCOVY PrEP in cisgender women.**

   The fact that Gilead did not perform any trials for cisgender women yet expects the FDA to approve DESCOVY PrEP in this population defies logic. While we are not opposing a broad indication for DESCOVY as PrEP for cisgender women, we also fear that approval of such an indication — without any efficacy or conclusive safety data — would establish a disturbing precedent discouraging other new HIV prevention technologies from being tested in cisgender women.

Put simply, Gilead's failure to establish high quality safety and efficacy data for DESCOVY PrEP in cisgender women has put advocates into an impossible quandary — either advocate for a delay in the approval of DESCOVY PrEP in cisgender women and effectively deny them the ability to choose which PrEP formulation they prefer, or advocate for the approval of DESCOVY PrEP in cisgender women while establishing a precedent that will disincentivize future PrEP modalities from being tested in this key population.

We believe that the FDA must carefully weigh these options when choosing whether to extend the indication to cisgender women and must follow the guidance of organizations and communities of cisgender women on this issue. If the FDA extends the PrEP indication to cisgender women today, the FDA must require Gilead to perform robust post-marketing studies to ensure that DESCOVY PrEP is safe and effective in this population. If it does not, the FDA must ensure that Gilead performs and funds a phase 3 trial to determine whether DESCOVY PrEP is effective and safe in cisgender women as a condition of approval in other populations (i.e., if only a narrow indication for DESCOVY PrEP is approved, the FDA must still require that Gilead complete studies of effectiveness and safety in cisgender women).

The DISCOVER trial (National Clinical Trial Registry No. NCT028420860) was a Gilead sponsored and led phase 3b, double-blinded randomized placebo control non-inferiority trial that aimed to evaluate whether the use of DESCOVY was non-inferior to TRUVADA (tenofovir disoproxil fumarate \ emtricitabine, commonly referred to as "TDF\FTC") in preventing HIV-1 infection in cisgender men who have sex with men ("cMSM") and transgender women. To our knowledge, this is the only trial that has been performed which evaluates the efficacy of DESCOVY for HIV prevention.

While no peer reviewed article on the results from DISCOVER has been published, investigators have shared data from the trial at various conferences. The data that have been made publicly available are concerning.

Indeed, our concerns about the lack of data for cisgender women are not purely theoretical. Previously published studies demonstrate that the uptake of TAF and pharmacokinetics of TAF activation vary substantially in the target tissue compartment (e.g., vaginal mucosa in cisgender women vs. rectal mucosa in cMSM) of these different populations. Of particular concern is a Gilead sponsored study which demonstrated that the concentration of tenofovir-diphosphate ("TFV-DP") — the pharmacologically active anabolite of both TDF and TAF — was below the level of quantification in most samples of mononuclear cells in the vaginal tissue compartment following oral administration of TAF.[1] The relative role of TFV-DP concentration in mononuclear cells in target tissues vs. peripheral blood mononuclear cells ("PBMCs") vis-à-vis PrEP efficacy is still a

[1] Cottrell ML, Garrett KL, Prince, HM, et al. "Single-dose pharmacokinetics of tenofovir alafenamide and its active metabolite in the mucosal tissues." *Journal of Antimicrobial Chemotherapy*, Volume 72, Issue 6, June 2017, Pages 1731–1740, https://doi.org/10.1093/jac/dkx064

question of open debate.[2]

Furthermore, there is evidence that the metabolic effects of TAF vary considerably by gender. The use of TAF instead of TDF has been associated in multiple trials, including DISCOVER, with statistically significant worsening of lipid biomarkers and weight gain.[3] In the ADVANCE trial, cisgender women living with HIV who were treated TAF\FTC plus dolutegravir ("DTG") gained statistically significant more weight than cisgender women who used TDF\FTC+DTG (mean change in weight, 96 weeks post enrollment; +10 kg in TAF\FTC+DTG vs. +5 kg in TDF\FTC+DTG, $p<0.001$). However, in the same trial, the difference in weight gain in cisgender men who were treated with TAF\FTC\DTG vs. TDF\FTC\DTG was *not* statistically significant (mean change in weight, 96 weeks post enrollment; +5 kg in TAF\FTC+DTG vs. +4 kg in TDF\FTC+DTG, n.s.).[4]

These unexplained differences are all the more concerning considering that even a putative mechanism for these metabolic changes in TAF treated persons has not been proposed.

Furthermore, the racial and ethnic make up of the DISCOVER did not reflect the make up of the populations most vulnerable to the HIV epidemic in the United States. For example, while 46% of new HIV infections in the United States are in black people, only 9% (n=474/5,387) of participants in DISCOVER were black. This is particularly concerning, given that previously published results indicate that the metabolic effects of TAF may be different in people of African descent.

Thus, the FDA should only approve Gilead's sNDA conditionally and require that a rigorous program of post-marketing surveillance be implemented in order to ensure that all communities most affected by HIV have accurate safety and effectiveness information as they decide which PrEP regimen is right for them.

2. Furthermore, the FDA should ensure that all marketing by the company is consistent with the scientific evidence. We are extremely concerned by the company's explicit efforts to undermine TDF\FTC as PrEP by over-inflating the benefits of TAF\FTC.

Gilead's activity positioning DESCOVY as PrEP is already alarming. We have reports of the company telling community advocates that DESCOVY "is 53% better than TRUVADA" at reducing HIV acquisition. This is misleading; DISCOVER was a non-

[2] Personal communication between Johnson JS (TAG), Krellenstein JB (PrEP4All) and Glidden D (University of California-San Francisco), 5 Aug 2019.

[3] Spinner CD, Brunetta J, Shalit P, et al. "DISCOVER study for HIV pre-exposure prophylaxis (PrEP): F/TAF has a more rapid onset and longer sustained duration of HIV protection compared with F/TDF." 10th IAS Conference on HIV Science (IAS 2019), July 21-24, 2019, Mexico City. Abstract TUAC0403LB

[4] Venter WF, Moorhouse M, Sokhela S et al. "The ADVANCE trial: Phase 3, randomized comparison of TAF/FTC/DTG, TDF/FTC/DTG or TDF/FTC/EFV for first-line treatment of HIV-1 infection." 10th IAS Conference on HIV Science (IAS 2019), July 21-24, 2019, Mexico City. Abstract WEAB0405LB

inferiority trial, and no statistically significant difference in efficacy was observed. We are hearing reports of potential benefits of DESCOVY in terms of time to protection and durability of protection. We have yet to see clinical evidence (versus pharmacokinetic data) that supports this claim.

Gilead is asserting that DESCOVY will be a "safer" PrEP than TRUVADA, again without evidence in terms of a clinical endpoint.[5,6] DISCOVER was inadequately designed to ascertain the clinical significance of the differences in bone, kidney, and lipid biomarkers that were found. This must be made clear to potential users of the product.

The product label and marketing should be given careful attention; all information presented must reflect the uncertainty on whether recent data on the potential renal and bone benefits of TAF\FTC are of actual clinical importance. It must also reflect the uncertainty regarding changes in lipid biomarkers and weight gain. As the current sole domestic source of both TDF\FTC and TAF\FTC, Gilead stands to benefit from cannibalizing its soon-to-be-generic TRUVADA prescription market with DESCOVY, which will not be off patent for the foreseeable future. This demands extra scrutiny.

<u>If the sNDA is approved, the FDA must ensure that Gilead does not engage in off-label marketing, overstate the alleged safety benefits of DESCOVY, and claim other benefits that are not backed by high quality evidence.</u>

3. Gilead intentionally delayed the development of tenofovir alafenamide ("GS-7340") by nearly a decade, so that it would not harm the market share or profits from its previous tenofovir prodrug, tenofovir disoproxil. We do not understand why there is a sudden rush to approve a PrEP indication for FTC\TAF before peer-reviewed publication of evidence and without further investigation of safety and efficacy in key populations.

Tenofovir alafenamide (known initially by its internal Gilead designator "GS-7340") was invented, at the latest, in the year 2000. Although Gilead filed an investigational new drug ("IND") application for GS-7340 in January 2002 and performed phase 1 and early phase 2 trials through 2003, in October 2004, the company announced that it was discontinuing development following an "internal business review"[7]— despite promising initial phase 1 and phase 2 results.

[5] Spinner CD, et al. "DISCOVER study for HIV pre-exposure prophylaxis (PrEP)" 10th IAS Conference on HIV Science (IAS 2019), July 21-24, 2019, Mexico City. Abstract TUAC0403LB

[6] Hare C, et al. The Phase 3 Discover Study: Daily F/Taf Or F/Tdf For Hiv Preexposure Prophylaxis (Abstract 104). Paper presented at: 26th Conference on Retroviruses and Opportunistic Infections; 2019 March 4-7; Seattle, WA.

[7] https://www.gilead.com/news/press-releases/2004/10/gilead-discontinues-development-of-gs- 9005-and-gs-7340-company-continues-commitment-to-research-efforts-in-hiv

In 2010, Gilead announced it was resuming development of GS-7340, and the first product containing the drug, GENVOYA [TAF\FTC\cobicistat\elvitegravir], would not be approved by the FDA until 2015 — a decade and a half after the drug was first discovered.

At a 2011 Royal Bank of Canada Capital Conference, the then Chief Operating Officer and President of Gilead (and future Chief Executive Officer) explained the company's rationale for this delay (emphasis ours):

> "One of the reasons why we were concerned about developing 7340 [TAF] was we were trying to launch TRUVADA [TDF\FTC] versus EPZICOM [abacavir \ lamivudine] at that time. **And to have our own study suggesting that VIREAD [TDF] wasn't the safest thing on the market, which it certainly was at the time. . . It didn't seem like the best. It seemed like we would have a mix[ed] message.** "[8]

It is completely unacceptable that a company would intentionally delay a drug that they think is safer in order to preserve the market share of another one of the company's drugs. It is also unacceptable for the company to then take TAF off the shelf after a decade, and rush through the research—including failing to perform the adequate studies to demonstrate this purported superior safety and equitably testing the product in key populations, and place pressure on regulatory authorities and community advocates to make decisions before even a single peer reviewed publication on the data from DISCOVER has been published.

We ask that committee members remember that it is within this context that this sNDA is being reviewed, and we recommend that the FDA consider how it may best ensure that research for future prevention modalities occur in a much more timely, transparent, and equitable manner.

We appreciate the opportunity to comment; please do not hesitate to contact us with any subsequent questions.

Respectfully yours,

James Krellenstein
Co-founder
PrEP4All Collaboration

Jeremiah Johnson
HIV Project Director
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[8] Gilead Sciences at RBC Capital Markets Healthcare Conference – Final, FD (Fair Disclosure) Wire, Mar. 2, 2011