FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEETING

(AMDAC)

Wednesday, August 7, 2019

8:30 a.m. to 4:54 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. BADEN: It's 8:30. Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contacts, Alison Hunt and Charles Kohler. If you're present, please stand. They're in the back. If there are questions for the press, please address them to Alison and Charlie.

My name is Lindsey Baden. I will be chairing today's meeting. I will now call the Antimicrobial Drugs Advisory Committee to order. We'll start by going around the table and introducing ourselves. We'll start with the FDA to my left and go around the table.

DR. FARLEY: Good morning. John Farley, deputy director of the Office of Antimicrobial Products, CDER, FDA.

DR. BIRNKRANT: Debbie Birnkrant, director, Division of Antiviral Products, CDER, FDA.

DR. MURRAY: Jeff Murray, deputy, Division of Antiviral Products, CDER, FDA.

DR. CARTER: Wendy Carter, clinical team leader, Division of Antiviral Products, CDER, FDA.

DR. MIELE: Pete Miele, medical officer, Division of Antiviral Products, CDER, FDA.

DR. ZHENG: Jenny Zheng, clinical pharmacology reviewer for antiviral products, CDER, FDA.

DR. CHEEVER: Hi. I'm Laura Cheever from the HIV/AIDS Bureau at the Health Resources and Services Administration.

DR. SWAMINATHAN: I'm Shankar Swaminathan, infectious diseases division chief at the University of Utah.

DR. SIBERRY: George Siberry, Office of HIV/AIDS, Global Health Bureau, USAID.

DR. GRIPSHOVER: Barbara Gripshover from University Hospitals Cleveland, Case Western Reserve University, adult infectious disease.

DR. GREEN: Michael Green, University of Pittsburgh School of Medicine, Children's Hospital Pittsburgh, pediatric infectious diseases.

DR. WEINA: Peter Weina, adult infectious diseases, Research Regulatory Oversight Office, Defense Health Headquarters.

DR. HOTAKI: Lauren Hotaki, designated federal officer.

DR. BADEN: Lindsey Baden, adult infectious diseases, Brigham and Women's Hospital, Dana Farber Cancer Institute, Harvard Medical School, Boston Mass.

DR. OFOTOKUN: Igho Ofotokun, adult infectious diseases, Emory University, Atlanta, Georgia.

DR. BURGESS: Tim Burgess, adult infectious diseases. I'm director of DoD's Infectious Disease Clinical Research Program at Uniform Services University.

DR. LE: Jennifer Le, professor of pharmacy at UC San Diego, pediatric infectious diseases.

DR. WALKER: Good morning. Dr. Roblena

Walker, EMAGAHA, Inc., Atlanta, Georgia, consumer representative.

DR. GIORDANO: Tom Giordano, adult infectious disease, Baylor College of Medicine and the Michael E. DeBakey VA Medical Center, Houston, Texas.

DR. DASKALAKIS: Demetre Daskalakis, adult infectious diseases, and also deputy commissioner for disease control at the New York City Department of Health and Mental Hygiene.

DR. READ: Sarah Read, deputy director of the Division of AIDS at the National Institute of Allergy and Infectious Diseases.

DR. SMITH: Hi. Dawn Smith, medical epidemiologist, Centers for Disease Control and Prevention.

DR. GOETZ: Matthew Goetz, VA Greater Los Angeles Healthcare System, David Geffen School of Medicine, adult infectious diseases.

DR. AWNI: Walid Awni, retired. I retired from AbbVie last year as vice president of clinical pharmacology and pharmacometrics. I'm the acting

industry representative.

DR. BADEN: Thank you. Dr. Dodd?

DR. DODD: Dr. Dodd, biostatistician at National Institute of Allergy and Infectious Diseases.

DR. BADEN: I think we may have someone on the phone. Ms. Lupole?

MS. LUPOLE: Yes, sir. Good morning [inaudible -feedback].

DR. BADEN: You have a bit of feedback.

MS. LUPOLE: I'm sorry. Can you hear me now?

DR. BADEN: Yes, we can.

MS. LUPOLE: Patricia Lupole, patient representative.

DR. BADEN: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without

interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

I thank everyone for making the time to be here to participate in this discussion. We know how busy everyone is.

I will ask Dr. Lauren Hotaki to read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. HOTAKI: The Food and Drug Administration is convening today's meeting of the Antimicrobial Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized the FDA to grant waivers to

special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 U.S.C. Section USC Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of

supplemental new drug application 208215, supplement 12, DESCOVY, emtricitabine 200 milligrams and tenofovir alafenamide 25 milligrams submitted by Gilead Sciences, Inc., proposed for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection among individuals who are HIV negative and at risk for HIV. This is a particular matters meeting during which specific matters related to Gilead's sNDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Lindsey Baden and Dr. Barbara Gripshover.

Dr. Baden's waiver addresses his employer's current research contract for related study by a competing firm for which his employer receives between $0 and $50,000 annually. Dr. Baden's waiver also addresses his employer's current research contract for related studies through the HIV

Vaccine Trials Network sponsored by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health and a competing firm, for which his employer receives $1.5 to $2.5 million annually.

Dr. Gripshover's waiver addresses her employer's current research contracts for four related studies involving competing/affected products for which her employer receives between $50,001 to $100,000 annually for two studies, and between $300,000 to $400,000 annually, and to $0 to $50,000 annually for the other two studies.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted at the FDA's website. Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose the Dr. Walid Awni is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Awni's role at this meeting is to represent industry in general and not any particular company. Dr. Awni is an independent pharmaceutical consultant.

We'd like to remind members and temporary voting members that if the discussions involved any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. BADEN: Thank you.

We will proceed with the FDA opening remarks from Dr. Murray.

FDA Opening Remarks - Jeffrey Murray

DR. MURRAY: Good morning. The Division of Antiviral Products extends its warm welcome to the committee and to the audience to discuss a new supplemental application for Descovy, for the prevention of sexually-acquired HIV infection, and we're happy to be talking about expanding the HIV prevention armamentarium today.

Some of you on the panel, and perhaps in the audience, may have been here in 2012, in this very room -- I know I was -- when the advisory committee voted on whether Truvada should be approved for PrEP. As you recall, the committee voted yes, and Truvada became the first U.S. approved product for PrEP, and really the first product for HIV PrEP for sexually-acquired HIV infection anywhere in the world. Fast forward to seven years, and that brings us to today's topics.

There are similarities and differences

between these two products. Both our fixed-dose combinations that contain emtricitabine. Both contain a prodrug of tenofovir with the same active metabolite. Both are approved for HIV treatment, both of the products. Tenofovir components are also approved as single agents for the treatment of chronic hepatitis B.

However, there are also differences, specifically as they relate to the bioavailability of tenofovir as delivered by these two different prodrugs in these fixed-dose combination. Descovy delivers lower levels of plasma tenofovir in tissue and organs and higher levels of intracellular tenofovir diphosphate of active metabolite.

As I said, there are also differences in tissue and organ distribution. This results in somewhat a different safety profile, but did not result in efficacy differences for HIV treatment. The other differences, Truvada is already approved for prevention and Descovy is not, and that's a topic for today.

To support the prevention indication of

Truvada, I remind you the applicant submitted two clinical trials, a clinical trial in MSM transgender women, iPrEx, and a trial in discordant heterosexual couples, Partners PrEP, which allowed for a broad indication among at-risk populations. Today we're dealing with one clinical trial.

What are some of the regulatory considerations about the basis of supporting an approval? Really, the number of clinical trials needed to support an approval depends on the regulatory situation.

For a new molecule entering the market, generally two or more drugs are expected -- or two or more trials are expected. However, for a new and related indication for a previously approved drug, often only one trial is needed to support approval.

Likewise, if there's a new dosing schedule, say twice daily to once daily, and you can't make a pharmacokinetic link, that's also been supported by one trial, or for a new population where PK is different, usually we rely on one clinical trial.

For Descovy, FDA's initial drug development advice was that clinical trials should be conducted in the relevant population, and that a PK link alone would not be possible. So for this application, as I said, we have one trial in MSM and transgender women but none in cisgender women at risk.

The primary issue for today and what you'll be asked in the question is given the uncertainty around the protective correlate, can extrapolation be used to further expand the indicated population?

With that being said, this application is a special case in the development of drugs for HIV prevention, and with that, I have the following caveat that the approach for Descovy may not apply to future new molecular entities because in this case, a prodrug, tenofovir for PrEP, has already been approved, and there is a possibility that data within and external to the Descovy program can be leveraged. So we ask the committee today for their advice on how this data can be best leveraged. Thank you.

DR. BADEN: Thank you. We'll now move on to the applicant presentations.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships they may have with the applicants, such as consulting fees, travel expenses, honoraria, an interest in a sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from

speaking.

We'll now proceed with Gilead's presentations. Dr. Brainard?

Applicant Presentation - Diana Brainard

DR. BRAINARD: Good morning. Ending the HIV epidemic requires not just highly effective treatments for people who have already been infected, but additional options for preventing new infections.

My name is Diana Brainard, and I lead the HIV and emerging viruses group at Gilead Sciences. I am an infectious diseases physician and have worked as a clinician and scientist in both the U.S. and Africa to care for people living with HIV and tackle the epidemic. It is a pleasure and honor to be here today to work with this committee to bring forward another HIV prevention option that will help us achieve our shared goal of HIV elimination.

Seven years ago, as Dr. Murray mentioned, Truvada was approved to prevent sexually-acquired HIV infection and remains today the only approved

therapy for HIV pre-exposure prophylaxis or PrEP. Truvada is the fixed-dose combination of 2 HIV reverse transcriptase inhibitors, emtricitabine and tenofovir disoproxil fumarate. Truvada is approved as part of a complete regimen for the treatment of HIV in adults and adolescents, as well as for PrEP.

Tenofovir disoproxil fumarate is also approved as a single agent for the treatment of chronic hepatitis B. Descovy is the fixed-dose combination tablet of emtricitabine and tenofovir alafenamide. It is approved for HIV treatment, and tenofovir alafenamide is approved as a single agent for treatment of chronic hepatitis B. Descovy is not approved for PrEP.

We are proposing an indication for Descovy for PrEP in adults and adolescents based on the data we are discussing today. Tenofovir disoproxil fumarate and tenofovir alafenamide are both prodrugs of tenofovir, but they have markedly different metabolism. Tenofovir alafenamide, or TAF, is dosed at one 12th that of tenofovir disoproxil fumarate, or TDF, because of the

difference in half-life.

TDF is rapidly converted to tenofovir, or TFV, resulting in high plasma tenofovir levels which have direct and indirect adverse effects on kidney and bone. The half-life of TAF is 75 times longer than that of TDF, which results in 90 percent lower plasma tenofovir levels. Descovy's lower levels of circulating tenofovir translate to fewer clinically relevant adverse renal and bone effects.

The longer half-life of TAF also allows it more time to enter peripheral blood mononuclear cells. Intracellularly, TAF is metabolized to the active metabolite, tenofovir diphosphate, or TFV-DP, where it achieves 4 to 7-fold higher levels of tenofovir diphosphate than those achieved by TDF.

For both TAF and TDF, tenofovir diphosphate within PBMCs and specifically CD-4 positive T cells, is responsible for the inhibition of HIV replication, which leads to protection against HIV infection in the setting PrEP, as well as viral

suppression in the case of HIV treatments.

Tenofovir diphosphate is an adenosine analog that inhibits the enzyme HIV reverse transcriptase, which transcribes HIV RNA into proviral DNA. This mechanism of action is the same for both the prevention of HIV acquisition as well as for suppression of viremia in the setting of treatment, and the level of intracellular tenofovir diphosphate correlates with antiviral activity.

Pharmacokinetic differences between TAF and TDF result not only in higher levels of tenofovir diphosphate with TAF versus TDF, but also a faster rise of tenofovir diphosphate levels within PBMCs, including the target cells for HIV replication, CD-4 positive T cells. After a single dose, Descovy achieves intracellular tenofovir diphosphate levels above 40 femtomoles per million cells within 2 hours.

This threshold is relevant for PrEP based on its correlation using Truvada clinical data from a trial in men who have sex with men, with a 90 percent reduction in risk of HIV acquisition as

compared to placebo.

In contrast, Truvada takes approximately 3 days for the mean level to reach this EC_{90}, and steady state levels remain lower than those for Descovy. Once steady state is achieved with either Descovy or Truvada, if drug is stopped, tenofovir diphosphate levels start to decline at a similar rate. However, since levels are so much higher with Descovy as compared to Truvada, they remain above this EC_{90} for 16 days with Descovy compared with 10 days for Truvada.

These pharmacokinetic advantages of Descovy suggested to us that Descovy could be highly effective for PrEP, and the safety advantages observed in people living with HIV taking Descovy could also be realized among those at risk for HIV infection.

In 2015, when the DISCOVER study design was coming together, there was uncertainty around whether drug levels in the genital tract or peripheral blood mononuclear cells best correlated with protection against HIV. The higher levels of

Tenofovir diphosphate in PBMCs with Descovy could potentially confer an efficacy advantage and offer a more forgiving regimen for PrEP, provided these levels correlated with protection. However, if genital tract tissue levels drive efficacy, Descovy could be less effective for prevention.

Data from healthy volunteers show that rectal tissue levels are 10-fold lower following Descovy administration compared to Truvada. Our hypothesis was that prevention efficacy for oral drugs would be best measured by peripheral blood mononuclear cell drug levels rather than tissue homogenate levels, and that, therefore, Descovy would be at least as efficacious as Truvada in spite of this difference in rectal tissue levels.

This hypothesis was based on advances in the understanding of mucosal transmission of HIV. HIV must first breach the epithelium to reach the subepithelium, and it is generally believed that a single cell first becomes infected and initiates subsequent events.

Chemokines, primarily secreted by

plasmacytoid dendritic cells, attract PBMCs. Specifically, CD-4 positive and CD-8 positive T cells from the pool of PBMCs traffic from the circulation to the tissue. This then results in a small founder population of initially infected CD-4 T cells located in the subepithelium.

The recruitment of target cells for HIV, the CD-4 T cells, from the periphery is critical in order for systemic infection to occur. Dissemination of these recruited and now infected CD-4 positive T cells occurs as they enter the lymphatic system to travel to regional lymph nodes and spread throughout the body.

Protection against systemic HIV infection can occur via both topical and systemic modalities. Topical antiretrovirals, such as investigational tenofovir gel, allow for the diffusion of drug into tissues within the genital tract. Efficacy depends on reaching therapeutic levels intracellularly within the local CD-4 positive T cells. These methods have generally proven less effective than PrEP delivered systemically.

Truvada and Descovy distribute widely throughout the body and can offer a greater degree of protection. They can both reach the genital tissues through the blood supply, where they can then access resident lymphocytes.

Importantly as well, PBMCs that contain the active metabolite of both Truvada and Descovy, tenofovir diphosphate also can reach the genital tract and can be among the cells recruited to the site of initial infection, as well as into the regional draining lymph nodes so as to prevent systemic infection.

While there has been no clear evidence of a correlation of preventive efficacy of Truvada for PrEP with tissue levels, efficacy strongly correlates with drug levels of tenofovir diphosphate within PBMCs.

A subset of participants in the IPREX study, in men who have sex with men of Truvada versus placebo, had tenofovir diphosphate levels assessed in PBMCs. Because of the wide range of adherence and that trial and the placebo arm to which a

direct comparison could be made, it was possible to construct a relationship between PBMC tenofovir diphosphate levels and risk production with respect to HIV incidence.

It was with these data that Dr. Anderson established the correlate of protection for 90 percent risk reduction for tenofovir diphosphate levels at 40 femtomoles per million PBMCs and showed that there's a range of protection above and below that level. These data are now well recognized and have been cited in the most recent CDC PrEP guidance issued on July 18th of this year.

When the DISCOVER study was being designed, the scientific and clinical understanding of HIV prevention was less mature. At that time, Truvada for PrEP was only approved in adults. Descovy was under review by the FDA for the treatment of HIV. We knew that rectal tissue levels with Descovy were 10-fold lower than those achieved with Truvada.

If the primary driver for prevention efficacy, with orally administered tenofovir prodrugs is local tissue drug levels, then Truvada

should be better than Descovy at preventing HIV infection. However, if obtaining high levels in PBMCs is what's important, then Descovy should be at least as effective as Truvada.

This question was addressed in the phase 3 DISCOVER trial. The DISCOVER trial, an international phase 3 study, was conducted to assess the safety and efficacy of Descovy for HIV prevention. This was a double-blind, active comparator, noninferiority trial, comparing Descovy to the standard of care for prevention, Truvada.

The study enrolled over 5,000 cismen and transgender women who have sex with men. The trial was designed and conducted in close collaboration with FDA and the community. Importantly, the study met its primary endpoint, demonstrating noninferiority of Descovy to Truvada for the prevention of HIV infection.

Among individuals randomized to Descovy, 7 acquired HIV infection for an incidence rate of 0.16 per 100 person-years. In the Truvada group, there were 15 infections resulting in an incidence

rate of 0.34 per 100 person-years. The incident rate ratio, the prespecified method for determining noninferiority, was 0.47 with an upper bound of the confidence interval less than the prespecified margin of 1.62.

Additionally, the prespecified alpha-controlled secondary safety endpoints were met, demonstrating superiority of Descovy to Truvada with respect to markers of bone and renal toxicity. Collectively, these data demonstrate that Descovy is highly effective at preventing HIV acquisition and demonstrates safety benefits over Truvada.

What we know now is that both Truvada and Descovy are highly effective for PrEP if taken. Adherence is the key determinant of efficacy. A correlate of protection has been established for tenofovir diphosphate levels in PBMCs. The DISCOVER trial confirms that 10-fold lower rectal levels of tenofovir diphosphate with Descovy versus Truvada are not relevant for HIV protection, and that the 7-fold higher tenofovir diphosphate levels

with Descovy versus Truvada might confer a potential efficacy advantage for Descovy.

These results support the conclusion that PBMC drug levels drive the efficacy of orally administered tenofovir prodrugs. This finding is an important consideration for the extrapolation of the DISCOVER results from cismen and transgender women to ciswomen.

To date, clinical trials in women have had heterogeneous efficacy results reflecting highly variable adherence. Data from clinical trials demonstrate that when controlling for adherence, Truvada is equally efficacious in women and men. There is a biologic rationale for this finding.

The biology of HIV as well as the intracellular antiviral activity of tenofovir diphosphate are independent of gender. HIV replicates within CD-4 positive lymphocytes, which must be recruited to the site of initial infection in order to successfully lead to systemic transmission. Adequate drug levels within these recruited cells are necessary and sufficient to

mediate protection against HIV infection.

Multiple lines of evidence support bridging the efficacy results for Descovy for PrEP from the men and transgender women in DISCOVER to ciswomen. In the setting of HIV treatment, the efficacy and safety of Descovy-based therapy have been well established in over 2000 women and are comparable to results in men.

Descovy and Truvada both inhibit HIV replication in CD-4 T cells through the same active metabolite, tenofovir diphosphate. Extensive pharmacology assessments have demonstrated that the levels of tenofovir diphosphate are similar irrespective of HIV status or gender. Taken together, these data support the use of Descovy for HIV prevention in women.

There is similar support for the extrapolation to adolescence. Descovy and the three other Descovy-containing single-tablet regimens are all indicated for HIV treatment in adolescence based on the safety and efficacy established in this group. HIV behaves similarly

independent of age, and therefore the extension of safety and efficacy of Descovy for PrEP to adolescents can be based on similar pharmacokinetic exposures to Descovy between the DISCOVER study participants and adolescents, as well as the similar mechanism of action of these drugs. We also know that HIV infection status has no relevant impact on these parameters. Taken together, these data support the use of Descovy for HIV prevention in adolescents.

Based on the data from the DISCOVER study, the established safety and efficacy of Descovy for HIV treatment across men, women, and adolescents and pharmacokinetic bridging, the following additional indication is proposed for Descovy. Descovy is indicated for pre-exposure prophylaxis to reduce the risk of sexually-acquired HIV in at-risk adults and adolescents weighing at least 35 kilograms.

You will next hear from Dr. Scott McCallister, who will provide an overview of the phase 3 DISCOVER trial and the efficacy results.

Then Dr. Moupali Das will present the safety of Descovy for PrEP, as well as the basis for its use for HIV prevention in women and adolescents.

We're honored to have Dr. Rick Elion with us today. Dr. Elion has a long-standing history of providing HIV treatment and prevention services to individuals in the D.C. area for marginalized communities, and he'll provide clinical context for the results of the DISCOVER trial. I will then return to lead our responses to questions. We have Gilead team members spanning multiple disciplines to address these questions.

In addition, we're pleased that Dr. Peter Anderson is here today to address questions around adherence. Dr. Anderson is a professor of pharmaceutical sciences at the University of Colorado. His laboratory specializes in the assessment of drug levels in dried blood spots, and they performed nearly 4,000 dried blood spot analyses in DISCOVER as part of our adherence assessments.

I'd like to now welcome Scott McAllister to

the lectern.

Applicant Presentation - Scott McCallister

DR. McCALLISTER: Thank you, Diana, and good morning, everyone. I'm also an infectious disease specialist with a long history of clinical patient care and clinical research in HIV. In this section, I'll describe the DISCOVER study design, the treatment population, and the efficacy results.

DISCOVER is an ongoing, randomized, double-blind, noninferiority trial that enrolled both cismen and transgender women who have sex with men. As shown at the top, participants were randomized 1-to-1 to either Descovy or Truvada daily. Each of the nearly 2700 MSM or transgender women received 1 tablet of active drug and 1 dummy placebo tablet.

The primary efficacy endpoint analysis was time based and was conducted when all participants completed 48 weeks in the study and half had completed 96 weeks. The primary endpoint was the HIV incidence rate per 100 person-years on study. The study was blinded to investigators and study

participants until the final person enrolled completed 96 weeks. At the next scheduled visit, individual participants are unblinded and offered a switch to open-labeled Descovy. Unblinding is currently ongoing and not yet complete.

Eligibility criteria were designed to ensure that the study enrolled a population at high risk of HIV infection. All participants were required to have at least 1 of the 2 following sexual risk criteria: two or more episodes of condomless anal sex with more than one unique partner in the 12 weeks before enrollment or a diagnosis of either rectal gonorrhea, rectal chlamydia, or syphilis in the 24 weeks before enrollment. All needed to be HIV and hepatitis B negative. Prior or current use of PrEP was permitted, and no washout of PrEP drugs was required.

DISCOVER sites were mostly urban. They were specifically chosen to be in locations with a high background HIV incidence, and all sites were required to be able to enroll people with significant sexual risk for HIV acquisition. We

also selected sites with the cultural competence to enroll and retain people of color and transgender women.

Ultimately, DISCOVER included 94 sites in 11 countries in North America and Western Europe. Some were hospitals, some private practices, and some local sexually transmitted infection clinics. Each site was responsible to determine the best recruitment practice within their own community. All of those who met eligibility criteria were allowed to enroll. It was our goal to allow each person who knew themselves to be at risk of our HIV infection to participate.

When we designed DISCOVER, we consulted with investigators from the prior PrEP trials in MSMs. We wanted to ensure that the study included the right design elements, comparable sexual risk eligibility criteria, optimal HIV testing, and STI testing, so that our study would yield reliable results. We also discussed design issues with both site investigators and with community members in North America and Europe to ensure that the study

was practical and aligned with existing clinical practice.

Community members encouraged us to establish advisory boards for ongoing dialogue with them. As a result, three community advisory boards were set up, one that was DISCOVER specific and two that dealt with broader HIV issues in North America and the EU. We drew valuable input from these interactions during the trial, during the design phase, during recruitment, and during study conduct.

The primary efficacy endpoint was based on the number of HIV infections diagnosed in DISCOVER divided by person-years of exposure in the study. Noninferiority of Descovy to Truvada was assessed by an incidence rate ratio in which the HIV incidence rate in the Descovy arm was divided by the rate in the Truvada arm.

We derived the noninferiority margin of 1.62 by pooling the incidence rates in the Truvada arms of the three prior randomized controlled trials in MSMs: iPrEx, PROUD, and IPERGAY. If the upper

bound around the confidence interval of the incidence rate ratio in DISCOVER was less than 1.62, Descovy would be noninferior to Truvada.

The incidence rate ratio analysis of the primary endpoint was a robust means of evaluating the effectiveness of Descovy, ensuring that the result was due to the drugs used in the study and that the treatment population was at sufficient risk of HIV.

At each visit, we assessed general safety, including graded adverse events, adverse events leading to discontinuation, serious adverse events, and general safety labs. There was renal lab testing at each visit, bone mineral density testing every 48 weeks, and sexually transmitted infection testing from 3 anatomic sites also at each visit.

We used an analysis cascade for 6 prespecified secondary safety endpoints, where previous data suggested a possible difference between the arms due to lower levels of plasma TFV in those on TAF. The safety's cascade began with changes from baseline in bone mineral density, or

BMD, at both the hip and spine.

If there were significant differences favoring Descovy on each of these, we then evaluated spillage of the specific proximal renal tubular proteins associated with plasma TFV, the beta-2 microglobulin, and retinol binding protein to creatinine ratios. Then with continued significant differences favoring Descovy, we moved to evaluate glomerular function with general urine proteins, serum creatinine, and estimated glomerular filtration rate.

All participants completed confidential questionnaires on an iPad at the screening visit and at all study visits. These questions inquired about the sexual behavior of each participant since their last visit, including the number of partners, the type of sex, the frequency of sex, condom use habits, and about recent study drug adherence.

At each visit, all participants received HIV risk reduction education, adherence support, and condoms and lubricant from site staff. In addition, opt-in/opt-out text messaging could be

used to remind the individual to take their study meds daily with the actual words used in the text chosen by sites and participants.

Adherence is a critical determinant of PrEP efficacy, so we measured it in multiple ways. We employed two subjective tests, the confidential iPad-based questionnaires and counts from returned pill bottles, both at each visit. We used one objective test, a dried blood spot collection to evaluate TFV diphosphate levels in red blood cells also at each visit. Dried blood spots provided validated analysis of chronic adherence over the 8 weeks prior to the collection date, and we looked at a randomly selected subset of 540 participants, about 10 percent of the DISCOVER population.

In addition to the randomly selected subset, we also analyzed dried blood spots in a case control analysis of those diagnosed with HIV in DISCOVER with matching controls for each. In our case control study, we compared every individual diagnosed with HIV on study and matched them with 5 uninfected controls. The matched controls were

specifically chosen to be geographically linked, to have similar time on the study drugs in DISCOVER, and to have comparable sexual exposure as evidenced by the on-study diagnosis of a rectal STI.

From the group of uninfected study participants who were a match for each case, 5 were randomly selected. Once all controls were selected, dried blood spot analyses of the TFV diphosphate level in red blood cells were tested on the date of the HIV diagnosis and also on one visit prior.

More than 5800 people were screened for DISCOVER; 364 did not meet eligibility criteria, including 49 who tested HIV positive; 5,399 were randomized but 6 in each arm were not treated. leaving 2694 treated in the Descovy arm and 2693 treated in the Truvada arm.

The full analysis set included 535,335 participants who were randomized, treated, and had any post-baseline data. Of those who were randomized and treated in the study, the median age was 34, 12 percent of the population or emerging

adults below age 25 and not yet at peak bone mass.

In the ratio breakdown, across the 11 North American and European countries, 84 percent self-identified as white and 9 percent as black; 25 percent reported being of Hispanic or Latinx ethnicity; 74 participants, or 1 to 2 percent of the population, self-identified as a transgender woman. From responses on the confidential questionnaire, the self-reported sexual orientation was gay or homosexual in 91 to 92 percent, bisexual in 6 to 8 percent, and heterosexual in 1 percent.

Baseline sexual behavior data from the confidential questionnaire showed that the treatment population was at significant risk of HIV infection. 58 to 60 percent had at least 2 condomless receptive anal sex partners in the 12 weeks prior to study entry; 9 to 13 percent reported rectal gonorrhea, rectal chlamydia or syphilis in the 24 weeks before study entry.

Two-thirds of DISCOVER participants had used recreational drugs, and nearly a quarter reported binge drinking, defined as 6 or more drinks on at

least one occasion and occurring at least monthly. A total of 23 percent had used Truvada for PrEP in the past, and 16 to 17 percent were on it at study entry. While on study, DISCOVER participants maintained this high level of sexual behavior throughout all visits.

Participants averaged just under 4 condomless receptive anal sex partners at baseline and continuing throughout the study, similar between the arms. They also had high rates of sexually transmitted infections; 57 percent of those on the study were diagnosed with gonorrhea or chlamydia from at least 1 of the 3 anatomic sites tested. And including syphilis, the overall rate on study for any one of these STIs range from 139 to one 145 per 100 person-years in DISCOVER.

Overall, 42 percent of participants had a rectal STI on the study, most likely due to condomless receptive anal sex, and 16 percent had a urethral STI associated with condomless insertive sex.

At the time of the primary endpoint

analysis, 16 to 17 percent of participants discontinued study drug in DISCOVER. The most common reasons for discontinuation from study drug were participant decision or lost to follow 6 to 7 percent each. Only 1 to 2 percent of study participants discontinued drug due to an adverse event, and the other reasons for discontinuation were less than 1 percent each.

As Diana described, the study met its primary efficacy endpoint for noninferiority. In over 8700 person-years on study across the 2 arms, a total of 22 HIV infections were diagnosed; 7 in the Descovy arm, 15 in the Truvada arm, corresponding to HIV incidence rates of 0.16 and 0.34 per hundred person-years, respectively. The rate ratio, where 0.16 is divided by 0.34, is 0.47.

For the primary endpoint analysis, the rate ratio of 0.47 represents a 53 percent reduction in HIV incidence for the Descovy arm relative to the Truvada arm. The upper bound of the confidence interval around 0.47 is 1.15. This is lower than the 1.62 prespecified noninferiority margin that's

establishing the noninferiority of Descovy to Truvada for PrEP.

We categorized the 7 diagnoses in the Descovy arm and the 15 in the Truvada arm based on whether or not they occurred prior to study entry. Evaluating all available data and prior to unblinding, a 3-physician panel concluded that 5 of the 22 HIV diagnoses most likely occurred prior to DISCOVER study entry between the screening and the randomization visits. The 5 with suspected baseline infections are shown here in the black section at the bottom of each bar. Just above are the 17 individuals, 6 in Descovy and 11 in Truvada, who acquired HIV while on study.

To better understand the impact that the 5 suspected baseline infections had on the primary efficacy endpoint, we went on to conduct a sensitivity analysis. By excluding the 5 individuals with suspected baseline infection, 1 in the Descovy arm, 4 in the Truvada arm, the incidence rate ratio in this sensitivity analysis is 0.55.

The confidence interval around it extends to 1.48, which is still below the prespecified 1.62 noninferiority margin. Therefore, even excluding the suspected baseline infections in the sensitivity analysis, the incidence rate in the Descovy arm remained noninferior to the rate in the Truvada arm.

We next looked at efficacy analysis by baseline subgroups. In this forest plot, the HIV incidence rates for the 2 arms are shown again at the top and just left of center. The rate ratio and surrounding 95 percent confidence interval are shown at far right. The rows of the table provide incidence rates for both demographic and baseline risk behavior subgroups.

For each of these subgroups, the incidence rates are low and consistent with the rates in the overall study, and the incidence rate ratios demonstrate that the effect of Descovy or Truvada was consistent with the rate ratio in the overall study across all demographic and baseline risk behavior subgroups.

In this diagram are genotypic resistance data of the 22 individuals diagnosed with HIV; 19 had samples that could be successfully amplified and evaluated. Of these 19, only 4 had Gina genotypic resistance detected to either of the study drugs.

All 4 occurred in the Truvada arm. All 4 were M184 mutations consistent with resistance to FTC, and all 4 occurred in those with a suspected baseline infection. Each of the 4 individuals with M184 detected were able to be successfully suppressed on ART, 3 with a Descovy-based regimen.

Our analysis of subjective adherence measures demonstrates that there was a very high level of adherence across the arms. With self-report from the confidential questionnaires, about 80 percent reported that they took their study meds more than 95 percent of the time across all study visits and similar across the arms. With pill counts from returned bottles of study drug, about 70 percent appeared to be using their study meds more than 95 percent of the time, also similar

across the arms.

The levels of TFV diphosphate in red blood cells from the subset of dried blood spots tested also demonstrate that there was a high level of adherence in DISCOVER for both study arms. From the nearly 4,000 dried blood spots tested in the random subset, 80 to 90 percent had TFV diphosphate levels in a range consistent with taking 4 or more tablets per week for both arms.

In contrast, very few, just 5 to 9 percent at any visit, had TFV diphosphate levels consistent with taking less than 2 tablets per week. In the case control analysis where the 22 HIV cases were compared to HIV uninfected controls, the dried blood spot data analysis there provides a clear explanation for the difference between those with HIV and their matched controls.

Low or no adherence was the most significant risk factor associated with HIV in the study for both arms. In the case control study, drug adherence as measured in dried blood spots was significantly lower among those who became infected

as compared to matched controls. Most cases had TFV diphosphate levels in red blood cells consistent with using study drug less than 2 doses per week, while more than 90 percent of controls had TFV diphosphate levels consistent with higher levels of adherence.

Finally, let's move from the TFV diphosphate levels in red blood cells, which provide us this measure of adherence, over to the levels in PBMCs, which provide a measure of efficacy. The data from dried blood spots showed a high and comparable level of adherence across both arms.

The levels of activated drug TFV diphosphate in PBMCs, however, were not the same across the arms. At week 4, once steady state was achieved, the median TFV diphosphate level in PBMCs was 6-fold higher in the Descovy relative to the Truvada arm; 404 femtomoles per million cells in Descovy and 61 femtomoles per million cells in Truvada.

The amount of activated drug in the PBMCs seen in DISCOVER is consistent with established PK

data observed from multiple clinical studies with TAF and TDF-based regimens in chronic HIV treatment. Given that 40 femtomoles per million cells represents the 90 percent effective concentration, or EC_{90}, of TFV diphosphate in PBMCs, 98 percent in the Descovy arm were above this EC_{90}, while only 68 percent in the Truvada arm had levels above this mark.

In summary, DISCOVER was conducted in MSMs and transgender women with a high baseline risk of HIV infection that was consistent over the course of the study. Over 8700 person-years, the HIV incidence rates were very low and the noninferiority of Descovy to Truvada for HIV prevention was established. Low adherence was the most significant risk factor associated with an HIV diagnosis on study.

While M184 mutations occurred in the Truvada arm, there was no resistance to study drugs reported in the Descovy arm. TFV diphosphate levels in PBMCs were over 6-fold higher in the Descovy arm as compared to Truvada with a

significantly higher proportion above the EC_{90} for HIV protection. This PK advantage represents a potential clinical benefit of Descovy for PrEP.

Thank you for your attention. I'd now like to turn our presentation over to my colleague, Dr. Moupali Das, who will describe the DISCOVER safety data, and she'll provide a description of the PK bridging data in support of an indication in ciswomen and adolescents.

Applicant Presentation - Moupali Das

DR. DAS: Good morning, everyone. My name is Moupali Das, and I'm also an infectious disease physician. My career has been devoted to helping end the HIV epidemic by increasing virologic suppression rates and PrEP uptake. For the last six years, I've worked exclusively on clinical trials comparing the efficacy and safety of the two tenofovir prodrugs.

The DISCOVER trial is the largest individual trial with a single variable comparison of TAF with TDF. It offers a unique opportunity to compare the safety of TAF with TDF in the absence of underlying

HIV or hep B infection and without any accompanying third agents.

The safety and tolerability of Descovy and TAF have been thoroughly established in HIV and hep B treatment with over 26,000 person-years of experience in clinical trials and over 1.6 million person-years of clinical experience. Descovy has a superior renal and bone safety profile compared with Truvada due to the 90 percent lower plasma tenofovir levels with TAF compared with TDF. Early favorable changes in renal and bone safety biomarkers correlate with fewer clinical renal and bone adverse events over longer term follow-up.

The DISCOVER results are the first demonstration that these well understood renal and bone safety advantages of Descovy compared with Truvada are also true for the HIV uninfected population. There was a meeting exposure of 86 to 87 weeks in Descovy and Truvada. The bone mineral substudy had 9 weeks of exposure. Both Descovy and Truvada were safe and well tolerated.

The type, frequency, and severity of adverse

events were similar between the Descovy and Truvada arms. Most adverse events were grade 1 or 2 in severity. There was a low percentage of study drug related serious adverse events or adverse events leading to discontinuation in both Descovy and Truvada.

During treatment, 1 person died in each arm. The most common adverse events in the DISCOVER trial were sexually transmitted infections; 6 of the 9 most common AEs were bacterial sexually transmitted infections or exposure to STIs. This is in contrast with Descovy treatment trials and may reflect increased STI screening in DISCOVER, which happened at every visit, or differences in sexual behavior among DISCOVER participants compared to the treatment trial participants, or a combination of both.

I will review the STI data for the next few slides and then come back to the general safety data. The rates of sexually transmitted infections were high and persistent throughout the trial. About 15 percent of participants had lab-diagnosed

gonorrhea or chlamydia at any of the 3 anatomic sites at baseline and throughout the study. There were no differences between Descovy and Truvada.

Two of the most common AEs were rectal gonorrhea and chlamydia. Approximately 10 percent of participants had rectal gonorrhea or chlamydia at baseline, and this did not change during the study. There were no differences between Descovy and Truvada. The by-visit positivity rates reflect high and persistent sexual behavior over the study with the persistent rectal STI rates reflecting continued high risk for HIV acquisition.

The most commonly prescribed medications in the DISCOVER trial were also different from our HIV treatment trials. Four of the seven most commonly prescribed medications are antibiotics used to treat sexually transmitted infections. More than half of the participants received azithromycin or ceftriaxone. There was a high burden of STIs, including rectal STIs diagnosed and treated during the study.

Returning back to general safety, the common

study drug related adverse events reflect the most common adverse events in the Descovy treatment trials. Twenty percent of participants in Descovy and 23 percent in Truvada had study drug related adverse events. Common related adverse events were low in frequency and similar between arms. The majority were mild GI events and headache. Laboratory abnormalities were also uncommon in the study. Grade 3 or higher lab abnormalities occurred at a low frequency and none were clinically significant.

In the HIV treatment trials and in the Truvada adherence subset in the iPrEx trial, the lipid-lowering effect of Truvada has been well documented. In DISCOVER, Truvada was also associated with a reduction in lipid parameters. Total cholesterol, HDL, and LDL cholesterol all declined. The magnitude of these declines is not clinically significant, whereas total cholesterol, LDL, and HDL levels were generally unchanged in participants taking Descovy.

Importantly, these changes resulted in no

difference in the total cholesterol to HDL ratios between arms, which is strongly associated with cardiovascular risks. While both Descovy and Truvada were safe and well tolerated, Descovy was significantly superior to Truvada on all 6 prespecified renal and bone safety endpoints.

To assess the renal safety of Descovy compared with Truvada, we reviewed cases of proximal renal tubulopathy, including Fanconi syndrome, as well as all renal adverse events leading to discontinuation.

To specifically assess glomerular function, we measured the prespecified renal safety endpoint of serum creatinine and calculated the estimated glomerular filtration rate using the Cockcroft-Gault equation. We also evaluated total urine proteinuria by dipstick and quantitative proteinuria by the urine protein to creatinine ratio or UPCR.

To evaluate proximal tubular function, we looked at 2 urine tubular protein to creatinine ratios. In DISCOVER, after 8600 person-years of

exposure to study drug, there were no cases of proximal tubulopathy or Fanconi Syndrome on Descovy. There was one case of Fanconi Syndrome on Truvada. There were numerically fewer discontinuations due to renal AEs on Descovy compared to Truvada, 2 versus 6.

Descovy had significantly improved glomerular function compared with Truvada. The differences in eGFR with Descovy and Truvada were apparent as early as week 4 and continued through week 48, the prespecified time point for the assessment of secondary safety endpoints. At week 48, Descovy participants also had significant and lower serum creatinine, the prespecified safety endpoint.

Glomerular proteinuria was significantly lower in Descovy compared with Truvada. At week 48, 21 percent of participants on Descovy compared with 24 percent on Truvada developed dipstick proteinuria. Fewer participants on Descovy, 1 percent, compared to Truvada, 2 percent, developed clinically significant quantitative

proteinuria as defined by the national kidney foundation as a urine protein to creatinine ratio of greater than 200 milligrams per gram.

Descovy also had superior outcomes to Truvada in the two markers of proximal tubular proteinuria. Retinal binding protein and beta-2 microglobulin are two low molecular weight proteins, which are freely filtered across the glomerularis and reabsorbed at the proximal tubule. Increased spillage of these proteins into the urine is a marker of increased proximal tubular dysfunction and is reflected in higher urine RBP to creatinine and urine beta-2 microglobulin to creatinine ratios.

On the left panel, the Truvada group had a 20 percent increase from baseline in tubular proteinuria indicating increased proximal tubular dysfunction, while Descovy remained stable. On the right panel, the Truvada group had a 15 percent increase in tubular proteinuria from baseline indicating worsening of tubular function, while the Descovy group had a 10 percent decline or

improvement in tubular proteinuria.

The superior renal safety of Descovy was also demonstrated in participants who were on Truvada at baseline who switched to Descovy compared to those who remained on Truvada. The DISCOVER trial included participants taking Truvada for PrEP at baseline and did not require a washout of Truvada. There were a large number, 905 people, who were on Truvada at baseline.

We prespecified sensitivity analyses of the participants on baseline Truvada for key renal and bone safety endpoints. As in the overall DISCOVER population, those on baseline Truvada who switched to Descovy had improvements in renal function compared to those who remained on Truvada. The improvements in eGFR and those who switched to Descovy were apparent as early as week 4 and persisted through week 48.

The improvements with switching to Descovy are also present in markers of proximal tubular function. Those who switch to Descovy had significant declines in tubular proteinuria

indicating improved tubular function, while those who remained on Truvada had an 11 percent increase in retinal binding protein to creatinine ratio on the left and a stable beta-2 microglobulin to creatinine ratio on the right.

These changes again became apparent as early as week 4 and continued through week 48. Descovy was superior to Truvada on all prespecified biomarkers of renal function. This was demonstrated in both the overall population as well as in the Truvada switchers.

We evaluated bone safety with the bone mineral density substudy. The median age of DISCOVER participants was 34, so approximately half of the participants were still building to peak bone mass, which is achieved in the early to mid 30s.

Descovy participants had a statistically significant increase in mean spine bone mineral density of about 0.5 percent from baseline and stable hip bone mineral density, whereas those on Truvada had statistically significant declines of

1 percent of both spine and hip bone mineral density from baseline through week 48. Descovy was statistically superior to Truvada in both prespecified bone endpoints.

Using the T scores from the Baseline BMD assessment, participants were classified into the clinically relevant categories of normal bone mineral density, osteopenia, and osteoporosis. At baseline, 27 to 29 percent of participants had either spine osteopenia or osteoporosis in the Descovy and Truvada arms. After 48 weeks, participants on Descovy had significantly less osteopenia and osteoporosis than those on Truvada.

As Scott showed you, there were 6 prespecified secondary safety endpoints. Descovy was superior to Truvada in all 6 prespecified, alpha-controlled bone and renal safety endpoints at the week 48 endpoint. We continue to follow long-term renal and bone safety in the DISCOVER study participants.

Both Descovy and Truvada were safe and well tolerated. The rates of serious adverse events or

adverse events leading to discontinuation of study drug were low and balanced between arms. The magnitude of the differences in the early safety endpoints between arms was similar to what is observed in HIV and hep B treatment trials comparing to Descovy to Truvada.

This large trial confirmed that the well-established superior renal and bone safety profile of Descovy to Truvada from HIV and hep B treatment is also true in HIV prevention. The safety benefits were seen in both the people starting PrEP for the first time as well as those switching from Truvada to Descovy.

This is a significant development from a clinical perspective, so we can now offer a similarly efficacious but safer drug as another choice for HIV uninfected people who are simply at risk for HIV acquisition. The efficacy and safety of Descovy for ciswomen, cismen who have sex with men, and adolescents can be inferred from DISCOVER.

The extensive clinical experience with Descovy and Truvada for treatment and prevention

allows for the inference of efficacy and safety in ciswomen and adolescents. We have over 15 million person-years of clinical experience with Truvada and TDF and 1.6 million person-years with Descovy and TAF in HIV and hep B treatment.

We have over 108,000 person-years in Truvada for PrEP and 6500 person-years for Descovy for PrEP from the DISCOVER trial. Both Truvada and Descovy are highly effective for treatment and prevention. Efficacy is driven by tenofovir diphosphate in peripheral blood mononuclear cells or PBMCs. In contrast, safety is driven by plasma tenofovir. The 90 percent lower plasma levels with Descovy compared with Truvada is associated with an improved bone and renal safety profile.

The PK of Descovy or Truvada is independent of intrinsic and in extrinsic factors. This means that the PK of plasma tenofovir and tenofovir diphosphate in PBMCs is not affected by sex at birth, current gender identity, or sexual orientation. HIV infection status also does not affect PK.

The active moiety for both Truvada and Descovy associated with both HIV treatment and prevention efficacy is tenofovir diphosphate in PBMCs. Tenofovir diphosphate levels are comparable with Descovy in the MSM and transwomen in DISCOVER on the left and Descovy in ciswomen and cismen.

In contrast, the tenofovir diphosphate levels are lower with Truvada on the right. Tenofovir diphosphate levels are 4 to 7-fold higher with Descovy than with Truvada, and this is consistent with findings in prior trials. Efficacy is high in both women and men on Descovy-based regimens for HIV treatment as it is with Truvada. Virologic suppression rates are similar on Descovy and Truvada-based regimens for HIV treatment and similar in women and men.

The key metabolite for both Truvada and Descovy associated with safety is plasma tenofovir. Plasma tenofovir with Descovy is similar in women with HIV and in HIV uninfected female volunteers. The PK is independent of HIV status. Plasma tenofovir is 10-fold higher with Truvada shown here

in women with HIV on the right. Women with HIV have improved renal safety on Descovy compared with Truvada-containing regimens for HIV treatment.

In 519 women who were switched from Truvada to Descovy or remained on Truvada, there were significant improvements in both glomerular function on the left and proximal tubular function on the right through 96 weeks in the women switched to Descovy. These renal improvements are consistent with the DISCOVER results in those on baseline Truvada who switched to Descovy.

Women on Truvada-containing regimens who switched to Descovy also had clinically significant improvements in osteopenia and osteoporosis within 48 weeks. At baseline, a third of women on Truvada-based regimens for HIV treatment had osteopenia or osteoporosis. Women who switched to Descovy had less spine osteopenia and less osteoporosis at week 48 compared to those who continued on Truvada. These results were statistically significant.

Descovy is also an efficacious and safe

treatment for HIV in adolescents. Descovy is approved for HIV treatment in adolescents weighing at least 35 kilograms in combination with third agents and in 3 Descovy-containing, single-tablet regimens. Descovy has similar renal and bone safety benefits compared with Truvada in adolescents with HIV. Truvada has been approved for PrEP in adolescents weighing at least 35 kilograms since 2018, based on the extrapolation of efficacy from adults.

Tenofovir diphosphates and PBMCs is the active moiety associated with both HIV treatment and prevention efficacy. Tenofovir diphosphate levels are similar in adults in DISCOVER and in adults and adolescents with HIV. As we saw before, HIV infection status does not affect PK, so we would expect similarly high levels in PBMCs in adolescents if they were taking it for PrEP.

Fifty adolescents who initiated a Descovy-containing regimen for HIV treatment were also evaluated. The mean age in the study was 15 years and over half the participants were female.

Descovy was highly efficacious in adolescence for HIV treatment. Efficacy was similar in adolescent girls and boys.

Plasma tenofovir is associated with safety. With Descovy, the plasma tenofovir levels in adults without HIV and adults and adolescents with HIV are similar across all three populations shown on the left. Plasma tenofovir is 10-fold higher with Truvada in adolescents with HIV, which is consistent with results from prior studies.

Truvada has adverse effects on bone mineral density in adolescents on Truvada for PrEP or HIV treatment. Importantly, due to the 90 percent lower plasma tenofovir concentrations with Descovy, there is no such impact on bone growth.

Bone mineral density in the two key pediatric metrics of total body less head and spine increased through week 48 with a 0.19 percent increase in total body and at 3.3 percent increase in spine. Adolescent participants continue to build bone mineral density similarly to an age-, sex- and race-matched population.

Descovy is noninferior to Truvada in HIV treatment and prevention efficacy. The tenofovir diphosphate levels in PBMCs are comparable in the men and transwomen in DISCOVER, in ciswomen, and in adolescents. Descovy is superior to Truvada in renal and bone safety.

Plasma tenofovir is 90 percent lower with Descovy than Truvada and comparably low in DISCOVER, ciswomen, and adolescents. The efficacy and safety of Descovy for PrEP can be inferred for ciswomen and adolescents. Taken together, the comparable exposures and the extensive efficacy and safety data support the purposefully inclusive indication.

We have planned multiple effectiveness studies of Descovy for PrEP in a diverse range of populations, including ciswomen and adolescents. We considered numerous approaches to studying the efficacy of Descovy in women in 2015 when we were designing the DISCOVER trial. Ciswomen were not included in discover because the HIV incidence rate in the sites where DISCOVER was conducted is about

13-lower in women with high risk for HIV compared with the MSM with high risk in those locations.

With respect to doing a dedicated trial in ciswomen, there are three generally accepted approaches to randomized clinical trials for efficacy. A placebo-controlled trial with Descovy versus placebo is not ethical, as Truvada is approved and highly effective for PrEP in adherent women.

A superiority trial for Descovy over Truvada was also not reasonable as both are oral daily pills differentiated, primarily, although not exclusively, on safety. Lastly, we considered a noninferiority trial. Unlike DISCOVER where we pulled treatment effects from three randomized control trials with similar efficacy in MSM and transwomen, the 5 randomized controlled trials in women lacked a consistent treatment effect from which we could conduct a defensible noninferiority margin.

Using only the two trials with the highest efficacy in women taking Truvada, we were able to

estimate that a noninferiority trial would require enrollment of about 22,000 women in the high incidence regions. This would require approximately 8 to 10 years to conduct.

The design of the DISCOVER trial was not amenable to the inclusion of adolescents. Truvada was not approved for adolescents until 2018, so we would be comparing this safety and efficacy of two investigational agents. More importantly, we knew from data with Truvada that adolescents require a higher visit frequency to maintain adherence and may benefit from age appropriate targeted interventions to maximize recruitment and retention in clinical trials.

The efficacy and safety of Descovy for PrEP in women and adolescents can be inferred from the totality of evidence for Truvada and Descovy for HIV prevention and our extensive safety database from HIV treatment. Clinical data are now needed to inform providers and individuals at risk for HIV regarding the clinical effectiveness of Descovy for PrEP in ciswomen and adolescents.

We are dedicated to generating these data, and we will be supporting a number of studies in over 3400 ciswomen and adolescents in the United States and in Africa. Key effectiveness research questions include the evaluation of the safety of Descovy for PrEP in pregnant and breastfeeding women and how the improved safety tolerability and smaller size of Descovy could improve PrEP uptake and persistence.

We are strongly committed to understanding how having an additional choice for PrEP with Descovy, which has an improved renal and bone safety profile and pharmacologic properties consistent with an earlier and longer duration of protection from HIV, can help address our shared goals of increasing PrEP uptake and helping to end the HIV epidemic.

Thank you. I'm now pleased to invite Dr. Rick Elion to talk about the clinical impact of the DISCOVER trial.

Applicant Presentation - Richard Elion

DR. ELION: Good morning. My name is

Dr. Rick Elion. My conflicts are I do research currently with Gilead, ViiV, and Proteus. I'm a member of an advisory panel for Gilead and ViiV. I'm on the speakers bureau of Gilead, ViiV, and Janssen. I have no stock or financial interest in these proceedings.

I have been active in the care of HIV patients since I left residency in 1983. I began in Brooklyn and moved to the East Village in Manhattan in 1985, at the time of the first HIV test in April of that year, and I've been continuously at the front lines of caring for HIV patients and seeking solutions and improvements in care for over 30 years. I've watched countless men and women die in my first 10 years of practice.

Advances in treatment and now prevention have transformed what was once a harrowing job to one of immense satisfaction. I'm currently director of research at the Washington Health Institute that serves a low-income population in the District and a clinical professor of medicine at George Washington University. I've been the

director of research at Whitman Walker Health, where we were a site for one of the first PrEP demonstration projects, and I have supervised hundreds of patients starting PrEP since 2013.

I also work at the Department of Health in Washington, D.C. in the Wellness Program, which is the Center for Caring for Those with Sexually Transmitted Infections and providing PrEP and research and methods to improve HIV prevention in the District. I also continue to follow patients at the Washington Health Institute, some of which I have cared for, for 20 years or longer. I'm grateful and honored to have the chance to share my perspective on why Descovy is an important addition to our prevention toolbox.

It's estimated that approximately 90 percent of all new infections are coming from people who either don't know their diagnosis, or they've been diagnosed and are not engaged in care, or not virologically suppressed. While treatment as prevention is very successful at preventing new infections, the bulk of new infections will not be

prevented with just treatment alone.

We need multiple options for patients to choose their ideal method of prevention, as when consumers have more choices, it leads to greater engagement. We will not likely have a vaccine soon to protect uninfected individuals, so PrEP is critical to help us cut down the rate of new infections.

Prevention is much broader than just a pill to protect against HIV. They have a variety of options, which allow each person to choose what's right for them. Choice is critical for patients, as they're much more comfortable and committed to the choices that they make rather than being told what to do.

Biomedical interventions including treatment as prevention and PrEP are among the most useful. Treatment as prevention has been fundamental in helping the decline of 18 percent of new cases in the United States. It's the future synergies of these approaches for treatment for HIV infected individuals and PrEP for uninfected individuals.

The analysis shown here looked at the change in new diagnoses of HIV over a 5-year period in states grouped by PrEP use. This data is controlled for rates of virologic suppression and in states with low PrEP use as defined as 3 percent on PrEP. You can see about a 1 percent increase in annual HIV diagnosis.

This can be compared to the high PrEP use group with 11 percent on PrEP where you see almost a 5 percent reduction in new cases. These rates of PrEP utilization are still quite low considering the risk profiles of patients in these communities and could be greater if there were greater adoption of PrEP.

This CDC report makes clear that communities at need are receiving PrEP. This slide demonstrates, however, the imbalance between the potential need for PrEP in certain communities and the actual use of PrEP. Dawn Smith, who's here this morning, and colleagues reported on the disparities between the potential members of various populations that would qualify for PrEP

versus those who are using PrEP.

These differences are staggering in the communities in need as can be seen in this life. Gross differences exist but only a fraction of these communities are benefiting from PrEP, ranging from racial disparities for blacks and Hispanic to women as well. Though not shown here, certainly adolescents , those from 15 to 25 years of age, who are sexually active are also facing these same disparities.

We know that Truvada for PrEP is efficacious in adolescents with adequate adherence. DISCOVER demonstrated efficacy in cismen and transgender women. Descovy pharmacology is consistent across different ages. The PK profile of Descovy could have some advantages for adolescents as reflected by the higher exposures that are achieved and the higher intracellular drug levels that stay elevated longer after missed doses.

This notion of forgiveness of suboptimal adherence is critical for this population. Aside from the potential benefits of a better PK profile,

Descovy will be a safer medication for a population that's actively building bone mass into their early 30's. They are depositing bone as part of their normal growth, and the bone mineral density loss with Truvada could potentially have a lasting effect on adolescents, who after using Truvada may not ever reach peak bone mass.

In this slide, we use the notion of a Z score. A Z score compares your bone density to the average values for a person of your same age and gender. A low Z score below 2 is a warning sign that you have less bone mass and/or may be losing bone more rapidly than expected for someone of your age.

Consideration of Z scores, which standardized bone mineral density for age, race and sex, is most important during adolescence when bone mineral density variability increases. Z scores are stable over at least three years during periods of rapid bone accrual. Persistent Z score decline, which you can see here, after stopping PrEP, especially in the younger participants, is a

concerning finding of these analysis.

The Z scores for individuals on Truvada for PrEP declined for both spine, hip, and total body during the 48-week period of PrEP, and then recover in a comparable time period but not back to baseline after at least 48 weeks of observation.

The clinical significance of this is two-fold. The first is that the bone mineral density based on the Z score does not recover to baseline 48 weeks after PrEP has been discontinued, suggesting that there is some insult to bone deposition that does not fully recover. Second, the insult is worse for those 15 to 19 who are more actively depositing bone.

TAF on the other hand has not been shown to have this impact on bone as reflected in HIV-positive adolescents on treatment. It is a better choice, therefore, for adolescents. Offering them a medication that will allow their bones to grow in a normal fashion is an important consideration in selecting the best medicine for HIV prevention for adolescents.

It's equally important for women. I previously mentioned the PK advantage for adolescents. The PK data that were presented earlier reflect a higher intracellular level of TAF in the PBMCs, and hence, a longer period that these levels stay above the threshold of efficacy, 16 days versus 10 days. This represents possibly a significant difference between TAF and TDF if we can accept the assumption that PBMCs have higher drug levels and had been correlated with levels of protection. This knowledge about HIV prevention continues to evolve.

The DISCOVER study has demonstrated that the failure of TAF to be present in higher tissue levels for men was not a detriment to the overall efficacy. This efficacy was likely driven by the higher drug levels in the various components of the PBMCs. The higher levels and the subsequent longer time, until those levels fall below the threshold of effectiveness, could portend a more forgiving regimen and merit further study.

But forgiveness of missed or late doses

could be a significant advantage for TAF/FTC and provide a clinical advantage for those who don't take their pills every day. This would be very important for both adolescents and for women who historically have had a greater percentage of failures of PrEP due to poor adherence.

PrEP with Truvada has already been approved for women based on the studies seen in this slide that show comparable efficacy to men when adequate adherence is maintained. VOICE and FEM-PrEP show poor efficacy when adherence was equally deficient. Women make up approximately 19 percent of new infections and have a great deal of unsafe exposure through sexual contact.

Ninety-three percent of HIV negative women reported having vaginal sex without a condom and 26 percent reported having anal sex.. Women therefore make up an important part of the population for controlling HIV infection and are underrepresented in their low use of PrEP. As of 2015, only 2 percent of women who were eligible for PrEP were on PrEP.

I work with colleagues at the Washington Hospital Center in the Department of Health in the District of Columbia on engaging women in PrEP in our STI program, known as the Wellness Clinic, and the Family Planning Program at Washington Hospital Center. We have screened nearly a thousand women who are at high risk through their sexual practices, and only less than 1 percent have opted to initiate PrEP despite a vigorous program using videos, peer counseling, free medications, and peer support. Despite our numerous efforts to explain and encourage the adoption of more tools for HIV prevention for women, we have been lagging behind.

This data of HIV incidence from demonstration projects show the comparable rates of new infections in men and women. There should be little doubt that PrEP with Truvada works equally well in men and women when adherence is appropriate. These low rates of seroconversion demonstrate real-world efficacy. There's no data to suggest that this efficacy is different between genders when adherence is similar.

These data from real-world experiences support the fact that women benefit in the same fashion as men with PrEP, with Truvada in the real world, not just in clinical trial settings. However, as mentioned earlier, women have not adopted PrEP in significant number.

The reasons for this are complex and involve multiple issues. This study of African Americans, both men and women, demonstrate some of these challenges. Denial of risk is a critical issue for women, as well as fear of side effects and trust that these treatments will actually work.

Other surveys have pointed out that mistrust of providers; stigma; fear of being ousted as needing HIV protection; partner notification and lack of support from one's partner; cost; and access to medicine remain key drivers for women's reluctance to start PrEP. There are multiple reasons in the decision-making exercise by women in adopting HIV prevention, so anything we can do to lessen this burden might help women make a better informed decision.

The safety of TAF versus TDF regarding bone demineralization is clear. There are clinical consequences as reflected in higher risk of fracture in the treatment population on Truvada. These differences in bone mineral density could potentially be even more important in women.

Bone mineral density in women can be impacted by age and hormonal status. Approximately 1 in 2 women over the age of 50 will break a bone because of osteoporosis. A woman's risk of breaking a hip is equal to her combined risk of breast, uterine, and ovarian cancer. HIV-positive women have a 50 percent higher risk of osteopenia at age 50 than men at a comparable age.

Descovy is a safer alternative for women than Truvada who are at any risk for issues related to bone health. Certainly in treatment settings, I've switched patients on Truvada to TAF-containing regimens to alleviate any concerns I would have or they would have about their bone health.

We know that Truvada for PrEP is equally effective in men and women. We know that PBMC

levels have been associated with efficacy for both HIV treatment and HIV prevention. There is no correlate of protection established for tissue levels, and only modest efficacy for topical regimens that may provide lower levels in PBMCs, as been mentioned already.

The low TFV tissue levels in men were not predictive of the success seen in DISCOVER and supports the notion that PBMC levels provide a correlate of protection. PBMC drug levels are similar for men and women and higher for Descovy in both men and women. And since the PBMC compartment is likely a significant predictor of efficacy, then women would have similar levels of protection as their male counterparts.

The key issues at this hearing are based on the evaluation of Descovy for PrEP and whether the indication should extend beyond the participants in the DISCOVER trial. There's a history of conflicting data regarding the role of tissue levels in protecting against HIV acquisition versus the role of systemic protection through components

of the blood. This is obviously one of the key questions before the committee today, establishing efficacy and safety in HIV prevention for all communities.

The data from the DISCOVER trial demonstrated that systemic protection drives efficacy in MSM and transgender women. There is an established correlate of protection for the levels of drug in PBMCs and iPrEx, and we see higher levels in PBMCs with Descovy and lower levels in rectal tissue. Yet, the point estimate in DISCOVER showed a lower rate of infection on Descovy.

We do know that Descovy was safer in men and transgender women, and we do know that there are improvements in safety with TAF versus TD as well, and we can debate whether these improvements will convey a significant clinical benefit. I believe they do convey a significant benefit from a safety perspective for both adolescents and women, as based on the data that has been shown today.

The differences in PK between TAF and TDF could be a significant differentiator between the

two options for PrEP, and the improved profile seen with TAF might improve outcomes by mitigating suboptimal adherence. This evidence supports the extension of the efficacy data from DISCOVER to women and to adolescents.

Further, at the end of the day, as a clinician, counseling men and women about the need for HIV prevention and PrEP, I can't stress enough how detrimental it would be to give men a choice of a safer medicine but not offer the same choice to ciswomen.

Ciswomen should have the same options that would be available to cismen and transwomen. They should not have to wait for a separate study to prove efficacy and safety in ciswomen that can take at least four years to result in approval for TAF or PrEP. Please at least allow women to have that choice. Let them decide if the safety advantages outweigh the concerns about efficacy.

There may be different opinions about the level of certainty that disclosure will work equally well in both sexes, and there is reasonable

certainty, based on the success with Truvada for HIV prevention, to extend this certainty from the male and transgender women in DISCOVER to HIV negative women and adolescents.

I am certain that if women and adolescents don't have that choice and are told they can't use a safer medicine that would have potentially been approved for men, it will be seen as a signal of uncertainty by these populations. They are likely to feel left behind, and it will not lead to increased engagement and use of HIV prevention. I hope we don't give those vulnerable populations that message and do allow them the option to choose what will be best for them.

I have taught clinicians in Uganda, Kenya, and Rwanda for the last five years, and these clinicians also look to the U.S. and the FDA for recommendations about indications for HIV medications. Providing an effective and safe medication for women in Africa, where women make up over half the cases worldwide, is fundamentally important, so these decisions today have

implications not just in the United States, potentially.

For the last 30 years as a clinician, my role has been to explain to patients their therapeutic options and help them make the best decisions for themselves. Please allow me to keep doing my job of guiding and helping patients to make the best decision and don't take the choice out of our hands. The totality of the evidence and the favorable benefit-risk profile of Descovy support making this drug available to all those in need. Thank you.

DR. BADEN: Thank you. I'd like to thank the applicant for a very thorough presentation of a tremendous amount of data.

Before we have clarifying questions to the presenters, we'll take a 10-minute break. Panel members, please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any members of the audience. We will resume at 10:25. Thank you.

(Whereupon, at 10:14 a.m., a recess was

taken.)

Clarifying Questions

DR. BADEN: We will now resume session. If everyone can please take your seats, we have little time and much ground to cover. We have about 50 minutes for clarifying questions for the applicant's presentation. We may not complete all of the clarifying questions, in which case we will then resume after lunch, after we have a chance to have the agency's presentations.

In the clarifying question process, for those of you who are new to joining us, what I'd like to do is to try to build on themes. I really asked for committee members to please use the honor system in how we do the clarifying question process.

When we start, if you are interested in asking a question, signal Lauren or I. We'll add you to the list. If a question is asked and there is a follow-on that builds on the theme, I would very much like to build on the theme. Please take your card, turn it on the side, and that will

indicate you want to build on the theme so that we can have a series of questions on the same topic and not be bouncing around with every other question, going back and forth between topics.

I just asked the committee members to really build on a theme and not have that -- a way so you can ask another question faster. We'll try very hard to get through all of the questions as quickly as possible, but I would like to, as much as possible, build on themes because I think that's more efficient and more effective.

We will start with our member on the phone. We'll start with the first clarifying question.

MS. LUPOLE: Yes, sir.

DR. BADEN: Please go ahead.

MS. LUPOLE: The question is, what, if any, are the long-term effects on bone density and renal [indiscernible] related to [indiscernible] adherence and failure?

DR. BRAINARD: I'm going to ask Dr. Moupali Das to come to the podium and speak to the longer term bone and renal effects of Truvada and Descovy

use. I believe that was your question. We'll start there. If you have an additional question, we'll take it from there.

MS. LUPOLE: Yes, ma'am. Basically, the failure to adhere and multiple incidences, occurring multiple incidences.

DR. BRAINARD: The failure to what?

MS. LUPOLE: [Indiscernible - feedback]

DR. BRAINARD: The failure to adhere. Okay.

So we'll present the safety data first in terms of the long-term effects, and then we'll talk about adherence and how adherence is related to efficacy.

DR. BADEN: And to our colleague on the phone, if you can go on mute, as we're getting feedback. Thank you.

DR. DAS: The bone mineral density biomarker, and the renal tubular biomarkers, and the glomerular function biomarkers chosen for evaluation in DISCOVER are associated with clinically meaningful differentiation between Descovy and Truvada over the long term. First

we'll look at bone, and then we'll look at renal.

Slide 1 up, please. The early declines in bone mineral density between weeks 24 and 48 widen over time through 3 years of follow-up in a representative example of hip BMD from 2 pooled clinical trials of Descovy- and Truvada-based regimen in HIV treatment.

On the right, you can see that that separation in the BMD curves is associated with clinically meaningful increase in discontinuations due to bone adverse events. This is over a 3-year time period. We have longer duration of data from the HIV treatment literature.

Slide 2 up. This is an analysis from the EuroSIDA cohort with 619 fractures in over 86,000 person-years of follow-up. What you see here in the multivariate analysis of fracture risk, which was adjusted for demographics, HIV-specific variables, and comorbidities, is having ever been on Truvada -- excuse me, TDF versus never being on TDF was associated with a 40 percent increase of fracture risk. Being currently on TDF versus never

being off of it was associated with a 25 percent risk. You may ask what does this mean for people on PrEP?

Slide 3 up. This is data from Chou, et al., published in JAMA earlier this year in terms of a pooled meta-analysis of PrEP trials that was done to support the U.S. Services Preventative Task Force Recommendation with a grade A for PrEP for HIV prevention. Here we see both TDF trials and Truvada trials. The duration of follow-up in these trials was significantly shorter than what we have in the treatment literature, however, there was an increased trend towards fractures in those participants receiving TDF or Truvada.

Now we'll switch to renal discontinuations in renal tubular biomarkers. Slide 1 up. A similar pattern exists for the 2 tubular markers, which are early markers of proximal tubular dysfunction. There are early changes as early as week 4, and the lines separate over time with longer-term follow up through week 48 and week 96. They continue to separate through week 144.

On the right-hand side, you can see that there were no discontinuations on people on Descovy-containing regimens, that the cumulative effect of tenofovir toxicity is evidenced by increasing adverse events from renal causes leading to discontinuations in a step-wise fashion through week 48 through week 144.

With respect to how this is relevant for people with PrEP, we turn again to Chou, et al's meta-analysis from JAMA earlier this year; slide 3 up. Here we see that either TDF or Truvada PrEP is associated with an increased risk of renal AEs. In summary, we chose these biomarkers because we were aware of their association with clinical meaningful differentiation in terms of renal and bone safety over a longer term follow-up, and we continue to follow participants in DISCOVER to follow them long term.

DR. BRAINARD: With respect to the adherence question, I'll say that there have been multiple clinical trials, as well as real-world data sets, demonstrating the close correlation between

efficacy to Truvada for PrEP and outcome.

Slide 1 up, please. This figure demonstrates that across multiple different clinical trials and real-world data sets, the higher the adherence within the study or within the subanalysis within the trial, looking at adherent participants based on plasma tenofovir levels or intracellular drug levels, the higher the efficacy with respect to risk reduction for HIV acquisition.

DR. BADEN: If I may, on the bone -- Ms. Lupole, do you have any follow-on questions? If not, we'll have some follow-on in the room.

(No response.)

DR. BADEN: Dr. Elion on slide 105 showed TDF and adolescent bone development. Do you have similar data for TAF and adolescent bone development?

DR. BRAINARD: I'll ask Dr. Moupali Das to review the data we have with TAF-containing regimens in adolescents.

DR. DAS: First, I'll show you the data in

adolescents with HIV. Slide 1 up. Descovy or TAF does not have the same impact on bone mineral density as does Truvada. Here is bone safety in adolescents with HIV. You can see both that the spine and total body less head continued to increase and grow, and that there are minimal changes in the Z scores, which reflect age, race, and gender-matched populations.

In the DISCOVER study, we included people who were 18 and older. The age range was 18 to 76, however, we did look at the bone mineral density in participants stratified by age less than 25.

Slide 2 up. This comparative data between Descovy and Truvada in the participants less than 25 years on the left with spine and in the middle greater than 25 years with spine. You can see that the participants on Descovy continue to have the same amount of increase in bone mineral density, whereas those on Truvada had significant declines, which is particularly relevant for this population. Similar trends were observed with hip in terms of continued growth on Descovy or stable on Descovy

but declines on Truvada.

This is consistent with the findings in PrEP that Dr. Elion showed.

DR. BADEN: Would these data -- compared to age-matched controls, HIV uninfected, not on a tenofovir compound, is the bone development on TAF equal or is there a difference? Because comparing it to tenofovir TDF, one may accept the decline and say the decline is not as bad. How does it compare to age-matched controls on none of these medicines?

DR. DAS: If we go back to slide 1, these are participants with HIV, so there is that consideration. But this is people who are on Truvada, and you're asking about participants on TAF.

DR. BADEN: Persons on TAF, and I'm interested in the TAF comparison to bone development in healthy age matched-controlled children not on a tenofovir compound, so that the bone development of a 20 year old on TAF and off TAF is not different.

DR. DAS: Okay. In this slide, because we

don't have any TAF data in adolescents without HIV -- this is TAF data in adolescents with HIV -- the dotted lines are the Z scores, which are matched by age, race and gender for the population. You can see in the dotted lines between zero and week 48, there's really no difference in the blue dotted-line Z score, which is a spine Z score, and the pink dotted-line Z score, which is total body less head.

DR. BADEN: And those would then be age-matched control unaffected?

DR. DAS: Yes.

DR. BADEN: That's what I thought you said. I just wanted that crystal clear --

DR. DAS: I'm sorry I didn't clarify that, yes.

DR. BADEN: -- that as best as we can tell, there is no abrogation of normal bone development, as best as you can tell, realizing they're HIV infected; otherwise they wouldn't be on this for a long term.

DR. DAS: Exactly. Thank you.

DR. BADEN: Thank you.

Did Dr. Goetz or Awni have a follow-on question?

DR. GOETZ: My follow-up was related to the adherence question rather than bone.

DR. BADEN: Please?

DR. GOETZ: The previous slide, the backup 1232, showed the relationship between adherence and efficacy. One of the considerations is the relationship between adherence and efficacy on Truvada-containing regimens, or TDF-containing regimens, the same in women as in men. I think that helps inform our thoughts as to where the local tissue concentrations are important.

So looking at the VOICE/FEM-PrEP versus iPrEP [ph] populations, I wonder if you can go into more detail as to regards to how levels of adherence, which then presumably correlate with PBMC concentrations, correlate with levels of protection in women versus men.

DR. BRAINARD: The levels of adherence measured across these studies varied. They weren't

all uniformly assessing adherence through the same mechanism. However, the association between adherence and efficacy by these measures, whether it was tenofovir plasma levels or tenofovir diphosphate within the peripheral blood mononuclear cells, that relationship held up across men and women.

These studies shown here represent some of the larger studies conducted to date. But since Truvada for PrEP was approved seven years ago, there's an even larger data set that has accumulated.

Slide 1 up, please. The CDC recently updated their website with the new data on efficacy and analyses across all available data and concluded that adherence is highly correlated with outcomes for both men and women and that the efficacy of Truvada for PrEP is estimated to be 99 percent for men and for women who are using Truvada for PrEP consistently.

DR. GOETZ: If I can follow up on that, then I guess my question goes into people who are

partially adherent. To the degree that it's knowable -- these are hard questions -- is partial adherence as effective in women as it is in men? This indirectly gets at the question, is partial adherence, we would think from the pharmacokinetic data would lead to similar concentrations of TFV diphosphate intracellularly and PBMCs, which may not be sufficient.

Does it protect women as well as men? Because if we get the same levels in PBMCs, they're at the lower level, so there may be concerns about tissue concentrations. So again, the question is, does partial adherence protect women as equally to men at thresholds? It's certainly going to be a relationship between adherence and success.

DR. DAS: There was some recent data presented just a few weeks ago at the IAS conference from the HPTN 082 study, which was a large study conducted in Africa in women. It was looking at different interventions to increase adherence. But in terms of the clinical outcomes of that trial -- put slide 3 up, please -- among

the 400 Women age 16 to 25, who were enrolled in this study, there were 4 infections. That gave an overall incidence rate of 1 per 100 person-years.

They used dried blood spots, which the methodology from the iPrEx study as well as from DISCOVER trial, and they found that the infections closely correlated with these measurements of adherence using the dried blood spots, which is to say that two of the infections occurred with no detectable drug level and the other two occurred in the setting of adherence consistent with less than 2 doses per week. This is suggests that in the setting of low adherence, there is a similar relationship.

DR. BADEN: Dr. Giordano?

DR. GIORDANO: The adherence question relates to the PBMC question in my mind. The argument is that you achieve high levels of the tenofovir active component in PBMC, and that is a correlate of protection. My understanding of the Anderson et al data is that those data were generated from people who were less adherent to

people who were more adherent to the tenofovir drug.

So the PBMC data, are they not simply a measure of adherence? And if you measured tenofovir in hair or tenofovir in some other body component, would you not arrive at the same conclusion, that hair is a correlate of protection for HIV prevention? So it gets to the strength of those data, which are critical to this argument that the company's making.

DR. BRAINARD: So tenofovir diphosphate, when measured in red blood cells as is done with the dried blood spot analysis, is a measurement of adherence alone and can be analogous to measuring tenofovir in hair levels or measuring plasma tenofovir.

The advantage of the tenofovir diphosphate in dried blood cells is that it allows for an integrated assessment of efficacy over a longer period of time, similar to a hemoglobin A1c. Nevertheless, it doesn't speak itself to efficacy, but we know that for tenofovir prodrugs orally

administered, the drug is acting within CD-4 positive T cells, which are a component of peripheral blood mononuclear cells.

We also can draw the correlation between the level of tenofovir diphosphate within the red blood cells and what the corresponding level is within PBMCs based on phase 1 studies in healthy volunteers that Dr. Anderson did to validate that analysis.

So the dried blood spot data is adherence data. You can get thresholds of adherence, and then based on the phase 1 studies done, where they were able to match those adherence bands to exactly how many doses were given per week, they can then correlate that to be expected intracellular PBMC levels, and we correlate that with efficacy because that's where we know that the virus replicates. It can only replicate in CD-4 cells

DR. GIORDANO: But that correlation with efficacy is still fundamentally based on adherence, as I understand it. How do we know that someone with the exact same adherence -- let me ask it

differently. How do we know that the levels in PBMC are the critical determinant of prevention, not of treatment efficacy for someone who has HIV, but of prevention? That's what I'm not -- you haven't really established that fact in my mind.

DR. BRAINARD: So we know that Truvada for PrEP is highly an equally effective in men and women and that adherence is the primary driver of that efficacy. When we look at the vaginal and rectal tissue levels of Truvada -- and I'll try to show you that slide in one minute -- what we can see is that the rectal levels of a tenofovir diphosphate following Truvada use are 100-fold higher than they are in vaginal tissue.

If genital tissue or rectal tissue -- and I'll put slide 1 up please. These are the data I just spoke to with the 100-fold higher rectal tenofovir diphosphate levels as compared to vaginal tenofovir diphosphate levels in the setting of Truvada with healthy female volunteers.

So if genital tissue levels were driving efficacy, then you wouldn't expect to see equal

efficacy in men and women. You'd see disproportionate efficacy, but we don't. We also know from the DISCOVER trial that Descovy is highly effective at preventing HIV acquisition in men who have sex with men and transgender women.

I'll put slide 2 up, please. These data add in the Descovy data in the vaginal and rectal compartments. What you can see is that for Descovy, rectal compared to vaginal, rectal levels are 10-fold higher. And within the rectal compartment, Truvada achieves 10-fold higher levels than Descovy.

So again, comparing Truvada to Descovy, if rectal levels were driving efficacy, then you would expect Truvada would be better than Descovy, but that's not what we saw in the trial. We saw that they were noninferior, and we saw that adherence was the primary driver of efficacy.

So we know that we have these high rectal levels. We know that vaginal levels with Truvada are lower, but we know that Truvada is highly effective in women who take the drug. Therefore,

that provides evidence, if you will, that the active tenofovir diphosphate and the circulating PBMCs is driving the efficacy and not the tissue levels within the homogenate of the tissue.

DR. BADEN: We have several more follow-on questions. Dr. Awni, did you have a follow on?

DR. AWNI: I actually thought it was a follow-on, but related to the size, there were a couple of statements saying the size of the two tablets between the Truvada and Descovy, how much difference in size? Size of the tablet could have an impact on somebody taking it, easy to take it somewhere else.

DR. BRAINARD: Yes. Descovy is substantially smaller than Truvada because it's such a smaller dose, 25 milligrams versus 300 milligrams.

Slide 1 up, please. Obviously not to size, but you get the relative comparison between the size of the two pills there. And size has been cited in patient surveys as a factor that's been seen as favorable.

DR. BADEN: Dr. Gripshover, we're still doing follow-ons.

DR. GRIPSHOVER: My follow-on is back to the PBMC question. I think the data that we've seen, that you tried to show that it correlated with efficacy, was based on the iPrEx study of men who have sex with men, I think, and then we've seen it in the DISCOVER trial with Descovy.

Do we have data from Partners PrEP, where we did see Truvada being effective in women? Do we know that that also works in women from any other trials, or is it just in these two trials?

DR. BRAINARD: There are other trials besides Partners PrEP that showed efficacy in women. For example, TDF2 was a study conducted in both men and women, and in the TDF2 study, if you look at the as-treated population, which censors people after they have no longer been taking drug for at least 30 days, then the efficacy in men and in women is comparable.

DR. GRIPSHOVER: Actually, my question was do you have the T of the PMBC data in women in all

to know that that marker of efficacy works in those trials? That was my question; not did it work. Sorry.

DR. BRAINARD: So within Partners PrEP, we had adherence, but I don't believe that there were tenofovir diphosphate levels; it's plasma tenofovir levels. So we can take a look and see if we can find specific data regarding tenofovir diphosphate levels in clinical studies within women.

But what I would say, I want to reemphasize that the connection between adherence and the tenofovir diphosphate within PBMCs is made based on the validation of the dried blood spot assay. So you get the dried blood spot assay -- and I might have Dr. Anderson come up and speak to this just so he can walk through how that connection between the dried blood spot tenofovir diphosphate is then related and corresponding to a PBMC level.

Because it seems like what we're talking about is tenofovir diphosphate within the CD-4 cells, within the PBMCs driving efficacy, but you don't actually measure the PBMCs during the study

for adherence; you measure the dried blood spot. Then we know from the validated assays what that level correlates to with respect to tenofovir diphosphate and PBMCs. I'll also say that we know across men, women, HIV infected, HIV uninfected, that tenofovir diphosphate levels are consistent.

DR. ANDERSON: Good morning. I have received grants and contracts from Gilead Sciences paid to my institution, as well as some consulting honoraria for my time here, but I do not have a financial interest in the outcome of this meeting or in the company.

So I wanted to explain the relationship between DBS concentrations in efficacy as well as PBMC concentrations and efficacy. If I can just have slide 2 up, please.

First, I want to start with DBS. DBS was used in the DISCOVER study as an adherence biomarker. What we measured is intracellular tenofovir diphosphate in red cells. And the reason is the half-life in the red cell is 17 to 20 days. That means the concentration will be proportional

to the exposure to the drug or adherence, so we'll have a proportional relationship there. It's a wonderful marker for assessing and quantifying adherence.

If I could have slide 3 up, please. The way that we operationalize this is dried blood spots come into the lab. We take a punch from that spot, so we normalize the amount that we assay. We then use a validated method. We get a result, the tenofovir diphosphate result. Then we have to understand what that result means.

To do that, we conducted separate directly observed dosing PK study in healthy volunteers, one Descovy and one with Truvada, and gave them varying adherence rates. Then we measured their concentrations. And we could tell by then the concentration, what adherence that person -- we made that a standard curve relationship.

Then we wanted to know do these bands of adherence relate with efficacy -- if I could have slide 2 up, please -- and they do. These are DBS results from the iPrEx open-label extension that

shows HIV incidence on the Y by the dried blood spot level on the X-axis. Then the different adherence bands you can see along the top, less than 2 doses per week on average, 2 to 3 and greater than 4.

People that had blood spot levels of greater than 4, there were no infections in that group. People who had blood spot levels of 2 to 3 had an approximately 90 percent reduction in HIV incidence relative to not being on PrEP. So if you hold those dosing categories in mind, this is very similar to what we see in PBMCs.

If I could have slide 2 up, please. Just switching your mind now from dried blood spots to PBMC intracellular tenofovir diphosphate, these are the active sites now in peripheral blood mononuclear cells. This is a case control from the iPrEx randomized-controlled trial, and the relationship between drug concentration in PBMC, tenofovir diphosphate in PBMC, and efficacy compared to placebo.

Now look at the bands along the top. These

are PBMC concentrations from a directly observed dosing study showing 2 doses per week on that as well as 4 or more doses per week. We saw approximately the same efficacy relationship in the PBMCs. Those that were in the roughly 2- to 3-dose range had about a 90 percent reduction. Those in the 4 or more had essentially a hundred percent reduction in HIV incidence.

That is the connection that we make through adherence. It's through adherence, and I think that was the point that was brought up earlier, is we're making a connection through adherence. The difference with PBMCs is we know that's the active site.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: So you've sort of drawn a line between --

DR. BADEN: Please talk closer to your microphone.

DR. SWAMINATHAN: You've sort of drawn a line between the levels from the dried blood spot test and PBMC levels, and the correlation with the

efficacy data. I guess the thesis is that because PBMCs or T cells are the sites of replication of the virus, and that TAF has good intracellular levels in PBMCs, that the efficacy would be expected to be as good or better.

But the connection between the PBMC levels in previous PrEP trials depends on the pharmacokinetics of Truvada. So whatever the actual target cell that's necessary for effective PrEP is, we know that it correlates with PBMC levels; not that the PBMCs are the actual target that makes PrEP efficacious.

How do we know that the correlation between the PBMC levels and cell X is the same with regard to the pharmacokinetics of these two different drugs?

DR. BRAINARD: So we know cell X. Cell x is a CD-4 positive T cell because that's the only cell within which HIV will replicate in order to spread infection. Now, that CD-4 positive T cell could be within the tissues or it could be within the peripheral blood mononuclear cells, recognizing

that these are not distinct subsets but that there is circulation around the body and trafficking of cells in and out of tissues.

I'll put slide 2 up, please, and then CC-15 and back, please. Just reviewing, again, how infection is established, infection is initially established, for mucosal transmission, by the infection of a local cell. But in order for infection to disseminate, two different things need to happen. CD-4 T cells need to be recruited to that site of initial infection so that a founder population can be established, and then that founder population needs to disseminate via the lymphatic system.

We know from nonhuman primate studies that these CD-4 T cells that form the founder population are coming from the peripheral blood mononuclear cells, and we know that when you're talking about systemic oral drugs, that systemic drugs load both peripheral blood mononuclear cells, but there are also drugs circulating throughout the plasma.

Slide 2 up, please. Again, understanding

how that infection is occurring, with systemic therapy or with oral tenofovir prodrugs, drug is loaded within these peripheral blood mononuclear cells, which are circulating around the body and trafficking to different locations, including the lymphatic tissue, and including to tissue, particularly when there's a chemokinetic signal. But also TAF, in the case of Descovy and plasma tenofovir in the case of Truvada, are also circulating throughout the blood and distributing throughout the body. As those drugs get into the tissues, they're also able to load resident cells and provide protection that way.

So there are really two different ways that systemic oral agents can provide protection against HIV infection. Topical agents can also provide protection, but the way they do that is not by sitting on top of the mucosa but actually diffusing into the subepithelium [ph]. Then in the case of tenofovir gel, for example, they still have to get inside that CD-4 T cell because that's the only place that HIV replicates, and that's independent

of female, male, vagina, and rectum.

DR. SWAMINATHAN: I agree with most of what you said, but I would just have to disagree with this idea that there's this instantaneous dynamic flux in equilibrium between peripheral blood mononuclear cells and cervical or other submucosal lymphoid populations.

The phenotype of resident memory T cells in different tissues has been demonstrated to be different, and there are high CCR5 resident lymphocytes in vaginal tissue, for example, that are different from rectal tissue, and certainly different from PBMCs. Dendritic cells in the vaginal tissue are also thought to play a role.

All I'm saying is that unless one actually knows what the pharmacodynamics of these different compounds, intracellularly, in different resident populations, which is the population -- there's not recruitment until after the virus gets there, and there's infection locally of cells to come into the site of infection. So the level of intracellular drug in the lymphocytes that are going to be

infected immediately after exposure is what's relevant, and no one has really been able to measure, from what I understand.

DR. BRAINARD: I would like to -- oh, sorry.

DR. BADEN: Unfortunately, it's 11:07, and we need to go to the agency's presentation. I would have you respond, except this is a longer discussion. So I think, as I anticipated, we almost got through one question. So I will be very interested, as all the committee members are, on further discussion on this point. I think you understand the key issue, and perhaps over lunch, you'll further clarify how to educate us on the rationale.

But we need to move to the agency's presentation and clarifying questions to the agency. And if there's time, we'll come back to further clarifying questions to the applicant or we'll do that after lunch.

DR. BRAINARD: Great. Thanks very much.

DR. BADEN: Thank you.

Dr. Miele, thank you for presenting the

agency's perspective on some of these key issues.

FDA Presentation - Peter Miele

DR. MIELE: Good morning. I am Peter Miele, a medical officer in the Division of Antiviral Products. I will be presenting on behalf of the FDA review team for NDA 208215, supplement 12 for Descovy, for pre-exposure prophylaxis or PrEP indication. Here's my agenda.

I'll begin with a brief discussion of the indication being proposed by this application, and then move on to some context and background; in particular, a brief discussion of the issues we've been having here with regards to the potential role of mucosal tissue drug concentrations in HIV prevention.

I'll summarize the FDA findings from the DISCOVER trial in men and transgender women who have sex with men, and conclude with a discussion of the extrapolation approach that's being proposed in this application to support a PrEP indication in cisgender women and the data that has been submitted to support that approach.

As you know, this application proposes a new indication for Descovy or F/TAF, which is pre-exposure prophylaxis to reduce the risk of sexually-acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kilograms.

To be clear, this indication would apply to adult and adolescent men and transgender women who have sex with men, men who have sex with women and cisgender women who have sex with men. As such, the proposed indication is similar to the currently approved indication for PrEP for Truvada, which is emtricitabine tenofovir disoproxil fumarate or F/TDF, and the indication is listed for you here.

Now, as you know, the data that the agency reviewed to support the PrEP indication for Truvada consisted of data from a phase 3 double-blind, placebo-controlled trial in MSM and transgender women, or the iPrEx trial; as well as phase 3, double-blind, placebo-controlled trial in adult heterosexual men and women in HIV serodiscordant relationships or the Partners PrEP trial; as well as data from a phase 2 open-label trial in

adolescent MSM. The Adolescent Trial Network study 113.

As you've heard already, there are some differences between TAF and TDF. Both drugs have been approved for the treatment of HIV-1 and chronic hepatitis B, but compared to TDF 300 milligrams, oral administration of 25 milligrams of TAF results in a 4- to 7-fold higher intracellular level of the active metabolite tenofovir diphosphate in PBMCs, while also resulting in 90 percent lower plasma levels of tenofovir.

It's these differences in the plasma exposure to tenofovir that may explain some of the differences in a safety profile observed between TAF and TDF, as if there's less circulating tenofovir in plasma, there's a reduction in the risk of off-target effects of tenofovir.

That said, there have been published single-dose PK studies that suggest that 25 milligrams of oral TAF achieves lower tenofovir and tenofovir diphosphate levels in rectal and

vaginal mucosal tissues as measured in homogenates compared to oral 300 milligrams of TDF.

Why is this important? As you've heard in the previous discussions, the relative importance of mucosal tissue versus systemic drug concentrations to PrEP efficacy is unknown. Importantly, the minimum drug concentration in mucosal tissues, if they are relevant, that would be considered protective against HIV-1 infection is also unknown.

But we have some indirect observations that might support a role for mucosal tissue drug concentrations in PrEP efficacy. For one, as has been mentioned before, topical microbicide experience suggests that vaginal mucosal tissue, drug concentrations, at high enough levels and with very limited systemic exposure can reduce the risk of HIV-1 infection. And as you've heard, we know that oral TDF dosing results in lower tenofovir diphosphate exposure in vaginal tissue versus rectal tissue.

It is this differential drug distribution

that has raised concerns that in combination with poor adherence, it may have contributed to the mixed efficacy results observed in PrEP clinical trials of F/TDF in cisgender women as compared with MSM. That's a controversial topic, and that has been greatly debated over the last few years, but the end result is that we're not entirely sure to what extent this differential drug distribution may have on the efficacy; or in other words, is suboptimal adherence less forgiven in women than men?

These concerns have practical implications. The CDC PrEP guidelines, for example, acknowledge the lack of scientific consensus on protective contribution of drug exposure in specific body tissues. The CDC addresses this issue by reporting the time to achieve maximum intracellular concentrations of tenofovir diphosphate in the various compartments as based on PK studies. Some state PrEP guidelines have followed suit in recognizing the tissue differential also in discussing the time to achieve protective

concentrations.

For example, the New York State PrEP guidelines recommend a 7-day lead in of oral PrEP use for protection with receptive anal sex. In contrast, they recommend 20 days of daily PrEP use for protection with receptive vaginal sex. Now, these differences would not be necessary if there was consensus that systemic PK was the prime motivator or the prime driver for PrEP efficacy. As we know, there are no gender differences with respect to systemic PK for TDF.

So given that there is a lack of consensus regarding the contribution of local tissue versus systemic drug exposure to PrEP efficacy, and these reports of lowered mucosal tissue tenofovir diphosphate concentrations with oral TAF versus TDF dosing, the agency determined that fully powered clinical trials would be needed to support efficacy of F/TAF for PrEP using F/TDF as the active control.

Back to this application, the data that's been submitted to support a PrEP indication for

Descovy consists of one phase 3 double-blind active control clinical trial in MSM transgender women or the DISCOVER trial. To support indication in cisgender women and adolescents, an extrapolation approach has been proposed. The FDA presentation will focus on the extrapolation approach in cisgender women.

The DISCOVER trial was designed as a double-blind noninferiority trial of 5,000 subjects randomized to F/TAF or F/TDF for at least 96 weeks. Following the day 1 visits, subjects returned for study visits at weeks 4 and 12 and then every 12 weeks. And at each follow-up visit, as you heard, they received at risk reduction counseling and adherence counseling, as well as STI screening at all three anatomical sites, oral, rectal, and urine.

The primary efficacy endpoint was the incidence of HIV-1 infections per 100 person-years when all subjects had reached a minimum of 48 weeks of follow-up and at least 50 percent had reached 96 weeks of follow-up or permanently discontinued

from the trial.

For the relative risk analysis, a noninferiority margin of 1.62 per 100 person-years was derived based on historical data from three clinical trials of F/TDF for PrEP and MSM, namely the iPrEx, PROUD, and IPERGAY studies. Based on equal weighing of the three trials, an HIV incidence of 1.44 was assumed for the control arm of F/TDF with a confidence interval of 2.64 and 9.7. Because the analysis for the DISCOVER trial was a rate ratio, the square root of the lower bound of this confidence interval provided the noninferiority margins. So the square root of 2.64 is 1.62.

5,399 subjects were randomized in DISCOVER, 6 subjects per arm were randomized but not treated, giving us a safety population of 5,387. The full analysis set was used for the primary efficacy analysis, and that consisted of subjects who were randomized and treated HIV negative at baseline and had at least one follow-up HIV test during the trial, and that population was 5,335.

In the safety population, the baseline characteristics and demographics were well balanced between the two arms. As you've heard, the median age was 34 years, and 99 percent of subjects were MSM and 1 percent were transgender women; 84 percent of subjects were white, black, or mixed black race made up 9 percent of subjects and Hispanics made up 25 percent.

At baseline, 16 percent of subjects were using Truvada for PrEP and 44 percent were uncircumcised. The median duration of exposure was 86 weeks, and that was balanced between the two arms. And as you've heard, adherence to study drug was high by multiple measures in this trial.

For the primary efficacy analysis, a total of 22 HIV infections were reported, 7 in the F/TAF arm for an HIV infection rate of 0.16, and 15 in the F/TDF arm for an HIV infection rate of 0.342. The HIV infection rate ratio was 0.468 with the confidence intervals shown here. Because the upper bound of the confidence interval was below the prespecified NI margin of 1.62, the DISCOVER trial

demonstrated noninferiority of F/TAF to F/TDF.

As an update, we received a report of an additional HIV infection after the submission was filed, one more HIV infection in the F/TAF group, but this does not impact the primary efficacy conclusion.

Data from the DISCOVER indicate that F/TAF provides a similar level of protection as F/TDF against rectal acquisition of HIV, but if we consider other potential routes of HIV transmission in men, such as penile HIV exposure, we do not have any direct evidence to support the efficacy of F/TAF for this relatively low-risk route of transmission.

That said, we can assume that insertive sex was occurring in the DISCOVER trial. At study entry, subjects reported a mean of 4 unprotective insertive anal intercourse partners in the 90 days prior to screening, and during the trial, 16 percent of subjects had urethritis diagnosed with gonorrhea or chlamydia likely from unprotected insertive anal intercourse.

Thus, given the low rates of HIV infection observed overall in the DISCOVER trial, it may be reasonable to assume that men who practice insertive sex were protected.

I'm now going to switch gears and talk about safety as observed in the DISCOVER trial. Both F/TAF and F/TDF were safe and well tolerated. We observed no notable differences between the two arms in the types, incidence, severity, or onset of adverse events, or laboratory abnormalities.

As you've heard, the most common AEs were sexually transmitted infections. If we exclude the STIs and other infectious adverse events, the most common AEs were diarrhea at 16 percent, nausea at 7 percent, headache at 7 percent, and fatigue at 6 percent, with comparable rates between the arms.

Six percent of subjects in the F/TAF arm were considered serious adverse events and 5 percent of subjects in the F/TDF arm had serious adverse events. The majority of these events were not considered related to study drug. We also observed low rates of adverse events leading to

drug discontinuation, 1 percent in the F/TAF arm and 2 percent in the F/TDF arm.

The most common adverse events leading to drug discontinuation were gastrointestinal disorders, which led to drug withdrawal in less than 1 percent of subjects in each arm. When we looked at GI events overall, they tended to occur in the first month of treatment, which is consistent with the start-up syndrome described in previous trials of F/TDF PrEP.

These issues did not seem to have a major impact on body weight, however, there was a mean increase of weight from baseline at week 48 of 1.1 kilograms for F/TAF and essentially no change in weight for F/TDF.

Looking at renal safety, when we looked at the mean absolute change in serum creatinine, there was minimal change in either group at both weeks 48 or 96. The graph on the right shows the mean change in estimated GFR from baseline. The blue line shows the changes in the F/TAF group, which essentially stayed pretty much consistent with

baseline, whereas in the F/TDF group, there was a 2 to 5 milliliter per minute decrease from baseline over the course of the trial, which became apparent as early as week 4.

The distribution of urine protein to creatinine ratio, or UPCR categories, was a key alpha protected safety endpoint in this study. UPCR is generally regarded by the FDA Division of Cardiovascular and Renal Products as a useful laboratory assessment of proteinuria.

As shown here, the proportion of subjects who had no significant proteinuria at baseline and who then went on to develop significant proteinuria at week 48 was low in both groups, but was higher in the F/TDF group at 2 percent versus 1 percent in the F/TAF group.

Conversely, the proportion of subjects who had significant proteinuria at baseline, of which there were only 25 per arm and who then had improvement in their UPCR category, was higher in the F/TAF group compared to the F/TDF group, at 57 versus 44 percent, respectively. These differences

were statistically significant at week 48, however, the differences were not significant at week 96.

We also observed a greater frequency of treatment emergent proteinuria by urine dipstick in the F/TDF arm overall at 24 percent versus 21 percent per F/TAF. Most of these abnormalities, however, were grade 1, and we saw no difference in the frequency of grade 2 proteinuria between the two arms.

Likewise, we saw very little differences in the frequencies of graded treatment-emergent laboratory abnormalities as they pertained to serum creatinine, 2 percent for F/TDF and 1 percent for F/TAF overall, and we saw no differences at all between the two groups with respect to hypophosphatemia regardless of severity.

Likewise, we saw very little difference between the two groups in the frequency of treatment-emergent adverse events related to renal safety. There was one case of Fanconi syndrome acquired in the F/TDF arm, but also a case of glomerulonephropathy in the F/TAF arm, as well as a

case of nephrotic syndrome in the F/TAF arm.

The cases in the F/TAF were not considered related to study drug, whereas the Fanconi syndrome in the F/TDF arm was. But when we looked at other adverse events as grouped by their MedDRA high level terms for renal failure and impairment, urinary abnormalities, electrolyte analyses, namely blood phosphorous, decreased renal function, and urinalysis not elsewhere classified, we saw no differences between the groups in the reporting of these adverse events. Likewise, there was very little difference between the two groups in renal adverse events that led to drug discontinuation, although the numbers were very small.

In summary, for adverse events or graded treatment-emergent laboratory abnormalities related to renal function or safety, we observed no major differences between the two groups in this particular subject population. I would also remind you that, as with Truvada, approved labeling for Descovy still carries with it a warning for new onset or worsening renal impairment.

Moving on to bone safety, mean percent change from baseline at week 48 and hip and spine bone mineral density were also key alpha-protected safety endpoints. As shown on the table here, there were differences between the two groups at both hip and spine and at both weeks 48 and 96, with essentially no great change in the F/TAF arm but decreases of about a mean of 1 percent at each time point, at each site for the F/TDF arm. These differences were statistically significant at both time points.

Consistent with other tenofovir-containing product labeling, we conducted a categorical analysis of the percent change in BMD from baseline using the falling cutoffs, 7 percent change from baseline for hip and 5 percent change from baseline for spine, as these are cutoffs that the agency considers clinically meaningful.

With regards to the hip, we saw absolutely no difference between the two arms, whether in decreases or increases. We also saw no difference between F/TAF and F/TDF for decreases from baseline

in spinal BMD. However, there was a slight or greater proportion of subjects in the F/TAF arm that had a 5 percent or greater increase from baseline in spine BMD at week 48.

The applicant has shown you results from a categorical analysis regarding the change in BMD clinical status from baseline to week 48 for the spine. We concur that there was a greater proportion of subjects in the F/TDF arm that had worsening status at week 48 and conversely a greater proportion of subjects in the F/TAF arm that had greater improvement of their BMD status in the hip at week 48.

However, when we did the same analysis for the hip, we saw no differences in the proportion of subjects at worsening status at week 48, and there was actually a greater proportion of subjects in the F/TDF arm that had improvement.

When we turn to adverse events as reported in the DISCOVER trial, during the course of the trial, we saw no differences between the two groups with respect to fractures, most of which were

traumatic and occurred at a relatively low rate of 2 percent, or in pathological fractures, as well as in reports of back pain, spinal pain, or bone pain. Likewise, we saw no differences between the two groups with respect to what the investigators themselves reported as bone density decrease, bone loss, osteopenia, osteoporosis, or hypophosphatemia.

We looked also at the median change from baseline in fasting serum lipids, and we noticed that there was an overall trend to decrease in fasting cholesterol and LDL in both arms, but the magnitude of the decrease from baseline was greater for F/TDF. We also noted that there was a slight increase from baseline in fasting triglycerides with F/TAF.

However, it's important to note that we saw no differences in the median change from baseline for the ratio of total cholesterol to HDL, either within groups or between groups. That said, the F/TAF group had consistently higher incidence of graded laboratory abnormalities related to total

cholesterol, LDL, or triglycerides, across all toxicity levels.

Lastly, we conducted a categorical analysis of the shifts from baseline based on LDL categories as adapted from the NIH's National Cholesterol Education program. As shown here, we found that a greater proportion of subjects in the F/TAF group had worsening LDL category at week 48 compared to the F/TDF group, 17 versus 10 percent. And conversely, a greater proportion of subjects in the F/TDF group had improvement in the LDL category compared to F/TAF, 40 versus 28 percent, respectively.

These findings did not translate into any major differences between the two groups with respect to adverse events, clinical adverse events, such as the cerebrovascular or cardiovascular events, which were very low in the trial anyway. That said, while the proportion of subjects who were on lipid-modifying agents at study entry was balanced between the two arms, a slightly greater proportion of subjects in the F/TAF arm initiated

these agents during the study at 2 percent versus 1 percent for the F/TDF arm.

In summary, again, both F/TAF and F/TDF were both safe and well tolerated. Differences between the groups were observed for various indices, namely changes from baseline in renal biomarkers, bone mineral density on DEXA scans, and fasting serum lipids, consistent with previous trials that compare TAF to TDF. In general, F/TAF and F/TDF had similar adverse event profiles, including low rates of serious adverse events or adverse events leading to drug discontinuation.

I'll now turn to our discussion of the indication for PrEP in cisgender women, but before that, we acknowledged that conducting a trial in women for a PrEP indication is challenging. As you know, previous clinical trials in women have demonstrated variable efficacy of oral F/TDF, mostly driven by adherence it seems. As such, FDA recommends superior designs whenever possible for trials in women because determination of a noninferiority margin is not readily feasible.

In this application, two extrapolation strategies are proposed. One is the extrapolation of F/TAF efficacy from MSM in the DISCOVER trial to support indication in cisgender women. For this, one must demonstrate comparable systemic exposures between men and cisgender women, including tenofovir and TAF concentrations in plasma, as well as tenofovir diphosphate concentrations in the PBMCs.

The second approach is to extrapolate efficacy from F/TDF to support F/TAF in women. And as you've heard, this approach makes use of a published EC_{90} value of 40 femtomole per million PBMCs as derived from the iPrEx trial of F/TDF in MSM. For this approach, one must demonstrate comparable or higher tenofovir diphosphate concentrations in systemic PK but also in cervical vaginal tissue with TAF relative to TDF.

With respect to the first approach, we don't expect that there's going to be any clinically relevant differences in the PK of emtricitabine, or TAF, or PBMC-associated tenofovir diphosphate

between men and women. However, for reasons that have been discussed already, matching systemic drug exposures alone may not suffice because of the unknown contribution of mucosal tissue concentrations to PrEP efficacy.

For the second approach, where we tried to extrapolate efficacy of F/TDF to support F/TAF, while there's some overlap with the prior approach regarding systemic drug exposures, for this approach, the applicant has cited 40 femtomole of tenofovir diphosphate per million PBMCs as a threshold, or EC_{90} value, for PrEP efficacy.

The two things to consider here, as you've heard, this threshold concentration was associated with adherence to 3 to 4 doses of F/TDF per week, specifically in MSM from the iPrEx trial. Also, this concentration has not been validated as a PK surrogate for tenofovir-based PrEP efficacy for all populations.

The concern with relying on this PBMC threshold concentration is that it may not accurately reflect the drug concentrations at the

tissue level. For example, we know that with F/TDF, with multiple dosing, we can achieve this threshold concentration of 40 femtomoles per million PBMCs in a matter of days, about 3 days. And we know that this concentration in PBMCs correlates to a rectal tissue concentration that is greater than the 100 femtomoles per milligram or significantly greater than the lower limit of quantification.

In contrast, a single dose of F/TAF can reach this PBMC concentration of 40 femtomoles in a matter of hours, but the vaginal tissue concentration can be reported as below the level of quantification. In both scenarios, we have achieved this threshold concentration that's being proposed as a surrogate in PBMCs with diverse results in relevant tissue concentrations.

The more conservative approach is to try to match PK, both systemic and tissue, to support an extrapolation of F/TDF efficacy in cisgender women to F/TAF in the same population. For the systemic part of this extrapolation approach, we already

know that TAF achieves higher levels of tenofovir diphosphate in PBMCs, so we can check that off.

With regards to the tissue concentrations, we know that single-dose TAF or TDF results in concentrations that are mostly below the level of quantification in tissue. What we don't know is whether multiple dosing with TAF or TDF achieves different results at the tissue level. And to that end, data from an external study in healthy female volunteers, study A15-137, was submitted to support this latter part of the extrapolation.

This is the study design for study A15-137. It was conducted in two parts, including a single dose and multiple dose part where subjects were treated for 14 days with F/TAF or F/TDF. We're going to focus only on the approved doses for F/TAF and F/TDF.

Multiple samples were collected for PK and plasma, PBMC, rectal and cervical vaginal fluid, as well as tissue biopsies, and we're going to focus on the results for the rectal cervical and vaginal tissue biopsies here, and in particular the

evaluations for tenofovir diphosphate concentrations.

I will also note one thing about this particular study design is that each woman contributed cervical vaginal tissue samples at only one given time point, and that's because tissue samples were collected at different clinical sites at different time points. Rectal tissues were collected 4 hours post dose following 14-day administration. Cervical vaginal tissues were collected at 4 hours post-dose following single-dose administration, as well as 4, 24, and 48 hours following 14-day administration.

The measurement in this study were tissue homogenates, and assuming a tissue density of 1 gram per mL, final sample concentrations in the lower limit of quantitation of 0.3 nanograms per mL were converted to fmol/grams for tenofovir diphosphate.

Here are the results that we obtained. Following single-dose administration of F/TAF or F/TDF, 83 percent of vaginal tissue samples were

below the lower limit of quantitation, or BLQ, at 4 hours. Following multiple doses of F/TAF or F/TDF, a significant proportion of tissue PK samples were also BLQ.

In vaginal tissues, tenofovir diphosphate concentrations were higher for oral F/TAF dosing compared to F/TDF only at 4 hours post-dose, but they were mostly unquantifiable at 24 and 48 hours. It is unclear if this isolated finding at 4 hours translates to comparable or higher tenofovir diphosphate concentrations in vaginal tissues beyond 4 hours after multiple dose administration.

This table represents the results from the multiple dose part of the study. It's a busy study, so I'll try to walk you through it. If you look at the first row, the 4-hour row and at the column for F/TDF, you'll see that 62 percent of vaginal tissue samples in the F/TDF arm were below the level of quantification. In contrast, none of the tissues in the F/TAF arm were BLQ. Correspondingly, a median tenofovir diphosphate concentration was calculated at 151 femtomoles per

milligram.

Similar results were seen with cervical tissue biopsies, and as for the rectal tissue, the results confirmed the previous reports that dosing with oral F/TDF results in higher tenofovir diphosphate concentrations in rectal tissue compared to F/TAF dosing.

However, for 24 hours and 48 hours, the majority of the tissue samples for the vaginal and cervical tissues were below the level of quantification, and we were not able to determine a median tenofovir diphosphate level for these tissues with any degree of confidence.

In conclusion, F/TAF and F/TDF afford similar protection against sexual acquisition of HIV-1 infection in MSM and transgender women at substantial risk. Both F/TAF and F/TDF are safe and well tolerated. F/TAF dosing results in smaller changes or improvements from baseline in biomarkers of proteinuria and bone mineral density compared to F/TDF, but with less favorable lipid changes. No major differences were noted with

respect to the side effect profile during the course of this study.

However, clinical data regarding the use of F/TAF for PrEP in cisgender women are lacking. Robust tenofovir diphosphate concentration data in the female genital tract are lacking. This application proposes a PrEP indication in cisgender women based on extrapolation of efficacy data via tenofovir diphosphate concentrations and peripheral blood mononuclear cells. However, the relative importance of mucosal tissue versus systemic drug concentrations to PrEP efficacy remains unknown.

That concludes my presentation, and I'll take any clarifying questions from the committee.

Clarifying Questions

DR. BADEN: Thank you.

We will now take clarifying questions for the agency's presentation, and I think Dr. Daskalakis has the first question.

DR. DASKALAKIS: Peter, thanks for that presentation. Just a question that may also overlap with a question to the sponsor. You state

that there's evidence that TAF/FTC is effective in preventing HIV in MSM and transgender women, but we've never actually seen the transgender female data broken out in any way.

Do you have a sense of what that really looks like or is that a better question to defer to the sponsor?

DR. MIELE: What I can say, and the applicant is free to chime in, first, there was a very small proportion of transgender women enrolled. I believe about 30 percent dropped out early during the course of the trial. None of the HIV infections were seen in the transgender women. Beyond that, I can't really say too much.

DR. DASKALAKIS: And a related question, any pharmacokinetic data on tenofovir and TAF versus TDF, versus Truvada, in regards to whether any of those transwomen were using estrogen?

DR. MIELE: I will defer to the applicant as to concomitant medications being used by the transgender women in the study. We have seen reports about the effect of PrEP with feminizing

hormone therapy, TAF, but no clinical drug interaction studies have been conducted with TAF and feminizing regimens.

I don't know if our clinical pharmacology reviewer would like to discuss this topic further.

DR. ZHENG: Yes. There's no clinical drug interaction study that's being conducted with TAF and feminizing regimens, CYP-based drug interactions are likely to be minimal. However, some studies suggest that the estrogen can change phosphorylation and the phosphorylation of leukocytes and their analogs.

The study conducted with TDF in transgender women receiving feminizing regimens, the paper published recently by Dr. Cottrell, showing minimum changes in plasma tenofovir concentrations for the transgender woman and minimal changes in tenofovir diphosphate concentration in PBMC for rectal tissue as well.

The similar dATP to cisgender men, there was significantly higher dATP in rectal tissues as compared to ciswomen. We know that dATP may lower

effective concentration of tenofovir diphosphate in rectal tissues. The sample size is very small, so it seems like the study shows that the lower concentration of tenofovir diphosphate is mostly driven by the higher dATP levels in rectal tissue, but we don't have any data for TAF. I don't know if the sponsor has more to add.

DR. BADEN: One second, Dr. Daskalakis. I would ask the applicant -- this is clarifying questions to the agency. We realize the applicant has important data in that space. So if you can keep a list of these questions, then we will come back and engage your data set after we clarify with the agency.

Do you have further --

DR. DASKALAKIS: I'll hold for that.

DR. BADEN: No other follow-on. Then, Dr. Green?

DR. GREEN: This is not a follow-on.

DR. BADEN: Correct.

DR. GREEN: Thank you. If we could see your slide 46 again. I just want to make sure I

understand it. It was I think the last slide you gave in your presentation, the one that you described as complicated.

Now, my question is, simplistically for percent BLQ, you want it to be lower because that's the percentage, below the level that's quantified. It's not really telling us what level is present; it's just whether anything can be quantified or not. And if I'm looking at this correctly -- I just want to make sure I'm reading this correctly -- I see that at 4 hours that F/TAF in the vagina appears to be better than F/TDF, and in cervical tissue, it appears to be better.

Then at 24 hours, F/TAF is not as good, but neither one of them are very good in both vaginal -- and it flips because it's better in cervical, but neither one's very good. And at 48 hours, basically they all are not good. But we're also demonstrating here that F/TDF doesn't have that level of protection over time either.

So if mucosal levels are important, this slide does not demonstrate that because you're not

seeing a difference that benefits F/TDF, which already has a drug indication and has been shown to be efficacious. Is that correct?

DR. MIELE: I don't know that we can say that one is better than the other. The tissue samples are just not quantifiable, so we can't really say much of anything about that. But I agree with you that the TDF samples were also not showing much. And it may be an issue with the assay. It may be the cutoffs that we used to determine quantifiable.

Again, I don't know if the clin/pharm reviewer has any other input here.

DR. ZHENG: Backup slide with the LLQ question.

DR. HOTAKI: Can you tell me which number it is?

DR. ZHENG: Slide 79. Oh, no, slide 80.

You can see the published study used compatible units for the lower limit of quantitations, and some are using a femtomole sample or nanogram per mL, which makes it difficult

to compare assays sensitivities across studies.

In this, A15-137, we have a higher LLQ compared to other study reported. The difference in LLQ can be due to tissue biopsy size, and because it's converted from the nanogram per mL to femtomole per gram, so you have a smaller sample size, it's more possible to have the LLQ values.

Also related to the sample storages, stability, and some of those studies may not have the long-term stability data, and also recovery efficiencies, and also the assay sensitivity. So it's probably related to, also, the assay sensitivity, also has other issues.

DR. BADEN: Dr. Siberry, a follow-on?

DR. SIBERRY: Thanks very much. In thinking about this problem of understanding whether the drug levels in the genital compartment are the actual proxy for protection, have you looked at the trials where the only difference in treatment was TAF and TDF in women to see if there was any difference in plasma genital discordance and suppression?

We know that some women who are on suppressive therapy still can have HIV present in the genital tract, and that may be an additional way to get at a differential impact of TAF versus TDF in the genital compartment.

Then just a follow-on, can you comment from the agency perspective about how we should view the appropriateness of an application for a drug that intended all the while to have an indication in men and women, coming in with clinical trial data only for men with an expectation to apply to women? I'm just concerned because often women are excluded because of concerns about fetal safety and possible pregnancy and other reasons, and this feels to me like a potentially concerning precedent. Thanks.

DR. MIELE: To your first question, we have not looked at that data. You're talking about an HIV treatment. We have not looked at that data, at least I'm not aware if the company has that information, but we have not.

Second question, ideally, the agency would like to see clinical trials in the populations for

which labeling is going to be indicated. We recognize that conducting trials in women in the current landscape with Truvada approved is challenging. I think our first initial hurdle was to agree on a trial, period; and that ultimately was decided to be conducted in MSM and transgender women.

Discussions about a trial in women were had with the applicant. And again, we noticed that there were challenges and difficulties, and the agency itself was struggling with the appropriate study design to recommend for this population. But it was never really agreed upon that this particular application, the way it appeared, would support the indications that are being requested.

So at this point we're trying to work with what was submitted to see if we can justify an indication across the populations based on a study that was conducted in one particular population. But going forward, no; we're were not recommending this particular approach. And again, as Dr. Murray noted, this particular case is unique because we're

talking about basically two prodrugs or the same drug, and we have an approved drug already for Truvada in all those populations. But ordinarily we would not rely on a single trial in one population to support an indication across multiple populations.

DR. BADEN: Dr. Siberry got two questions in there, and I have two follow-ons, one for each of his questions.

Given your review of the sum total of the data, what is your impression, or the agency's impression, of a marker of protection in the vaginal compartment? Has that emerged or is that still unclear given the state of the data?

DR. MIELE: I think that remains very much unclear. I also want to emphasize that it's not a one or other. It's not necessarily mucosal tissue versus systemic. There may be a contribution of both going on here, and that's the part we don't understand.

If vaginal tissue concentrations are relevant, are they acting as the primary line of

defense, and is systemic acting as a backup? I think that was a theory that was floated by Dr. Anderson actually. But we don't know at this point. The only thing we can measure are these tissue homogenates. Some studies have looked at mononuclear cells within the vaginal tissues themselves and have had mixed results with respect to differences with the vaginal compartment and the rectal compartment. I think the field itself, at least to us, is a bit mixed or conflicted. So that first question you asked is very much unclear in my opinion.

DR. BADEN: Part of the challenge -- and other members of the committee have mentioned this, and I'll ask this of the applicant as well later -- the vaginal compartment, there are menstrual cycle issues, microbiome issues, behavioral issues that are different than other compartments, and it may be adherence or PBMC concentration that may be all that matters, or there may be an interaction with these other factors.

Trying to understand from the data available to determine if perhaps adherence is all we need, which is in part what's being suggested, still I am struck by VOICE and the other trials that did not show even results in protection, although there are explanations. It always worries me when there are lots of explanations and were asked to embrace the positive but not worry about the negative, and then assume that it should just work the way we want it to.

So I guess my question is, should we just assume the vaginal compartment is an extension of the systemic component, in this setting? And obviously, this will be asked of the applicant later, which is building on the conversation we've been having for an hour or two.

DR. MIELE: I think it would be challenging to do that given that we know that the pharmacokinetics are very different between TAF and TDF, and I think part of that difference that we see systemically may be extending to the compartments in question, for various reasons. TDF

itself may be cycling in the GI tract and achieve a high protection in the rectal tissue, for example. I don't know that we can confidently say that we can extend the systemic to tell us what's going on in the vaginal tissue.

DR. BADEN: My other follow-on I will take in a minute. I will continue to follow on, on this line of questioning.

Dr. Ofotokun?

DR. OFOTOKUN: Kind of along this line of discussion was the significance of the time for achieving protective concentration. That was different for TDF, for different populations. It was different for men and also different for women from what we saw. And I think the guidelines vary from state and different regions of the country based on this time to achieve a protective concentration for TDF.

Do we have a sense of that variability with TAF?

DR. MIELE: I'll say this. I think the guidelines are being conservative because of this

uncertainty around the role of tissue concentration. I think CDC has presented the data for prescribers to be aware of, and then some state guidelines have pushed that even further into actual prescribing recommendations.

Again, I think in the services trying to be the most conservative, for TAF, we don't have any information like that. It really depends on whether you believe that systemic PK is the driver of protection, in which case you probably don't need this lead-in time. But if you believe at all that tissue may be contributing to PrEP efficacy, I don't think we have any data to even help us with what's going on with TAF, at least in the vaginal tissue.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: These are drugs that stop viral replication; they're not disinfectants. So the applicant's very valid points that it's T cells that are the issue, is it really useful to look at drug concentrations of homogenates of biopsies, which are primarily everything but lymphocytes?

DR. MIELE: Well, in retrospect, probably not. Going into this, what we had were these single reports out there that were surprising I think to the community that TAF was acting so differently in local tissue compartments. And it's probably what drove us to be conservative and request a clinical trial to begin with.

If it had been established that systemic PK were the main driver, we probably didn't need the DISCOVER trial and 5,000 men. But there was a fair amount of uncertainty, as I've tried to describe to you, both in the literature and in the guidelines, so the trial was conducted.

Now, I will say this. Granted, rectal tissue concentrations with TAF are lower compared to TDF, and the DISCOVER trial shows comparable efficacy results regardless, but we don't know what the minimum concentration would be. It may be that whatever concentration is being achieved with TAF and rectal tissue may suffice; we don't know.

But you're right. I don't know that tissue homogenates is really the best measure to give us

valuable information at this point. I don't know.

DR. BADEN: Dr. Giordano?

DR. GIORDANO: Switching topics a little bit, you mentioned the idea that penile transmission or acquisition seemed reasonably protected against here. Did the sponsor gather data on types of sex? Is there any signal that the acquisition was more likely in men who reported anal receptive versus anal insertive, or was there so much overlap between the two in any single person that you can't distinguish that?

DR. MIELE: My impression is that within each individual, there's a variety of sexual practices such that we can't really decipher whether there was a subgroup that was strictly practicing insertive sex. I believe pretty much all of the HIV seroconverters were practicing anal receptive intercourse. But that said, some of them also had reports of insertive sex in there.

There were individuals who reported -- for the most part, insertive sex had showed up with rectal STIs. And again, all these reports are

self-reported in the patient diaries. Like I said, I don't think we have any direct evidence. Given the low number of HIV infections, and the fact that we presume that a lot of these individuals were practicing insertive sex, that the protection probably did confer to them as well.

DR. BADEN: Dr. Daskalakis, a follow-on?

DR. DASKALAKIS: Just a brief follow-up, again, for clarification on this issue. If I remember, I think about 60 something percent of the folks in the DISCOVER trial were uncircumcised. Any special circumcision signal with seroconversion?

DR. MIELE: No. It was 44 percent.

DR. DASKALAKIS: Forty-four; sorry. I knew it was high.

DR. MIELE: Yes. No, in terms of baseline characteristics and HIV infection, we didn't see any real correlation.

DR. DASKALAKIS: I do remember the confidence interval for outside the U.S. was a lot higher. Is circumcision at all involved in that?

DR. MIELE: I have to defer to our statistician if you recall anything.

DR. BADEN: Please state your name at the microphone.

DR. ZENG: Wen Zeng, statistical reviewer for this NDA. For the subgroup analysis, I think the sponsor already presented. There's no such baseline characters that have a great impact on the final result.

DR. BADEN: Follow-on? Not a follow-on, a new topic.

Dr. Daskalakis, a new topic?

DR. DASKALAKIS: Yes, just a question about a citation that you had in your briefing document is a meta-analysis by Hale et al., that compares TDF, that compares tenofovir, and Truvada versus Descovy. Then subsequently, the safety data presented talks about statistically significant margins of safety.

Are any of these, from your perspective, clinically significant?

DR. MIELE: I think in the clinical setting

probably not, but over the long term they might be. I think the current average use of PrEP at this point is 6 to 12 months.

DR. DASKALAKIS: Just again, a quick follow-up on that.

DR. MIELE: Anyway, no. We didn't see anything different between the two arms in terms of clinical events.

DR. DASKALAKIS: If you stratify the bone and kidney complications or adverse events by age, is there anything that sort of flushes out in terms of just being more common among older adults? Because there are some 60 year olds and 50 year olds in the study.

DR. MIELE: There were a small number of older participants. We didn't see any differences come up on either end of the age spectrum.

DR. DASKALAKIS: Great. Thank you.

DR. BADEN: Dr Goetz?

DR. GOETZ: My question relates to the nature of risk in the patient population and the expected rate of HIV in the patient population. I

know the study was projected at a rate of infection that was somewhat higher. I wonder if someone from the agency could run through the calculations that predict what the expected rate of HIV infection was in the absence of a prophylaxis.

Taking to the extreme, if the study is done in a low-risk patient population, of course, no infections are expected, and the two agents perform similarly. So having confidence of the projections of what the expected rate of infection is, I think is an important consideration.

DR. MIELE: Do you mean without PrEP? This wasn't a placebo-controlled trial, so to that end, I think you're asking how would this compare. I think the applicant did do a comparison to local geographic areas in the U.S. based on epidemiological data, looking at concurrent HIV incidence in MSM not on PrEP. I think there were 4 to 5 incidents per 100 person-years. At least in the U.S. population of MSM, in the geographical areas where this study was conducted, the incidence was much higher.

DR. BADEN: And the STI rate, how does that influence your thinking of being in a high-risk population?

DR. MIELE: Dr. Murray has published a meta-analysis looking at various PrEP trials, and trying to correlate the STI rate, at least for rectal gonorrhea and what the predicted HIV incidence would be, as you heard, there was actually a high amount of STIs going on in this trial. And based on the correlations that we've looked at, that should have correlated to an HIV incidence, I believe, of 6; so a much higher incidence.

DR. BADEN: Six what? Six of a thousand?

DR. MIELE: Six per hundred.

DR. BADEN: Okay. So 10-fold higher.

DR. MIELE: Much higher.

DR. BADEN: If no other follow-ons, then I have another follow-on to Dr. Siberry's earlier comment. The issue of a trial in cisgender women, you mentioned that it was hard to come up with a noninferiority margin. Can you help us understand, does that mean it's not possible or how would you

frame a -- could that have been done or what might it look like for us to understand the challenges in a more fully powered trial?

DR. MIELE: The challenge is that we have two trials that essentially showed no effect in women, VOICE and FEM-PrEP. Then we have one trial, the Partners PrEP trial. That did show statistically significant protection, the TDF2 trial I don't think was powered for efficacy but did show a point estimate that favored efficacy in women.

So when you have such divergent results from the historical trials, I think it becomes a challenge to try to come up with an NI margin. I don't know if the statisticians want to discuss this any further, but that is basically -- the main conundrum is that we would not be able to adequately construct an NI margin with such divergent variety in previous trials.

DR. BADEN: So in the MSM trans population, where we have consistent results with Truvad, then it's easier to design a trial that shows consistent

results.

DR. MIELE: Exactly.

DR. BADEN: And in cisgender women, where the data are very uneven, it's difficult to have a trial, but we should assume that it should work. I'm just trying to follow the logic that's being put before us.

DR. MIELE: I think a strict NI margin, a noninferiority trial, would be difficult to construct. That said, there might be other possible study designs such as comparisons to local HIV incidence in the population of study and the community it studied. These are novel study designs that we're grappling with ourselves in the agency, given that we have a product on the market that is highly effective.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: What about a switch study? Is that something that the FDA would consider it would be appropriate? So if we have women who are already taking Truvada for PrEP, would that be a study design that could be considered flipping half

to TAF and going forward? You may not have a high incidence rate, but at least you're comparing it to an already approved drug.

I'm curious what the agency would think if that's a study design that would work since you don't have a noninferior number.

DR. MIELE: Yes. I don't know what the comparison would be in a switch study other than safety. We haven't really considered a switch study for a registrational study.

DR. BADEN: Dr. Green?

DR. GREEN: This is a direct follow-on. You can't easily come up with a strategy to give a noninferiority study, but there's no reason to presume that if you did a head to head, that it would be superior. And it also seems like it would be unethical to do a placebo study.

So you may be telling us that we're back to the argument of the sponsor, that there's no feasible way to assess it, so we have no choice but to make a decision using extrapolation. I don't know if that's your intent to say, but I'm hearing

that at least. Tell me why that's not true.

DR. MIELE: No. I think you've hit the nail on the head. The question is how confident do we feel that an extrapolation approach would be reasonable to extend the indication. At this point, we haven't really discussed any other alternative study design, so that may still be on the table. But where we are right now is you're right. And it's not a question of whether we think this is appropriate, but whether in the absence of other supporting data, we feel confident that this might work.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: I don't seem to buy the argument that we cannot construct an inferiority margin around the data that we currently have for women because we know from looking at the data, and all the four studies in PrEP in women, the reason that those studies, where efficacy was not demonstrated was that way because of poor adherence.

So in studies where women took those drugs,

the drug was effective, and we can construct a margin around those studied. There's nothing that says that you have to include all the studies that have ever been done in order to construct an inferiority margin in the study design. I remember when the sponsor represented, they had a series of planned studies in women. So how are they planning to do that, if it's going to be impossible to have what is a sample size calculation for studies in women?

DR. MIELE: I'll answer your second part first. We have not seen any of these proposals in the agency that the applicant has proposed. We have not seen any protocols. My understanding is that these aren't going to be powered for efficacy comparisons. They may be safety demonstration projects.

To your first question, I think I'll defer to our statistician colleague about constructing an NI margin using just a select number of trials.

DR. BADEN: Please state your name.

DR. VALAPPIL: Yes. My name is Thamban

Valappil. I'm team leader for statistics. Based on the noninferiority guidance document that has been published, you need to have a clear evidence of treatment effect historically, meaning that -- especially for this population, there is no treatment effect compared to placebo. Both the studies have failed.

So unless you have a measurable treatment effect based on historical trials, you won't be able to construct a noninferiority margin. So the compliance or the adherence cannot be adjusted to be able to look at the margin if the plans have already failed.

DR. BADEN: Dr. Smith, you have a follow-on?

DR. SMITH: Yes. There's a lot of work going on to develop new agents for PrEP, for pre-exposure prophylaxis, and it's not clear to me whether you're saying that from now on, no studies will be done in women because we can't define the margin, and therefore we can't do a noninferiority trial.

The current PrEP is so effective, I don't

understand what the implications of this decision are for future trials. Given that, it may be difficult to find a high incidence population of women in the U.S. It's certainly not the case in the developing world, and I think, in fact, in the world at large, women are the largest number of new infections.

So the need for effective prevention options for women is even greater than for MSM, although not in this country. So if we're saying from now on that we'll do the studies in men and we'll do some PK studies to extrapolate to women, that doesn't sound like a good scientific approach. So I'm trying to understand the boundaries that you're drawing around this argument here and how that will apply in the future.

DR. MIELE: Yes, Dawn, we're not saying that at all. There is a path forward in terms of superiority designs. A lot of new agents that are being developed for PrEP are not necessarily once-a-day pills. The challenge here is we have two drugs that are very similar in terms of their

route of administration and their dosage.

If you're looking at long-acting agents, for example, you can do a superiority trial, so that's what we've been advocating. Again, like I said, this is a particular circumstance here that is complicated because we have two very similar products. But no, this PK extrapolation that's being proposed is not meant to be precedence setting for future trials in women at all.

DR. BADEN: We do need to remember that the business at hand is the current application. There are broader questions that I think are appropriate for us to highlight, as we've been doing, to set the stage for data in the future that are needed to make informed choices. So your points are very well taken. I'm not sure we'll resolve agency policy going forward, but I think the points have been heard.

Dr. Goetz, did you have a follow-on?

(Dr. Goetz gestures no.)

DR. BADEN: Dr. Giordano?

DR. GIORDANO: Can you clarify from the

agency's perspective how much of a study needs to be done in the U.S. versus abroad to achieve an indication?

DR. MIELE: The guidance suggests we can accept clinical data from foreign studies if the sponsor has provided a justification or rationale why that data are applicable to a U.S. population. In this case, 60 percent of the subjects were in the U.S., so I think we're covered.

I mean, it's not that preponderance of foreign data here. But for PrEP in general, for example, for women where most of these studies will be conducted ex-U.S., the mechanism of transmission of HIV and the mechanism of action for the drug should be the same regardless of the geographical populations.

DR. BADEN: Other questions for the agency about their presentation and their analyses of the data submitted?

(No response.)

DR. BADEN: If not, it is 12:20, and 12:25 is when we're supposed to take a break. I don't

think we have enough time to delve into another line of questioning, but to the applicant, I think you've heard issues around, and perhaps after we'll do the open public session, and then we'll come back to clarifying questions to the applicant.

Crisp data on the efficacy in trans and crisp data on the insertive male partner, if you have it, were some of the issues raised that I think you have the data, and it would be just great for the committee to see.

Comments around the design issue in the cisgender female, which have come up, I think would be very helpful for the committee to hear your thoughts on that. You've touched on them, but I think they're central to our discussion. Then after lunch, we'll have the open public hearing session, and then resume the discussion with the applicant and the agency, but I think the agency has finished their clarifying component.

So we will now take a break for lunch. We'll reconvene again in this room at 1:30 sharp. Please take any personal belongings you may want

with you at this time. Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, the press, or any member of the audience. Thank you.

(Whereupon, at 12:20 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:30 p.m.)

Open Public Hearing

DR. BADEN: It is now 1:30, and we shall resume. This is now the open public hearing part of the meeting.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have related to the topic of the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this

issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization that you're representing for the record.

DR. HALL: Christopher Hall, San Francisco

AIDS Foundation. Good afternoon. In my capacity as vice president of medical affairs for the San Francisco AIDS Foundation, I oversee the provision of HIV pre-exposure prophylaxis through SFAF sexual health clinic, serving populations at high risk for HIV acquisition. Sorry. My disclosures are listed in the previous slide. Thank you.

To date, these programs have prescribed Truvada for PrEP to over 5,080 individuals. I will present our position in support of the proposed supplemental NDA by Gilead Sciences for the fixed-dose combination of emtricitabine and tenofovir alafenamide, which I will hereby refer to as F/TAF for HIV PrEP.

We believe that FDA approval of F/TAF as an additional PrEP option will expand the number of individuals who will choose to use PrEP as an HIV prevention method. And furthermore, F/TAF for PrEP will allow centers like the ones we operate to enroll more clients, especially those at higher risk for HIV acquisition.

Before I continue, for transparency, I will

state that where SFAF has received programmatic support from Gilead, accounting for less than 4 percent of its total annual revenues in the last fiscal year, 3 percent of which are programmatic and 1 percent are research-related, this statement is derived in my own professional medical review in the position of the foundation leadership, and has in no way been influenced by Gilead or its staff.

SFAF enrolled 59 participants in the DISCOVER trial through May 2017. We understand that early results demonstrate a very low incidence of HIV in both treatment arms, only 7 infections in the F/TAF group and 15 in the Truvada group. Thus, we do not draw the conclusion that F/TAF is better than Truvada but agree that it is shown to be at least as good as Truvada for preventing HIV.

In addition, preliminary DISCOVER data suggests better renal and bone outcomes for those participants on F/TAF, that we agree with the interpretation that such improved outcomes are likely marginal in significance. Yet, based on remote and recent understanding of motivators for

PrEP engagement, we believe individuals at risk for HIV, including those most at risk such as black and Latino persons, may be more likely to engage with PrEP, as more agents with improved side effect profiles are available for approved use.

Additionally, F/TAF offers a PrEP alternative for those who have compromised renal function who cannot use Truvada for PrEP. As 12 percent of our PrEP patients are over 50 and thus more likely to present with comorbidities, including preexisting renal compromise or osteopenia, an agent with a marginally better side effect profile may promote engagement, and in fact be meaningfully safer.

A strategic priority of the foundation is to center its prep services on communities disproportionately faced with alarming HIV incidence rates, and this includes Black Americans. Our recent efforts enrolling such persons on PrEP have demonstrated the need for new approaches and tools.

As black and African Americans face over

3 times the rate of kidney failure in the U.S. compared to Caucasians, choice of a PrEP agent with a marginally improved renal safety profile may predispose engagement based on both real and perceived advantages.

The approval of F/TAF may also enhance programmatic capacity to provide expanded PrEP services at CBOs like ours. PrEP service delivery is affected by local and/or other structural factors such as depicted hopefully here.

Innovation of an express model of STI screening supporting clinical PrEP follow-ups, in 2018 facilitated sustained increases in our program capacity and was associated with an approximate 30 percent increase in the number of active PrEP patients.

Clinical management of PrEP patients using Truvada requires renal function and monitoring, including a baseline check and others every 3 to 6 months. In our setting, that includes confirming creatinine elevations with a secondary point of care assay, and in some cases scheduling earlier

and/or closer follow-up for those evidencing such elevations. In the last year, for example, 1 in 15 clients required additional laboratory tests and/or intensive follow-up while on Truvada.

With conventional use of F/TAF as an antiretroviral, a lower threshold of diminished renal function is tolerated before recommended discontinuation. We believe that we can project a more streamlined renal function monitoring algorithm with use of F/TAF for PrEP, and in turn an ability to follow more individuals on PrEP with decreased laboratory expenditures, less intensive lab monitoring, and fewer staff resources dedicated to closer follow-up demanded by present use of Truvada alone.

With all other circumstances held unchanged, F/TAF, if approved for use and prescribed for a portion of our PrEP patients, we project a future internal PrEP capacity increased based on these renal monitoring factors alone such that we can enroll and follow an estimated 10 to 15 percent more individuals on PrEP in the first year.

Features of U.S. PrEP programs vary, but the foundation believes that the impact of F/TAF's introduction as the second FDA-approved agent indicated for PrEP will lead to meaningfully enhanced capacity to reach more individuals in need of this proven biomedical HIV prevention intervention, especially African American, Latino individuals served by the foundation, and elsewhere. Thank you for your time and attention.

DR. BADEN: Thank you. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Stephanie Fox-Rawlings. Our center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

A new treatment to prevent HIV infection could be beneficial considering the safety concerns of the currently available PrEP treatment. However, Descovy would only provide benefit if it is at least as effective and safe as Truvada for each population for which it is indicated. Otherwise, users could be at an unnecessarily increased risk for HIV.

The DISCOVER trial found similar rates of protection against HIV infection among participants taking both drugs. While the trial seems well designed to demonstrate comparable effectiveness of these two drugs, it is still a single trial. Replication is a key to scientific evidence, and independent trials could result in different infection rates due to differences in demographic or treatment profiles of patients or other factors.

For example, study participants were more likely to be white, older, and better educated than the general U.S. population that is at risk for HIV, which is the target audience for the drug. While this population may be consistent with the

people who are currently using Truvada, there are questions about the generalizability of the data to the whole population who could consider using this drug. It is important to study the general U.S. population that is at risk for HIV.

The study also found improvements for biomarkers related to kidney health and bone density, suggesting that this was safer than Truvada, however, this is only relevant if it translates into clinically meaningful difference in the number of adverse events related to kidneys or bone fractures, which were similar in both treatment groups in the clinical trial.

The trial suggests that the benefits outweigh the risks for men who have sex with men. However, the benefit-risk ratio was less clear for transgender women. This is due in part to the relatively low number of transgender women in the trial, the high dropout rate, and the lack of subgroup analysis. If FDA is considering approving Descovy for transgender women, then the efficacy and safety of the drug for transgender women should

be analyzed.

This is especially important given the recent finding that feminizing hormone therapy can interact with PrEP drugs. Similarly, there is insufficient evidence that the drug is effective and safe for PrEP for cisgendered women or adolescents.

There are too many unanswered questions regarding the levels of drug achieved, and relevant tissues, and the amount needed in these tissues to consider extrapolation for PrEP for use for cisgendered women and girls.

Similarly, the benefits and the risks for adolescent boys differ from that of men and should be considered separately. Clinical trials demonstrating effectiveness and safety for cisgendered women and adolescents are needed if the FDA is considering approval for them.

We understand the desire to provide a new PrEP treatment indicated for a broad population, especially when a new treatment may be expected to have fewer risks for kidneys and bone density.

However, it is inappropriate and potentially dangerous to approve this drug for subgroups of patients that haven't been adequately studied. The FDA law requires substantial evidence that benefits outweigh the risks for each subpopulation, and the new indication would include. Thank you.

DR. BADEN: Thank you. Will speaker number 3 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MS. JOHNSON: Thank you so much. My name is Jeremiah Johnson. I'm the HIV project director at Treatment Action Group in New York. We appreciate that this hearing is being held today. Considering how centrally Gilead has controlled this entire process around TAF development, all the way from delaying it for a decade when they purported safety and preventive benefits for this medication; all the way to centrally controlling the DISCOVER trial without adequate participation of community; all the way to rushing us through this regulatory process, we believe it is extremely important that

this regulatory agency and the community be given time to have a transparent discussion about this, and for us to take control of this process again, and away from an applicant that has a vested interest in maintaining a $2 billion a year market in biomedical prevention in the U.S.

You may be familiar with TAG's work on hepatitis C and tuberculosis as well. That's a little bit about us. Within my 6 remaining minutes, I'm going to go over three main points in a small amount of time, so please pay attention. To start, we're going to be talking about what we've been talking about a lot here today in terms of representation within DISCOVER and within the broader body of evidence that we have as part of this sNDA discussion today.

We have a number of concerns about Gilead's active campaign against its own product, Truvada, and what will be generic TDF/FTC PrEP within the next year, and overstatement of efficacy and safety benefits of Descovy compared to that, and have a general discussion about the lack of transparency

in this whole process and a rushed process when these involve important discussions that clearly the community was not adequately consulted on early on in the process.

I won't go into this slide too much. Obviously, the trial participants within the DISCOVER trial do not represent the broader epidemic that we see in the United States and around the world. With 84 percent of trial participants being white and 99 percent being cisgender men, and only 74 participants identifying as transgender women, clearly we are not seeing a body of evidence that is reflective of all populations that need to be considered in terms of efficacy, safety, and effectiveness for scale up of a new prevention option.

Right now, you're hearing here at this podium, and there's a lot of discussion online right now, there's a lot of debate amongst community advocates about what does this data mean and what should we be advocating for considering that we don't have sufficient data? And for no

good reason do we have insufficient data.

Some of us believe that we have to continue to advocate for an indication for cisgender women because we don't believe that the company sees it as beneficial to their bottom line to do the follow-up efficacy research in order to get an indication for cisgender women. And if we miss out on this opportunity, then there will be PrEPs for different populations, and that's clearly a problem.

But at the same time, we're concerned that we're sending a message. Dr. Smith's comment earlier was well taken that we're sending a message that if we don't do adequate research within these populations, that you don't have to do that, and you can get a broader indication anyway, and that's an enormous problem.

So it's up to the FDA here today and going forward in this discussion whether you believe that the information and the evidence presented thus far is indicative of a broader indication or a narrow indication. But what must be clear is that

cisgender women cannot be left behind; neither can any of the populations that have been left behind in this entire process.

If it is not approved with a broad indication, there must be a guarantee and there must be requirements that the company continues to fund efficacy, effectiveness, and safety studies within cisgender women so that they are not left behind in this process.

If it is approved, it needs to be contingent upon open-label studies that continue to give us more information for that population. That is essential, and it must happen, and this regulatory body needs to make up for the deficit of actions that took place earlier in this process. We also need to see that for all of the communities that are highly prioritized within our broader epidemic work but were not prioritized within this research.

In terms of efficacy, DISCOVER was a noninferiority trial. We are very aware that Gilead is trying to paint Descovy as a superior option in terms of efficacy. That is not borne out

in the evidence, and it stands to sabotage scaling up of generic TDF/FTC next year, and to generally sabotage Truvada's scale up for individuals who are already stably avoiding HIV infection on that regimen when there is no medical or efficacy related reason for them to switch over.

They're also trying desperately to, even in this room today, boldly assert that it is a safer option when in fact we do not see clinically different outcomes in the DISCOVER trial, and in fact they continue to downplay statistically significant increases in weight and challenging issues around lipids that certainly indicate that it is not necessarily a safer option.

It is important that this regulatory body operate with the highest level of scrutiny with the labeling, with the marketing, and with the educational materials that come out of the applicant should an indication be provided for Descovy as PrEP.

Just quickly, these are slides that of course Gilead will not be presenting today, but we

saw from the DISCOVER trial that there was a statistically significant increase in weight in the TAF arm. And of course in terms of treatment, we are seeing a disproportionate impact on weight within cisgender women and individuals of African descent, which further stresses the need for additional research in those populations considering that the DISCOVER trial was not representative of these populations.

Ultimately, we have to ask what is the rush in this entire situation. There's not one peer-reviewed publication that has come out of the DISCOVER trial. There is little transparency. Today, we are just starting to see some of the information from the trial. And all of this is coming after a decade of delaying TAF development. We are frustrated as community members that Gilead continues to centrally control this process, the FDA does not, and that community has not been adequately involved.

So going forward, this body needs to send a clear signal that any manufacturer engaging in the

field of biomedical prevention research must do a better job. They actually have to adhere to GPP; they actually have to work with community from the start; and they actually have to allow this regulatory body to come up with a robust research protocol that covers all populations and not just their bottom line.

So with that, I will close in just saying that we require robust postmarketing research following this discussion today, that the labeling and all materials need to be under high scrutiny, and that we need a clear message from the FDA that this process will go better in the future with future provincial modalities. Thank you.

DR. BADEN: Thank you. Will speaker number 4 step up to the podium and introduce yourself. Please state your name and any organization you're representing for the record.

MR. KRELLESTEIN: Hello. My name is James Krellestein. I am a cofounder of the PrEP4All collaboration. We are an all-volunteer group of activists who are dedicated to ensuring universal

low-cost access to HIV-1 pre-exposure prophylaxis.

I just wanted to review, before we begin -- next slide, please -- what Descovy is. Descovy of course is a co-formulation of two different drugs, tenofovir alafenamide fumarate, which was first approved back in 2015 as part of Genvoya, a fixed-dose, single-tablet regimen for HIV treatment, and emtricitabine, which was first FDA approved as Emtriva back in 2002.

One of the things that has been talked about extensively today is that tenofovir alafenamide has some alleged advantages over tenofovir disoproxil, which is that the prodrug catabolism occurs intracellularly rather than tenofovir disoproxil, which is actually metabolized primarily systemically, allowing lower plasmic exposures to tenofovir but higher levels of tenofovir diphosphate, the pharmacologically active anabolite, compared to tenofovir disoproxil, at least in PBMCs. This is alleged to convey certain safety benefits compared to TDF.

I think that one of the things that's really

important, though, to realize in this entire process is that TAF is not a new drug despite being FDA approved in 2015. In fact, Gilead first filed a patent application for TAF, claiming priority all the way back to 2000, using of course its code name at that time as GS7340. And of course, Gilead scientists published a peer-reviewed scientific journal in nucleosides, nucleotides, and nucleic acids, all the way back in 2001 regarding the metabolism of GS7340 now known as TAF.

I think the question that we should all be asking ourselves is two things. First of all, why in 2019 are we discussing an FDA application for F/TAF as PrEP? And number two, why don't we have better data on cisgender women?

Had F/TAF actually been developed when it was supposed to be developed, we would have had an F/TAF arm in iPrEx. We would have had an F/TAF arm in Partners PrEP. We would have high-quality, randomized-controlled evidence in all populations that are being sought in indication for today.

So let's go through the development of TAF,

if you would. Gilead began early phase 1 and phase 2 trials back in 2001 and 2002 and filed an IND with this agency for the development of TAF back in January of 2002. But in October 23, 2004, they, based on an internal business review, discontinued development of TAF, only on October of 2010 to restart development of TAF.

What was the reason for this stop-start approach to drug development? You don't have to look to me, you don't have to look to Jeremiah, and you don't have to look to anyone in this room to actually understand what Gilead was doing. You can look to their former CEO, Dr. John Milligan, who stated that "one of the reasons why we were concerned about developing TAF was we were trying to launch Truvada versus Epzicom at the time. And to have our own study suggesting that TDF wasn't the safest thing on the market, which it certainly was at the time, it didn't seem like the best. It didn't seem like we would have a mixed message." That was in 2011.

So as someone who takes TDF every single

day, I have to say I'm highly disturbed by the applicant's behavior to basically delay a drug that they knew was going to present at least some safety benefits compared to TDF, to protect their bottom line rather than to protect the public health, and I only wish that the FDA would share that very same feeling. But instead, the FDA rewards Gilead's decision to delay.

First of all, I was quite surprised by Dr Murray's statement that TAF is similar to TDF, or at least that it has the same active moiety as TDF considering that the FDA had granted TAF new chemical entity exclusivity in 2015, which prevents any challenges through the patent paragraph 4 process until this year. It also recommended that the USPTO give the maximum patent term adjustment allowable under U.S. law, counting the entire period of Gilead's delay as a testing phase. This will prevent Americans from accessing generic Descovy for an additional five years.

I think it is an extraordinarily disturbing precedent that the Food and Drug Administration is

rewarding the decision of a corporation to delay the development of a drug that it is now purporting is safer than TDF/FTC.

As a final note, I will say that we are placed today -- this entire committee is placed today -- in an incredibly difficult position. We are basically placed with a catch-22. Either on one hand we deny the ability for Descovy or TAF/FTC from getting a broad indication for cisgender women and other populations, and despite having no effective efficacy data for this population, or we choose to deny the extension of that indication. That, unfortunately in today's environment, would basically work to deny women the choice to make the decision of the drug that they would like to take.

I believe personally, and not representing my organization, that the right choice is to extend the indication of F/TAF to cisgender women. But I have to admit that I am incredibly disturbed by the precedent that that would set. We have to say, today and more than two decades after AIDS activists seized control of both the Food and Drug

Administration and the Centers for Disease Control and Prevention, that cisgender women get HIV.

More than 50 percent of global infections are in cisgender women, and the idea that an applicant would decide not to basically provide high-quality evidence supporting efficacy in this population is disturbing. The fact that this agency may be forced to grant a broad indication with no efficacy data is also disturbing, and this can never happen again.

I want to make that incredibly clear. Cisgender women, transgender women, transgender people, men who have sex with men, all of us deserve -- that medical technologies that are scaling up to fight one of the deadliest pandemics of our time, they deserve high-quality evidence, and we should never again encourage companies to delay the development of innovative technologies, and we should never allow them, once again, to not provide high-quality evidence for these very important technologies. Thank you.

DR. BADEN: Thank you. Will speaker number

5 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

DR. GIPSON: Hello. June Gipson, CEO of my Brother's Keeper in Open Arms Health Care Center located in Jackson, Mississippi. My Brother's Keeper is a community-based organization with a mission to reduce health disparities throughout the United States by enhancing the health and wellbeing of minorities and marginalized populations through the leadership in public and community health practices, collaboration, and partnerships.

We do it through an array of programs and services, including our center for community-based programs, and we also have a center for research evaluation and policy change. One of our most prominent centers is going to be Open Arms Health Care Center. That's our primary healthcare clinic.

Open Arms Health Care Center is an innovative, holistic, primary healthcare clinic that offers preventive clinical mental health services to underserved, uninsured,

underrepresented populations with an emphasis on the LGBT population. We utilize a community-based model that's a community health team led approach to provide services to our clients that optimizes their healthcare. We provide an array of services, including women's health, family planning, men's health, PrEP, HIV care, mental health, preventive screenings, transportation, and emergency food assistance.

When you look at our HIV and PrEP in Mississippi, we've struggled, but we've been able to accomplish some things. If you look at our linkage for HIV testing and linkage to care, we're either exceeding or we're meeting the national goals. However, we continue to struggle in retention and care and viral suppression.

When you look at our PrEP data, this is data from Open Arms Health Care Center. This data is of particular interest because we provide 75 percent of all the PrEP in the state of Mississippi. As you can tell, it's sparse. We are not hitting the entire state. You have one red spot in the center

that really optimizes and says who we're reaching, so we have more to do. There are multiple reasons why we aren't able to do this in Mississippi. We've done assessments with our patients and our staff, and of course there's a lack of access. That's a prevalent thing; it's around the country.

We also have a stigma. Stigma exists in every form of HIV care that we provide. There's also some other concerns that have come up throughout our assessments with our patients. Not only is there a low perception of risk -- and you would think in Mississippi that that wouldn't be the thing, but it is -- but there's also a concern about side effects.

When you live in a state like Mississippi, side effects are huge because we are already existing with so many other negative health outcomes. When we see the commercials that talk about the benefits of the medication and how wonderful they are, and that last 15 seconds when they run through all of the side effects, that's what we hear. And I hear it in particular when you

speak about Truvada because my dad is on dialysis. My uncle is on dialysis. My cousin's on dialysis. So we're living the side effects, and we need a safer option.

We need a safer option for no other reason that we have gone through enough. We have high diabetes rates, high blood pressure rates, kidney failure; you name it, we have it, and all of this combined with HIV. We need Descovy for PrEP so we can increase utilization. If we gave pills free to everyone, that's access, but access is not indicative of utilization.

So we need to have a safer option for our community, and particularly with African Americans. Again, we live these health disparities. We live these side effects. And with women in particular who may have a low perception of risk, it seems as if we're taking Truvada, we're trading illnesses. I get rid of one just to get a another? That's not something that we want.

Particularly for adolescents, and I'm going to include parents with our adolescents, parents

generally want the best for their children. And they really don't want to think about their kids having sex, but we know that that's a real thing. But if they see the advertisements for Truvada, and they see the side effects, it gives an impression that they're going to expose their children to something that's going to give them a lifelong problem.

When you're in the state of Mississippi, you see your family in a dialysis clinic. If you ever have an opportunity come and visit, stop by a dialysis clinic. You'll see that it's filled with African Americans.

As it relates to adolescence, I actually have a call tomorrow with a parent. Her 16-year-old son came to us. He tested positive for syphilis and chlamydia. We put him on PrEP. She called a month later wanting to take him off of PrEP because she's so concerned with the health issues and the side effects associated with PrEP. Now, you and I, we understand the correlation between syphilis and HIV, but that's not her

reality. That's not her perception. And we all live within our perception because that's our true reality. So I will like for Descovy to be approved for PrEP for utilization broadly between African American women and adolescents.

DR. BADEN: Thank you. Will speaker number 6 please step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MR. MYERS: Good afternoon. I'm Kirk Myers of Abounding Prosperity in Dallas, Texas. I am the founder and chief executive officer of an HIV and AIDS prevention agency in Dallas, Texas. The mission of my organization is to provide services that address health, social, and economic disparities among Black Americans with an emphasis on the GBTQ community and their families.

I'm also a black man who has sex with men, MSM, and who is living with HIV for over 26 years. Through my lived experiences and managing my own disease, and the leadership experience of managing my agency, dedicated to decreasing new incidence of

HIV and AIDS via various prevention programs, I know the delays and deliberations that are surrounding the prompt approval of Descovy for the proposed use of PrEP for black women, MSMs, and trans individuals is out of sync with our real-world reality.

For me, the simple language that best captures the reality among my people, especially those black women, MSMs, and trans individuals, is overwhelmed by the social, economic, and health disparities that they confront daily. So while some people have privilege on their side for time-consuming contemplation over the prompt approval of Descovy for the proposed use of HIV as PrEP, my community makes immediate choices on a day-to-day basis that ultimately could result in the acquisition or spread of HIV-AIDS.

Therefore, I urge the prompt approval of Descovy for the proposed use of HIV PrEP because it is right to give black women, MSMs, and trans people the option to make a safer effective choice on a daily basis to protect their lives as they go

about their business as usual. Whether their business is at the level where I work as the CEO or the street level of a sex worker, I will be standing as an authentic voice to compel the advisory community to consider the fact that I have immediate access to those who would benefit from Descovy for the proposed use of HIV prevention.

I have organized community forums, focus groups, and one-on-one individual level interventions to speak with authority that this drug is wanted. The young women and gay men who confide in me have expressed receptivity to a drug that has the potential to protect them from HIV-AIDS with lower side effects.

Finally, if anything is right at this historical moment in HIV prevention efforts, it is options to go beyond the past practice of normalizing the majority and ignoring the pressing needs of the minority. The right thing to do is to empower black women, MSMs, and trans individuals with the additional tools on a daily basis that are purposefully designed to protect public health.

Without this option, expediency, desperation, and ignorance will continue to drive up the statistics of new incidence of HIV and AIDS

With all due respect, I am asking the advisory committee members to join me in doing the right thing and assist on the prompt approval of Descovy for the proposed use of HIV-based prevention on my intimate relationships with MSM and transgender individuals, who expect me to speak out and share our testimony. This is the right step.

Furthermore, we implore that this drug be approved not just in gay men and transwomen, but women need this drug, and it will not be in the interest of public health to have this drug approved without including women, and to then be further stigmatizing by being looked at as a gay drug. Everyone deserves the same choices of prevention options as the rest of us.

Now, as a black man living with HIV here in America

for the past 26 years, there has been this divide

between black gay men and black women, and when we look at our options, this is the best option for all of us possible. I'm not a scientist. I didn't have all the beautiful slides and all those things to compel you to do anything, but I can tell you from the grassroots level and at the street level that this drug is needed. And again, if we only approve it for one indication, it's going to create further stigma that we do not need. Thank you.

DR. BADEN: Thank you. Will speaker number 7 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. WARREN: Good afternoon. My name is Mitchell Warren, and I'm the executive director of AVAC, a New York-based global, nonprofit organization focused on accelerating the development and delivery of new prevention options. We take no money from any pharmaceutical companies, including from Gilead Sciences, although I should note I was a member without any compensation of the Independent Data Committee of the DISCOVER trial.

I stood here, as some of you in this room did as well, seven years ago, and the task was easy. The data was robust, the evidence was clear, and I'm delighted that that committee then, and the FDA shortly thereafter, followed the evidence and approved TDF/FTC for oral PrEP for all populations.

I wished the task were as easy today. There, while the evidence was clear, today we sit in somewhat of an evidence-free zone, at least in some areas as has been well discussed today. It's a dynamic space and one that I hope we don't return to ever again, and I have some thoughts about that toward the end. But the data are the data, and we must act on that most urgent data point presented, and that is an epidemic that continues in multiple places, in multiple populations. And what we do today matters, not just in the United States, but particularly for women at great risk of HIV infection in Africa.

I recognize full well that that is outside of the purview of the FDA and certainly of this committee. Your job is to look at safety and

efficacy for the United States. That said, decisions made in this room today, recommendations made in this room, decisions made subsequently by the FDA, will resonate and influence the global response. And I realize that's a heavy burden, but one that is real.

I'm going to take just a few minutes to go through the two questions that you have on the table, F/TAF for PrEP for men and transgender women, first and foremost. It is very clear to me and to AVAC, the organization I lead, that the data presented in the application does indeed support a noninferiority claim for F/TAF compared to F/TDF for oral PrEP for gay men and transgender women.

I emphasize that as noninferiority. The DISCOVER trial was set out to design for noninferiority, and it certainly met that task. I think that's a very important point not only as you make your vote today in the committee, but as the FDA works around the labeling with Gilead, that this be very clearly registered as a noninferior oral PrEP option.

Any claims of superiority I think are unfounded. Yes, there's a different safety profile, and we saw data today that made it seem both safer on some level but concerns in others with lipid and weight gain. But we need to be very clear so there is no confusion to PrEP users today on TDF/FTC, or PrEP users of tomorrow that we are somehow promoting one as a safer and more effective drug. This is a noninferior oral PrEP option, and I support that wholeheartedly, but all labeling must be consistent with that and be strongly enforced.

In terms of the second question you all will consider, it's perhaps the more challenging in so many respects, and that is F/TAF for cisgender women. It is extremely unfortunate that similar safety and efficacy data for F/TAF were not collected in an efficacy trial. We can spend a lot of our time Monday morning quarterbacking why that was and why decisions were made.

I would argue that the best time to debate that is not sitting in an FDA hearing to consider a drug approval. Those should've been open

conversations we had with the company, with the FDA, and with community groups far and wide to discuss the best pathway for product development. I do trust that that is the case, and I think Dr. Murray in his introductory comment described that for next generation new chemical entity PrEP agents. That is not a change; that what we discussed today is not creating a new status quo. We do have to recognize that this is a tenofovir prodrug and tenofovir-based prep, and I use my comments in that regard.

If F/TAF is not extended to include cisgender women, the one group, the only group that will suffer and pay the price for that decision are women at risk of HIV infection. The FDA won't suffer, Gilead will not suffer, and other agencies will not suffer. That said, we have to always be clear that safety and efficacy matter.

Based on the data presented today, and I should say in addition, not taking money from pharmaceutical companies. I am not a statistician, a trialist, an ethicist, or scientist of any type.

I'm an advocate. But I will say that based on the data presented here, recognizing the systemic levels as monitored in a range of studies both for the safety study presented, although less robust than we would like, as well as the treatment studies, there's a very clear rationale for F/TAF to work as well as F/TDF in women.

I believe that that is critical to approve. That said, I believe that that PrEP indication needs to come with an incredibly strong, robust, and enforceable postmarketing surveillance, research agenda, and a risk evaluation mitigation strategy that makes it very clear that over the next 12 to 24 months, Gilead will be responsible for collecting, in collaboration with other research groups, the relevant data for safety and effectiveness.

As well discussed here, efficacy of PrEP in women is hard to measure currently with oral prep; not impossible, but hard to do. Let us focus on effectiveness, and let us ensure that an FDA-enforced postmarketing surveillance in REMs

ensures that we have that data.

I will say, too, in our work, in Africa particularly, and has been reported in a number of studies, including work that we have done, that pill size does matter. It is one of the leading reasons that women in programs in Africa talk about not continuing with F/TDF. While again, I realize Africa is not in the purview of this committee or of the FDA, your decision will matter, and a smaller drug, not necessarily safer or more effective, but a smaller drug will be of enormous benefit.

I want to emphasize again in closing that the education prescriber information and supportive materials that are part of any package going forward with F/TAF need to be heavily monitored by the FDA, and not just between the FDA and Gilead but with community input; not tokenistically, but in an active way to ensure that the language used to describe this indication as a noninferior product for all populations is clearly described, clearly enforced, and robustly done.

So we do urge the committee to approve for all populations F/TAF for PrEP. We do urge the committee to consider the consequences of you voting no, which would send a signal of delay and distrust of the research community in a product development, and at the same time committing together that we are not changing the rules for future products of new PrEP agents, that we ensure that we have better conversations earlier in the process so the products coming to this committee and to the FDA are done with the most robust and complete package possible. Thank you very much.

Clarifying Questions (continued)

DR. BADEN: Thank you.

Once again, the open public hearing speakers have presented us with incredibly powerful insights in the challenge at hand before us, and we thank all of the speakers for sharing your thoughts and convictions and insights in balancing this very difficult problem.

The open public hearing portion of this meeting is now concluded and we'll no longer take

comments from the audience. We'll now turn our attention back to the business at hand, which is evaluating the data presented before us, and we will continue with our clarifying activities with the applicant.

Prior to the applicant presenting some of the follow-up, I just had one clarifying question to the agency, which is adolescents, as I look at all the materials we've received, seems to be defined by a way to greater than or equal to 35 kilograms, and that is not how I've always thought of adolescence. So I just want to know if there's an age parameter there or simply a weight parameter.

(Laughter.)

DR. BADEN: Is it 15 to 17 and of sufficient weight or is it down to 10, or down to 5? I just want to know are there any parameters around the adolescent category?

DR. MURRAY: I think we're sticking with weight. It becomes tricky to decide what age one should be starting to use.

DR. BADEN: So could it be 10 then?

DR. MURRAY: Well --

DR. BADEN: If it's purely weight, then I guess it could be a big 10 year old, could be 36 kilos.

DR. MURRAY: We know the safety and how to dose down to 35 kilograms, and exactly when a physician or a person who's of adolescent age should consider it is probably up to them. And when you put an age in there, it kind of boxes you in, with a lot of respect.

DR. BADEN: Is Truvada 15? I thought Truvada was 15 to 17, or is that purely weight based? It's purely weight based.

DR. MURRAY: Weight based.

DR. BADEN: Okay. Well, thank you for the -- I just wanted to make sure I was reading weight as the determinant and not other factors.

So back to the applicant, who wanted to clarify some of the concepts from this morning that needed your input, and then we will come back to the many questions we have on the list from the

panel members.

DR. BRAINARD: Thank you. We have four clarifying answers to prior questions. The first is around the data for Descovy in vaginal tissue, and I'd like to just walk through what the available data are, so everyone has a clear understanding of the data in the literature.

Slide 1 up, please. There have been three different studies of Descovy in vaginal tissue. One was a single-dose study of Descovy, and in the discussion of that manuscript, they compared those results with another study that the same group had conducted several years prior with Truvada.

The second study was done with a single dose of Descovy and Truvada within the same study. The third study was done by the same group and was multiple doses of Descovy and Truvada looking at vaginal tissue levels.

Slide 2 up, please. Here are the results from those studies. In the first study, looking at Descovy vaginal tissue levels following a single dose of Descovy, the tissue levels of AUC was

reported as 132,098. This was compared in a cross-study comparison to the Truvada levels, which were noted to be 1.3 to 1.8-fold higher than those with Descovy.

The second study that was done with a single dose of Truvada or Descovy in the same trial demonstrated that after 4 hours, all of the samples with Truvada were below the limit of quantification, and 69 percent of the samples with Descovy were below the limit of quantification. The conclusion from that was that multiple dose data are needed.

In the setting of multiple doses, which is indeed the more relevant setting to assess tissue levels for a daily administered drug, 4 hours after dosing of Descovy or Truvada, levels were 2.6-fold higher with Descovy as compared to Truvada. FDA presented these data in their presentation. At 24 hours and 48 hours after dosing stopped, there were comparable and low levels between Descovy and Truvada in the vaginal tissue.

I'd like to now put these vaginal tissue

data into context with what we know about the rectal tissue data. Slide 1 up, please. The vaginal tissue are just now a graphical representation of the data I showed you at the 4-hour time point in the table, where you can see that Descovy achieves slightly higher levels than Truvada 4 hours after dosing.

As compared to rectal tissue levels, the first thing to note is that Truvada achieves about 10-fold higher level than Descovy in the rectal tissue. It's also relevant to note that the rectal tissue levels with Truvada are somewhat of an outlier as compared to the vaginal tissue levels with both Descovy and Truvada, and the rectal tissue with Descovy.

This has been hypothesized to be related to the low bioavailability of Truvada, and the fact that there may be drug delivered directly through the GI tract to the rectal tissue with Truvada. That's done so to a lesser extent with Descovy, which has higher bioavailability. This is a hypothesis without clinical or scientific proof.

Nevertheless, what we know about Truvada is that despite the lower levels in the vaginal tissue as compared to the rectal tissue levels with Truvada, Truvada for PrEP is highly an equally efficacious in men and women. So these lower levels of vaginal tissue nevertheless correlate to having efficacy in the setting of Truvada for PrEP use in women.

Similarly, what we now know with the DISCOVER trial is that despite having 10-fold lower levels of tenofovir diphosphate in the rectal tissue as compared to Truvada, both drugs demonstrated that they were highly effective and Descovy was noninferior to Truvada at preventing HIV acquisition. These data contribute to the increasing body of understanding that systemic drug levels are what's driving efficacy, and efficacy is not related to particularly homogenate tissue levels.

I can keep going to the other issues or we can stop for comments, Dr Baden.

DR. BADEN: Thank you. Your point's well

taken. Since this is such an important issue, comments from the committee to better understand these data since these bridging data are a critical element.

DR. DODD: Lori Dodd, the statistician. One of the concerns I have looking at these data is they're extremely small numbers, and the box plots you're seeing are really the interquartile range as opposed to some confidence intervals. So I need some help understanding how generalizable these results are to the larger population. I'm unable to do that based on the data presented.

DR. BRAINARD: In terms of the generalizability, all tissue-level studies that have been conducted have generally been in less than 10 participants for group, occasionally somewhere between 10 and 15. This is just related to the invasive nature of conducting these studies and the requirements for a biopsy.

In addition, we haven't seen any data looking at tissue-level data in prevention studies because, of course, taking biopsies in the setting

of individuals who are at risk for HIV infection could actually increase their risk. So those data are not available, nor are they likely to be generated.

I would agree that the data are variable and that there are not a large amount of data. Nevertheless, when we think about what these data mean in the setting of a high amount of clinical data around the efficacy of Truvada for PrEP in both men and women, those data can provide reassurance.

DR. DODD: A little more clarity would help, too, then. How is it that states are coming up with guidelines on the amount of time needed to obtain maximum intracellular concentrations and pushing in that direction when we're only able to get 14 participants from this study? I might also ask if it would be appropriate to ask the agency to comment on this as well.

DR. BADEN: Yes.

DR. BRAINARD: During the lunch break, we tried to track down the data that actually were

behind the timeline recommendation around 20 days, and the data really come back to very sparse tissue data, and there are no data that connect to 20 days.

One study showed that when assessing vaginal tissue levels and rectal tissue levels over time, it seemed that at the 10-day time period, there were stable and steady-state levels within the rectal tissue obtained with Truvada, whereas in the vaginal tissue, levels were still seen to be increasing. It seems like that is the basis for the extrapolation to 20 days required for prevention. But this has never been validated, and we don't know of any clinical data to speak to the time to protection for women.

DR. BADEN: Would you like the agency to comment if anyone is aware of the basis for those recommendations?

DR. DODD: And also if they can comment on their understanding of the uncertainty associated with the concentrations in the tissues given the small numbers.

DR. MIELE: Right. We actually have concerns about the reliability of that data because of the inconsistency and the small numbers, and the differences in methodology. But that's all we have right now, and the extrapolation approach is what's being proposed.

As to the time to achieve protection, I don't believe the CDC has a recommendation in that regard. What they're stating is the time to achieve maximum concentrations. Some state guidelines have interpreted that to mean protective levels, which kind of makes sense. But I agree that I don't know that the data are very robust to that extent, and these are very conservative measures.

We have not introduced any of that to the labeling, for example. We have not reviewed any of that data because as it stands right now, PrEP is meant to be used in combination with safer sex practices, so it's sort of counter-productive or counter-intuitive to suggest a lead-in period when you could come off condoms for example.

So we have not entertained that and we have not really reviewed that data, but I was pointing it out that that concern about the differential distribution is out there, and it's guiding some of these recommendations that are being put out there by states.

DR. BADEN: Do you have another follow-on, Dr. Dodd?

DR. DODD: Just one final comment, and I don't know if one of the statisticians who've looked at the concentration data could comment. But when I hear a number like a 10-fold increase in the tissue concentrations. That can tend to stick in everybody's mind, but we have to understand the uncertainty associated with that.

Has the confidence interval been estimated so that we don't get hung up on that number or something like that? I think this actually is a pretty important to point. I'll leave it at that, but I just want to make that as a final point.

DR. ZHENG: This is Jenny from FDA. The numbers we have for tissues normally were small

numbers and presented as median quartiles because a lot of below limit of quantitation was observed in those tissue concentrations, so there are some limitations.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: Mine is just a minor clarification about the method. These tissue concentrations are generated in the rectal and the vagina. Can you confirm or clarify to me whether the vagina data, is it a biopsy of the vagina tissue, or is this CVL, or aspirate, or swab? How were they -- I know they are different sometimes when you look at those different compartments as opposed to rectal drug concentration.

DR. BRAINARD: There are a range of methodologies used for these compartments studies, and cervical vaginal lavage is often a method where tissue or cells are washed from the cervix, and sometimes with or without scraping. The data that I shared with you are biopsy data.

Slide 1 up, please. This slide provides a very high level schematic of how these tissue

levels are measured. Whether it's in the rectum or in the vagina, forceps are used to take biopsies. Generally with rectal tissue, more biopsies are taken than with vaginal sampling, where it's generally limited to 1 to 2.

These biopsies consist predominantly of epithelial cells and fibroblasts, which make up the majority of the tissue and point to some of the limitations of the sampling. Also contained within that biopsy will be a variety of immune cells, including relevant CD-4 T cells, but also macrophages, B cells, neutrophils, NK cells, and dendritic cells.

That tissue block is incubated with enzymes in order to break up the cells because the tenofovir diphosphate only exists inside cells. So it's released from the cells through enzymes, and then generally the amount of tenofovir diphosphate is quantified using mass spec. So the total tenofovir diphosphate level that is reported is the tenofovir diphosphate across all of these different cell types, recognizing that the predominant cells

that are contributing to these levels are epithelial cells and fibroblasts.

It's been hypothesized that part of the reason those vaginal tissue levels drop off at 24 hours and 48 hours, and why there are so many BLQ measurements at those time periods is because epithelial cells have a more rapid turnover, and therefore tenofovir diphosphate within the epithelial cells, which are representing a higher proportion of contribution to the levels, are turning over and are no longer having tenofovir diphosphate at the 24-hour and 48-hour time point. That's just a hypothesis.

DR. BADEN: Thank you very much. Please continue with the other follow-ons from this morning.

DR. BRAINARD: Dr. Daskalakis asked about transgender women. There were 74 transgender women enrolled in the DISCOVER trial. None of those participants acquired HIV infection. There was also a question about gender-affirming hormone use, and 53 of the 74 transwomen reported using

gender-affirming hormones. We did look at the subset of those participants who had PK sampling down at the week 4 time point, and found that there was no difference in tenofovir diphosphate levels within that population.

Slide 2 up, please. This slide just shows data on the 18 women who were part of the substudy that had tenofovir diphosphate levels within PBMCs measured at week 4. And you can see that there trough concentration of tenofovir diphosphate is similar to what was seen in the MSM population, despite being on gender-affirming hormones.

DR. BADEN: Thank you. Any questions? I think these are fairly clear. Thank you. Continue.

DR. BRAINARD: The third issue was providing some additional information about insertive anal intercourse, and I'll ask Dr. Moupali Das to speak to that.

DR. DAS: Just to remind everyone, the eligibility criteria for the DISCOVER trial were in two parts. The first piece was requiring two

episodes of condomless anal sex with more than one unique partner in the past 12 weeks prior to enrollment, or the second criteria was evidence of rectal gonorrhea, rectal chlamydia or syphilis in the past six months, past 24 weeks. A high proportion of people in the study, as you saw, reported condomless anal sex.

We're going to share the data with you of the people reporting condomless insertive anal intercourse in terms of number of partners at screening prior to baseline. Slide 2 up. The mean number of insertive anal intercourse partners was 4, which is the same as the report of condomless anal intercourse partners. There were no differences between arms. All the people who are infected in this study, the 22 people who acquired HIV, had data and biologic evidence of condomless anal intercourse.

DR. BADEN: Just to clarify, so I'm understanding these data and what's implied, do you have data on men who were insertive but not receptive? So purely insertive, and what degree of

transmission occurred in that population?

DR. BRAINARD: We don't have data on people who were purely insertive, but the criteria for eligibility in the study required evidence of receptive anal intercourse that was unprotected. There was no infections -- all the people who were infected had evidence of receptive anal intercourse.

DR. BADEN: Follow-on questions or clarifications for this?

(No response.)

DR. BADEN: Okay. Please continue.

DR. BRAINARD: The last topic I'd like to just proactively follow up is the question about study design issues in ciswomen. As has been pointed out by panelists, community members, and FDA, there are challenges with conducting a clinical trial in women, a superiority study for 2 oral drugs that are tenofovir prodrugs as infeasible, and a placebo-controlled trial is not going to be ethical given Truvada is effective in women.

We talked a little bit about noninferiority and the challenges around establishing a noninferiority margin and FDA's perspective on the inability to construct a noninferiority margin because of the lack of consistency. We did look at taking the effect from the two most effective randomized clinical trials in women Partners PrEP, which was one of the registrational studies for Truvada, and then the Bangkok study, which was actually a study in injection drug users, but, most of the HIV acquisition in women was due to sexual transmission.

So using the treatment effect from those two studies, we calculated a noninferiority margin using the same methodological approach we used for DISCOVER, and came up with a sample size of 22,000 in a high-risk population. That would take 8 to 10 years to conduct, which was part of the reason that we didn't initiate that study, particularly in the setting of the ongoing DISCOVER study.

However, we also recognize there's been a lot of discussion since 2015 about this conundrum

of what can be done to assess the efficacy of PrEP in women, and also now where we are because of the DISCOVER results and because there's highly effective active comparator in Truvada, and now Descovy, going forward in men as well.

Dr. Murray from FDA has been one of the leaders in this area. We've been participating in discussions as well as with PrEP experts, and academics, and community members. There are some novel trial design methodologies that don't fall within the standard rubric, but I'm going to ask Dr. Wulfsohn to discuss some of those approaches from a statistical standpoint.

DR. WULFSOHN: Thank you. And just to clarify, the 22,000 that Diana referred to would be a study in Africa, so you're dealing with a high incidence rate of 4 per hundred person-years. In order to find the best noninferiority design, we also selected 2 of the 5 women studies which had the most benefit from Truvada. So we've cherry picked the two studies to try and help us reduce the sample size, and the lowest we can get it to is

22,000.

Now we're certainly open to more innovative ideas. And fortunately for us, Jeff Murray gave a great talk at IAS a week ago, and we're very receptive to some of the ideas that Jeff proposed, and I'd like to go through some of these in terms of how a woman's study could look. All of these are our proposals from Jeff, so I won't mention his name anymore.

It was proposed that there should be at least two placebo anchors in order to interpret a woman study. The two that come to mind would be, firstly, an epidemiologic assessment of the placebo incidence. We would envisage a study in Africa where that would be known based on current epidemiologic data, what the incidence is in women not on antiviral protection.

The second approach to estimate a placebo incidence could be based on the screening period from the study. Knowing how long it was from the last test to beginning treatment, that being the risk period, we could look at the subset of women

who are not on Truvada and assess the incidence. And that would be a reference, placebo incidence.

The other thing that was proposed in order to assess whether a PrEP drug is effective is that it should lower the incidence by 5 to 10-fold. The idea came from oral contraceptives, where oral contraceptives actually lower the incidence about 40-fold, but we're trying to be realistic.

Just for reference, if you look at the DISCOVER study where, granted, the adherence was very high, we're estimating that Truvada lowered the incidence by 10- to 20-fold based on two different ways of estimating the placebo incidence, and Descovy lowered the incidence by 20- to 40-fold. So these are both effective agents.

I'd like to bring up slide number 1, which is the noninferiority study we were talking about. But just with reference to these five studies, the two best studies, Partners PrEP and the Bangkok study, which had the lowest risk ratio, in Partners PrEP, we're lowering incidence 3-fold, and in Bangkok, we're lowering incidence 5-fold. These

are just the point estimates.

I would also add that in our own demonstration project where we've got a lot of real-world data in women, our estimate is that we're lowering incidence approximately 5-fold based on observing an incidence of 0.8 per hundred person-years, largely from cohorts in Africa where you'd expect of incidence of 4 per hundred person-years.

The 5-fold is as far as we are currently getting with current adherence rates. It's potentially possible to improve adherence and get greater effect sizes, but clearly the metric for what constitutes good enough efficacy will need to be tailored to the population and adherence that we're getting.

Another criteria, which is an extra criteria, not a different option, is that the incidence rate in the experimental arm should be no more than 0.5 higher than the active control, which would be Truvada, and that seems somewhat reasonable.

Another separate approach was proposed, and that is to look at the adherence subset of a study. So in DISCOVER, if you look at the individuals who are taking 2 or more tablets per week, we're only seeing 2 infections, one in each arm. So we are observing an incidence of less than 1 in a thousand in adherence subjects. And it was proposed that that threshold of 1 in a thousand is a reasonable measure of what constitutes an effective agent.

These are all good ideas and very innovative creative approaches that we can leverage and work with the FDA on to try and design a woman's study that answers the efficacy question, and we're committed to doing this.

DR. BADEN: Thank you. If FEM-PrEP and VOICE in the placebo groups had 5 per hundred person-years, I'm having trouble understanding how you come to a 22,000 person study, when if we look at the DISCOVER, which had a 1 per hundred person-years, you have a 5-fold increased event rate, yet a 3-fold increase in sample size? I'm having trouble understanding.

DR. WULFSOHN: Slide number 1 up. The main thing that's driving up the sample size is the weaker performance of Truvada in these women studies. In the design of DISCOVER, we estimated, based on the three historical controls, that we would lower incidence 5-fold. Here, when you pool these two best studies, you're lowering incidence 3-fold. So it becomes a lot harder to retain 50 percent of a weak effect.

DR. BADEN: I see your point. Still, I'm concerned with the assumptions, but I see your point.

Other questions? Please, Dr. Goetz?

DR. GOETZ: I want to come back to what you just said, the weaker performance of Truvada in these women. Are you stating that irrespective of adherence?

DR. WULFSOHN: No.

DR. GOETZ: And it comes back to Dr. Baden's question, then, as to why the sample size must be so large. Are you projecting that the women you will enroll will be non-adherent?

DR. WULFSOHN: Our interpretation of the data is that adherence is a primary driver of efficacy. As you've seen presented today, there are several thousand women who've been, uh, given PrEP and over a hundred thousand men who've been given PrEP. And if you look at the literature, there's a total of 6 case reports of individuals getting infected while on treatment.

So it's highly unusual to get infected while on adequate treatment or with adherence and that's why the threshold for what constitutes good enough is you need to have less than one in a thousand individuals getting infected, because that's what the current drugs can deliver.

DR. BADEN: Dr. Giordano?

DR. GIORDANO: But then, why did the DISCOVER study work?

(Laughter.)

DR. BADEN: It's a circular problem we're dealing with.

DR. GIORDANO: Because you expected a 10-fold higher rate of HIV than you saw in both

arms. The adherence was extremely high, higher than was across the board in the previous studies, and yet you ended up with a noninferior drug, statistically proven noninferior drug in this population. I don't get it.

DR. WULFSOHN: My understanding is that if you're perfectly adherent to both Truvada or Descovy, there's no advantage to one or the other drug from an efficacy point of view. That's a hypothesis. In the data from Truvada, and similar for Descovy, we're seeing 1 and 2 and a half thousand approximately infections in individuals who are adherent; to find a DBS that's done every 3 months, showing adequate drug levels.

On the other end of the spectrum, if you stop taking the drug completely, there's no difference between what the drug can provide you because it's not providing you any benefit. So the benefits, to the extent there is a benefit, is in the middle, the individuals who are not fully adherent but are taking some drug, and the PK properties of the drug lead us to believe that, at

least from the PBMC levels, that there could be an advantage to the efficacy with Descovy.

These data are somewhat suggestive, an unproven advantage. We don't have enough data to say even in that subset there's an advantage, and certainly the study overall hasn't shown superiority, but that's a hypothesis that can be tested in the future as well.

DR. BADEN: Dr. Walker, you had a question?

DR. WALKER: Yes, and it may not correlate to the discussion that's going on at hand. And forgive me if you have mentioned this. It's been a lot of information that's been presented here. But I just wanted to know, could you go back and let us know some information about these baseline demographics and exactly how the sites were selected? I'm just curious to know, especially within the U.S., knowing that HIV is not evenly distributed amongst states and regions.

So I'm just curious to know how your sites were selected, the 94 sites, and if you could just kind of give me some details on the states, rural,

urban, and if that led to the disproportion of African Americans in this study.

DR. BRAINARD: I'll ask Dr McCallister to come and describe our site selection process. While he's coming to the podium, I will say that the DISCOVER study enrolled 9 percent overall African American subjects. Within the U.S., that proportion was 13 percent. As I believe was pointed out earlier today, the population that we enrolled into DISCOVER was largely reflective of people taking PrEP today. It was not reflective of the people who are at highest risk for new infections right now.

Slide 2 up, please. This slide shows the percentage of blacks and Hispanic and Latino individuals enrolled in the DISCOVER trial on the left as compared to the percentage of blacks and Hispanic or Latino individuals taking PrEP today in the U.S. As you can see, our proportions were similar for DISCOVER for black participants, and we enriched somewhat for participants who self-identified as Hispanic or Latino.

I'll have Dr McCallister speak to the efforts we took to enroll a diverse range of sites in the study.

DR. McCALLISTER: We did specifically seek out sites that were in high background HIV incidence areas, in the U.S., Canada, and in Europe. In so doing, we went to -- almost all of them were urban centers, and they were in hospital, in STI clinics, and health departments.

Within the U.S. population that wound up in DISCOVER, we had a large percentage that were in the northeast and southeast in particular. One of the findings that has come out of our attempt to understand what the background epidemiology was of our sites, we used CDC data to get the HIV incidence rate in these sites, and then compared it to places where DISCOVER was conducted.

Could I get slide 1 up, please. These data are incidence rates over time at 25 metropolitan statistical areas inside the United States that overlapped with DISCOVER sites. These are incidence rates in MSMs in those locations who were

not using PrEP. What you see is over time, the general incidence rate in both the DISCOVER sites as well as non-DISCOVER sites has gone down a bit, but the DISCOVER sites were in places where the incidence was higher consistently over time.

DR. BADEN: Dr. Giordano, you had a follow-on?

DR. GIORDANO: Yes. Can you clarify if that comparison was adjusted for the racial and ethnic distribution of the participants matched for what the distribution is in the MSAs, weight sampling, in essence?

DR. McCALLISTER: Right. These data on the screen are all people at risk with a CDC indication within these MSAs. However, when you do break it down racially, the numbers are very close. They range from 3.3 to 4.2.

DR. GIORDANO: I'm not sure I understand that.

(Laughter.)

DR. GIORDANO: In other words, what I'm asking is does this comparison, where you're saying

these are high-risk people in high-risk areas, yes, they're in a high-risk area, but are they from a racial and ethnic group, that is at high risk in that area? So half of the HIV in Houston is in African Americans right now. If you only enrolled white people in Houston, you would get a lower rate of HIV incidence than you would otherwise expect.

Does this adjust for that difference?

DR. McCALLISTER: It doesn't adjust -- it is inclusive of all people in these MSAs.

DR. GIORDANO: So the answer is no.

DR. McCALLISTER: It's not adjusted --

DR. GIORDANO: Thank you.

DR. McCALLISTER: -- specifically just for African Americans; that's correct. The rate in African Americans and the rate in Caucasians from these locations are very close to these numbers.

DR. GIORDANO: Am I being obtuse? Is he being obtuse? We're not communicating.

DR. BADEN: The point has been made.

DR. GIORDANO: Okay. Thank you.

DR. BADEN: Dr. Le, did you have a

follow-on?

(Dr. Le gestures no.)

DR. BADEN: Okay. Dr. Goetz, a follow on?

DR. GOETZ: Yes. I'll try to follow up on what I think is Dr. Giordano's question. You had presented data on MSA, 1 metropolitan statistical area -- I believe that's what the MSA is -- would be Houston and another one would be Boston. The MSAs from which you recruited patients on average have higher rates of HIV acquisition than other MSAs.

But I think Dr. Giordano's question is, or my question is, the patients enrolled in the study, though, are they representative of the ratio makeup of that MSA, and thus it would be predicted to have that higher rate, or were patients who were enrolled in this study be from populations of lower risk, which gets back to the whole question of what's the risk of the population enrolled and thus, the efficacy of the intervention?

DR. BRAINARD: I think what your question is driving at is how confident can we be that we were

in the right population with high risk for HIV, and to address that, I'll ask Dr. Wulfsohn to come to the podium and speak to the two ways we tried to estimate the putative or potential placebo rate to understand whether we were in the right population.

DR. WULFSOHN: Just to answer the question directly, we did an analysis where we forced the racial makeup in the MSAs to match that in DISCOVER, and the rate went down by 0.3. It was 3.8 overall in 2017, and 3.5 when you force it to match the racial makeup in DISCOVER. And we have looked at another method of assessing the placebo rate, and that's using the rectal gonorrheal approach, which I can show.

Slide 1 up. There have been 8 different cohorts within controlled trials of placebo control. Each of the 8 black dots on this graph represents a placebo cohort. What's notable is that the higher the rectal gonorrheal rate, the higher the HIV incidence rate in these placebo cohorts, and that's a linear relationship.

On this graph, we've also superimposed the

DISCOVER data, so just above 20 on the X-axis, you'll see 2 little dots, and these represent data from DISCOVER, gray for Truvada and blue for Descovy. For both arms, we have the erectile gonorrhea incidence, as well as the HIV incidence. These 2 dots with the vertical confidence intervals, which are hard to see because they're so tight, are well below what the projected placebo incidence would have been, and that gray area is the 95 percent prediction interval around the placebo rate.

DR. BADEN: Dr. Smith, did you have a follow-on?

DR. SMITH: [Inaudible - off mic].

DR. BADEN: Microphone.

DR. SMITH: I had a question about the MSA slide.

DR. BRAINARD: We'll pull that up for you; just a sec.

Could we get the MSA slide, please?

DR. SMITH: Remind me the years in which the DISCOVER trial was actually happening, '16 to '17

or '15 to '17?

DR. WULFSOHN: It started at the end of '16, and it was largely in '17 as the bulk of the follow-up.

DR. SMITH: So the incidence was falling in both sets of communities before the start of the study, and you really only have the last two time points that are presumably related to the DISCOVER trial?

DR. WULFSOHN: That's correct. If I could have the slide on the fold increase relative to placebo from Truvada, with the MSAs? When we designed the study relative to the three historical studies that were used for the design, we expected Truvada to lower incidence 5-fold. So 1.44 was expected for Truvada versus 6.96 in placebo from the three studies.

Slide 1 up. When you look at the actual data from DISCOVER, we're noticing that Truvada is lowering the incidence by actually 8.6 fold if you were to use the MSA data; that's this middle CDC estimate of the placebo rate. The placebo rate we

estimated to be 3.83 during the duration of the study versus the USA subset of DISCOVER, where the observed Truvada incidence was 0.446.

Our active control was actually substantially more active than we anticipated. Using the rectal gonorrhea, it's actually 19-fold reduction that we're seeing with our active control, Truvada. So DISCOVER was actually a better test of a new agent than we anticipated it to be.

DR. SMITH: Okay.

DR. BADEN: Dr. Dodd?

DR. DODD: Yes. Was it really a better test or was it just that the prevalence of circulating HIV in the populations tested might have been lower, and therefore exposure to HIV may have been lower? I think you made the case that their at-risk behavior was relatively high, but how do we know that the gonorrhea curves that you showed and the really low rates in the DISCOVER cohort weren't just really because there was lower exposure to HIV?

DR. WULFSOHN: If I could have the gonorrheal slide back? If you look at the lower bound of the interval around the projected -- slide 1 up. If you look at the lower bound of the interval around the HIV incidence that we projected for placebo, while we projected an incidence slightly above 6, the lower bound is slightly above 3. So even in a conservative way of looking at this, there is a big gap between how placebo would have performed relative to how these two agents are performing.

DR. BADEN: Thank you. We're close to our break, but before we go to break, which I'll shorten to 10 minutes, one last question on ciswomen. Separate from this committee's deliberation and the agency's action, what is your commitment to studies in ciswomen in terms of generating the data that are absent?

DR. BRAINARD: We're firmly committed to generating data in women. As Moupali showed in her presentation, we've got a number of studies that we're supporting, that we're hoping to initiate

within the next year. These are not traditionally powered for efficacy studies; these are clinical effectiveness studies, and they are planned to be conducted both in the U.S. as well as in high incidence settings within Africa to demonstrate the safety as well as the clinical efficacy across a broad range of populations.

In addition, we are committed to generating clinical data with Descovy for PrEP in women using one of these novel approaches if we can come to an agreement on what that approach should be. Dr. Wulfsohn walked through some of the ideas. We're in active discussions with investigators and with experts on how to best get this done, and we're committed to do it, and we're planning to incorporate the feedback that we receive from FDA and from the panelists into this decision.

DR. BADEN: So whether or not the indication is granted, you will conduct studies in ciswomen to determine the effectiveness.

DR. BRAINARD: Without a doubt.

DR. BADEN: And that's the hundred, in the

tens, hundreds, or thousands? I'm just looking for a zip code.

DR. BRAINARD: The indication allows us to go more broadly into clinical effectiveness demonstration projects, so it clearly allows us to get to a higher number and reach a higher number of women more quickly because we have endorsement from a regulatory agency that this drug is safe and effective in the population.

If we don't have an indication, we're still generating data in women, but the nature of that type of data has to be restricted until we get the endorsement from the regulatory bodies that we can then go and do these demonstration projects. So we're committed, we're going to generate data, and I think that the proportion and maybe the velocity of that data depends on where we land, but the commitment is there, and it will happen. The time period is it just depends.

DR. BADEN: Understood the constraints you have to work under.

It's 3:04. We will take a break and resume

at 3:15 sharp.

(Whereupon, at 3:04 p.m., a recess was taken.)

DR. BADEN: [Inaudible - mic off] -- before that, we need to clarify as much as we can from the applicant.

We have several committee members who still have questions from this morning. I will ask the committee members, as well as the applicant, to be as pointed as possible in the question and the response so that we can cover as much ground in the next 15-20 minutes before we have to get to discussion about the questions at hand.

I'm going to start with questions from this morning. Dr. Daskalakis, you are on the list.

(Dr. Daskalakis gestures no.)

DR. BADEN: Thank you. Dr. Green?

DR. GREEN: Yes. Thank you. I have a question that relates to the slide CC-50 from this morning, which was the forest plot looking at the different subgroups. I know there's been conversation. I thought that adolescence was part

of the populations that you were contemplating, including in your request for indication.

I wonder if you could explain, because the closest thing we have to adolescence is the age less than 25, and it's one of the only two data points on this curve that show a favoring to TBD, although not clinically significant, so maybe you could just comment on that.

DR. BRAINARD: Yes. I'll first make the point that there are wide confidence intervals around this point estimate related to the relatively small sample size as compared to the entire study design. The incidence rates within the population of participants who are less than 25 are higher than the overall incidence rates.

This is related to the relationship between younger age and lower adherence, which has been demonstrated in many PrEP studies and certainly demonstrated in the adolescent ATN study with Truvada, and reflects that those participants had lower adherence in that age bracket. However, I would point out that both Descovy and Truvada

nevertheless were highly effective and substantially lowered the risk of HIV acquisition.

DR. BADEN: Thank you. A follow-on to that, safety in the younger ones, I have learned that adolescence is defined by weight of 35 kilograms. The data you have on how low an age bound, you have data. Do you have data on 10 year olds on Truvada, 12 year olds, 20 year olds? I just want to have some sense of where we're are in the data-free zone if we may be giving it to our 10 year olds.

DR. BRAINARD: We have Truvada, Descovy, and then three other single-tablet regimens that contain Descovy, as well as multiple regimens containing Truvada, are indicated for adolescents greater than or equal to 35 kilograms. And then we also have indications in younger populations based on the data that we've generated in treatment trials.

So we have a fairly large body of evidence to suggest that the Descovy-based therapy is safe and well tolerated in these younger populations, even extending less than 35 kilograms.

DR. BADEN: When you say younger, is that from 0 to 10 years old in treatment?

DR. BRAINARD: In the setting of HIV treatment, our youngest -- I think our lowest weight indication is 25 kilograms.

DR. BADEN: Again, any labeling is going to need to take into consideration the absence of data.

DR. BRAINARD: I'm getting a signal that the age cutoff is 6 --

DR. BADEN: Six.

DR. BRAINARD: -- so down to age 6.

DR. BADEN: Okay. So you have safety data down to that obviously with indication.

Dr. Goetz, do you have a follow on?

DR. GOETZ: Not a follow-on.

DR. BADEN: So moving down, Dr. Gripshover, you have a question from this morning.

DR. GRIPSHOVER: Actually, yes. I had one question about weight, because we did see one slide from the audience earlier, too, especially in the HIV treatment world where being concerned with

obesity, they think some may be related to TAF, some also the ACE inhibitors. I think in this study they gained a kilogram in the men. It seems that sometimes women gain more weight.

So I just wondered if we have any data maybe in women on TAF outside of this if we're trying to extrapolate this to a broader population of women.

DR. BRAINARD: I'll ask Dr. Das to come in and discuss the weight gain in the DISCOVER study and place it into context around what we know from other PrEP trials. I'll also note that the data we have from our HIV treatment setting suggests that there are many factors associated with weight gain, integrase inhibitor therapy being one of them, and that's seen across different integrase inhibitors.

TAF in and of itself is not associated with weight gain. What we see in the HIV treatment space is that TDF is associated with a weight suppressive effect, and when TDF is switched to either a TAF-based regimen or a regimen without TAF that doesn't contain TDF, that can be associated with weight gain.

DR. DAS: The difference in weight in the DISCOVER study was driven by the TDF weight suppressive effect that Diana just discussed. Slide 2 up, please. We've known about the potential for Truvada to potentially suppress weight since the iPrEx trial. The USPI has weight loss as a known adverse drug reaction for Truvada, based on the iPrEx trial.

On the left-hand side, you see placebo across the top and Truvada across the bottom, and you see that with iPrEx, there was a weight loss through week 48 with Truvada and a weight gain on placebo. This is in median percent changes in weight. In DISCOVER, the Truvada arm looked very similar to the iPrEx arm with initial weight loss and a little bit of stabilization towards the end, and the Descovy arm looked very similar to the placebo.

The average placebo weight gain -- excuse me. The average amount an American age 18 to 40 gains in a year is 1 kilogram, and the placebo weight gain in the iPrEx trial and the weight gain

in the DISCOVER trial on the Descovy arm are consistent with that. Further, if we look at HPTN 077, at 41 weeks, the placebo arm also gained about 1 kilogram. The cabo arm in that trial also gained 1.1 kilogram.

So I think what we're seeing in trials that compare TDF to TAF is the TDF weight suppression or stabilization effect versus the release of that effect in switch or the lack of that effect in the TAF arm.

DR. BADEN: Thank you. Dr. Le?

DR. LE: Can you please go back to slide CC-50 that you had earlier n in the subgroup analysis of those less than 25 years? You alluded to that this may have been where the incidence rate is a little bit higher than the overall -- was perhaps due to adherence as a reason for this.

What was the adherence for that group, and was it similar to the treatment trials that you see in adolescents? I'm trying to correlate this, for younger people would we see the same trends?

DR. BRAINARD: I'll ask Dr. McCallister to

address the issue of adherence by age within the DISCOVER trial, and I will say that, overall, we've seen lower levels of adherence within studies of PrEP in adolescents and younger individuals.

That was really one of the drivers for why we didn't include adolescence in the DISCOVER trial, was because of the data suggesting that they really benefit from an increased visit frequency. They're going to benefit from increased interventions to improve adherence and have age appropriate retention and recruitment methodology.

DR. McCALLISTER: Adherence in the individuals less than age 25 was lower than in those above age 25.

Could I get the slide 1 up please? This is the pill count data that is broken down by less than 25 years on the left, 25 to 50 in the middle, and above age 50 on the right. These are, as you can see, far lower for those less than age 25.

Another way of looking at it is through the dried blood spot data, so slide 3 up, please, and we really see the same pattern in the less than 25

using the TFV diphosphate levels in RBCs. There were fewer of them in a range of 4 tablets per week or higher. Of the 22 infections in DISCOVER, 7 of them did occur in this group, and all 7 of them did not have the detectable drug levels.

DR. BADEN: Thank you. Dr. Read from earlier in the day.

DR. READ: Yes, my questions have already been addressed. Thanks.

DR. BADEN: Dr. Giordano from earlier in the day.

DR. GIORDANO: I have a question for the agency. Is it within your -- two questions actually for the agency. One is, is it within your purview to say a registrational study should include X proportion of people in Y category? In other words, let's say a certain proportion are black, African American, from U.S.. Is that something you can say or is it really up to the sponsor to design that?

DR. BIRNKRANT: We can make the recommendation, but we wouldn't want to hold up a

trial or an approval if they didn't meet what the suggested rate would have been in that certain population.

DR. GIORDANO: Another question is, this request to approve based on essentially drug level extrapolation for women, do you have other examples of when the agency has allowed that to happen? Can you give us any guidance on when that's appropriate or considered inappropriate at the agency's level to help inform the committee?

DR. BIRNKRANT: I don't think we have any other examples, based on --

DR. MURRAY: The tissue level, we extrapolate efficacy for children all the time, and we still get the safety data. So we've matched efficacy in different populations based on systemic PK. I don't think we've ever made a regulatory approval decision based on a tissue a non-systemic PK argument.

DR. BADEN: And presumably the prior decision, you inferred the correlate of protection, so to speak, an antibiotic level in blood, where

there's an understanding of what the protective moiety supposedly is.

DR. MURRAY: We've always tried that, and we've tried to match it to be as much bioequivalent -- I use that term loosely -- to the population that had the clinical data.

DR. BADEN: Yes. Dr. Goetz?

DR. GOETZ: That leads me to what I think I can call a follow-up question. I want to go back to one of the backup slides that was shown, which showed correlation between dosage inferred from PBM of red blood cell spots and protection. I think that was BU461, is what I wrote down this morning, and that was in the iPrEx study.

What I was interested in is trying to build this bridge, which may or may not be buildable. Are there similar data that are inferred based on PBMCs or RBC studies in women that correlate the same level of protection to 2 to 3 tablets per week as being the cutpoint?

DR. BRAINARD: I'll ask Dr. Anderson to address this question about the thresholds for

adherence for women and for men.

DR. ANDERSON: I would say not this level and formal analysis in women. We just don't have that yet. We do have, though, the -- if I can show O82, perhaps. There's a very recent study HPTN 082; it was in women.

Slide 2 up, please. This study is one of the very few studies in women that have collected dried blood spots or a marker where you can tell different gradients of adherence, and this study did actually collect those. They had 4 infections in this study, and none of those infections occurred at the middle or the high drug, the DBS level. They all occurred at the low level.

DR. GOETZ: So aside from this sparse data set, there are no data at your disposal that allow us to map adherence -- a proxy for taking drug based on a biological measure that correlates, in some degree, with drug levels to protection in women, and shows equivalence between the level of protection that we expected in men with that level and the level of protection demonstrated in women,

because that's the bridge that we're trying to build, I think.

DR. ANDERSON: I think these results here on the screen are consistent with what we saw. And iPrEx OLE, it's a smaller data set, but it is consistent; I would say that. And I think you had something to add.

DR. GOETZ: Wide confidence interval.

DR. BRAINARD: I would also say that in the Partners PrEP study, there was an assessment of adherence based on tenofovir blood levels. And unlike tenofovir diphosphate within red blood cells, which is an integrated assessment of adherence over 6 to 8 weeks, tenofovir plasma levels reflect dosing within the last 4 days.

This is a measurement of adherence. It's less precise, but it does offer an objective assessment. And it is referenced in the new CDC guidance as a meaningful assessment of what they call recent PrEP use, which they correlate as associated with a 90 percent protection for both men and for women. Within that case-controlled

study, Partners PrEP, where they looked at both men and women who had detectable tenofovir diphosphate levels -- I'll put slide 3 up please -- the overall efficacy was 92 percent, and in men, it was 89 percent, and in women, it was 94 percent.

So this represents a lower level of adherence than, for example, we saw in the DISCOVER trial. But nevertheless, it shows that there's no difference between men and women.

DR. BADEN: Thank you.

We've made it through the list. Are there other questions from the committee? We're not all satisfied given the nature of the data, but are there other questions that could help inform the committee in our deliberations?

(No response.)

Questions to the Committee and Discussion

DR. BADEN: If not, we'll now proceed with -- don't go yet to the questions to the committee, but thank you. We'll now proceed with the questions to the committee and panel discussions. I'd like to remind the public

observers, while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

I would like to thank Dr. Brainard and the entire Gilead team for covering an incredible amount of information. Given the size of the problem, the amount of data could never approach the magnitude of the problem. We were able to get through I think about 15 percent of the slides you had prepared. If I'm reading the lower right-hand corner correctly, you have at least 1500-1600 slides. I think we got 150 to 200 of them in front of us. So thank you for preparing the information and sharing it with us.

Now we must turn to the questions at hand. Before we move to the questions at hand, I have some guidance I would like from the agency, and if others have questions, let me know.

We're being asked -- and would be interested in the agency's guidance, too -- particularly in the cisgender women conundrum, I want to make sure I understand the problem correctly. There are

multiple studies with Truvada. At least two showed no benefit; two showed benefit. One of them led to the indication. However, these data were not strong enough to allow a determination of a study design with a noninferiority margin, yet these data are strong enough to guide us with a bridging study to lead to an indication.

Is that the position we're sort of in as we're reflecting on how to move forward with our deliberations?

DR. MURRAY: That's correct. Even though we had low efficacy in some studies, it was attributed to low or no adherence, but we think if women are adherent, that they should be 90 percent effective.

DR. BADEN: But that wasn't strong enough to set a noninferiority margin so you could have a female trial analogous to a male trial.

DR. MURRAY: Well, noninferiority studies are tricky; rely on historical data you're supposed to use as much as possible. I think the problem with noninferiority studies is you need that constancy assumption. You need to assume that what

you saw in the past is going to be repeated going forward, and for studies in Africa, we're not sure what the adherence rate is going to be, and then that really hampers our ability to do a noninferiority margin unless we did some novel way of looking at noninferiority margins, which we haven't done, Bayesian based on adherence and things that we've really never looked at.

DR. BADEN: What tools do you have if broad indications were given to mandate or require future studies versus goodwill and intent to do future studies?

DR. MURRAY: Well, obviously, I think this would be a postmarketing commitment. Requirements are for pediatric studies and for safety. This is really expanding indications, so it would fall under kind of a legal postmarketing commitment. But those studies, particularly in the HIV arena, are almost always completed, especially where they're important, like this would be, to expand the indication to women.

Anybody else want to comment on that?

(No response.)

DR. BADEN: Any other clarifying -- we have to deliberate -- sorry. Dr. Green?

DR. GREEN: So again, I'm going to be the pediatrician. On the packet that you have, it looks like the application -- again, it does include adolescents weighing at least 35 kilograms, but I noticed that neither question 1 nor question 2 addressed our opinion on adolescence.

So you're not interested in any opinions from the committee on adolescents?

DR. MURRAY: Yes, we were planning to ask that question. We were willing to extrapolate to adolescents based on what's known for PK and safety for the treatment and the fact that there's an indication in adolescence for Truvada. We're willing to kind of make that leap for the same gender in adolescence, because it's the route of transmission that we think could be the variable or acquisition.

DR. BADEN: Dr. Giordano?

DR. GIORDANO: Does an indication have to

specify sex or can it specify behavior? So approved for men who have sex with men or can it be approved for men -- but does it have to be approved for men? Do you see the distinction I'm making? Is that something within the labeling options?

DR. MURRAY: It is. Are you talking about MSM and heterosexual men, or those who have insertive intercourse with women, or men who have sex with men?

DR. GIORDANO: Before we get to that discussion, because there's no -- essentially --

DR. MURRAY: Yes. It gets a little bit tricky. But if the indication was limited just to MSM, we'd really have to think about how the indication would be worded for men in general.

DR. GIORDANO: Right.

DR. BADEN: Dr. Daskalakis?

DR. DASKALAKIS: Another labeling question. On a label, are you able to say that this drug has been studied in these populations; there's a recommendation for use in another population, but it's based on extrapolation? Is that something

that can be explicitly stated in the label?

DR. MURRAY: I think so. We do that, to a certain extent, when they describe pediatric data.

DR. BADEN: Dr. Smith, do you have a question?

DR. SMITH: Yes. Is it possible to discuss the MSM indication separate from the transgender women recommendation? Right now, they're in a single statement, and I think I have questions about one but not the others.

DR. MURRAY: Well, we didn't plan to have the question answered that way, but you might have that as a comment after your vote. But I think if we're prepared to go ahead with MSM, the agency was prepared to go ahead with the transgender women as well, realizing that you're not going to be able to do a powered study in transgendered women. There were zero seroconversions out of 74 probably indicative of some protection in and of itself in the DISCOVER trial.

DR. BADEN: But Dr. Smith, you're getting at just the power issue, given the population sizes.

DR. SMITH: Yes. I mean, if you look at the iPrEx subset analysis that had 200 transgender women defined slightly differently, there was no evidence of the impact, statistically significant evidence of protection.

So to me it's an extrapolation question. I mean, they didn't include enough transgender women in order to do a separate analysis, and now we're asking to make an indication based on the fact that it works for MSM. It was just my question.

DR. MURRAY: I think we're going to have it voted on as a package deal, and then you can explain why or why not you voted for it or not. And if that's one of the issues, you can explain that.

DR. BADEN: I think we'll vote on the questions as written, but I think your point is the guiding principle. We can then explain our concerns or our reinforcements of how we look at the different indications. After we vote, the agency finds our comments even more helpful than our vote. So it's very important that we'll vote,

which looks yes/no, but in reality, we can express different elements that we find reassuring or concerning where they should pay attention to.

I will be mindful of time, so we have about 50 minutes, and we all have been very energetic, and it's a complex arena for all the reasons discussed earlier.

Any other discussion amongst the committee before we move to the vote? Are there any aspects of the data or what would charged with that it would be helpful to discuss or clarify?

(No response.)

DR. BADEN: If not, we can move to -- I can read -- we will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing. It is a new system, so hopefully we won't get confused.

(Laughter.)

DR. BADEN: They'll continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you're unsure of your vote or you wish to change

your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we'll go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We'll continue in the same manner until all the questions have been answered.

We will now move to the first question, and I will ask if there are any questions about the question before we vote. Has the applicant provided substantial evidence of the safety and effectiveness of Descovy for pre-exposure prophylaxis, PrEP, to reduce the risk of sexually-acquired HIV-1 infection in men and transgender women who have sex with men?

If yes, provide your rationale. If no, provide your rationale and list what additional trials are needed. Please provide any additional

comments or thoughts on your vote. If yes, you can still have a rationale about studies that are needed.

So any questions about the question?

(No response.)

DR. BADEN: If not, then let's proceed to voting.

(Voting.)

DR. BADEN: I assume the voting from our online member is being handled. Okay, so that is being handled. So I'll wait until you close the --

DR. HOTAKI: For the record, the vote is 16 yes, two nos, zero abstentions, zero no votes.

DR. BADEN: We will now go around the room and state your name and your vote into the record. And if you have comments to the agency, please share them. We'll start with Dr. Goetz.

DR. GOETZ: Thank you. Matthew Goetz. I voted yes, that the DISCOVER trial supports the approval of the Descovy, et cetera. I think the word "support" is totally appropriate here because

it certainly supports the efficacy, and I use the word "efficacy" appropriately as well.

I think what is really needed to enhance this are the phase 4 trials to show the effectiveness in real-world populations that span transgender men -- I think I'm getting my phraseology right here or I mean to you -- and also in other populations and larger populations of African American men, and populations where all patients are to be fully adherent to PrEP.

The population that was tested here was gratefully a highly adherent population, and we saw a few infections. The real world I'm afraid includes individuals who are less adherent, and it's very important to demonstrate the effectiveness in other populations that may face challenges not seen in individuals who enrolled here. Certainly, you want to see long-term safety outcomes to see whether the biological signals that favor TAF lead to clinical outcomes that are favorable as well. I can go on, but I should leave my panelists to say more.

DR. BADEN: Dr. Smith?

DR. SMITH: I voted yes because I think there is substantial evidence to support an indication for men who have sex with men. I am not convinced that there's substantial evidence for transgender women, and I think that additional studies are going to be necessary, as my colleague said, to understand how this is actually used in populations that are at the highest risk of HIV acquisition and who stand to benefit from it.

Adolescents, black men and women, and transgender persons all have documented adherence problems with Truvada, generally, and I think it will be important to understand how TAF adds protection or not in those populations.

DR. BADEN: Thank you. Dr. Read?

DR. READ: I voted yes, and my comments largely have already been stated, but I think they bear repeating. I think the data provided by the applicant do support the safety and efficacy of Descovy by demonstrating noninferiority to Truvada in men who have sex with men and transgender women.

I think although there were a few infections in the trial, the high rates of STI infections and other indicators do support the high risk characterization of the study population. And further, Descovy appears to be safe as demonstrated both in DISCOVER as well as the extensive treatment experience in people living with HIV.

I do think that it has been stated throughout the course of the day that the study population enrolled in DISCOVER did not represent the populations most at risk for HIV, and therefore, if Descovy is approved for use in MSM and transgender women, the applicant should be required to collect postmarketing data on safety and effectiveness in those underrepresented populations, including transgender women, as has just been stated, as well as people of color.

I think it's important, as was raised during the public comment period, that the labeling and advertising for Descovy, if approved, should only speak to the noninferiority, not the superiority of both the effectiveness as well as the safety of

Descovy. I think it's important to note that the markers for kidney and bone toxicity were biomarkers only and did not indicate a clinical benefit. And I also think that it's important not to disregard some of the potential negative adverse events, including weight gain and lipids.

DR. DASKALAKIS: I'm Demetre Daskalakis. I also voted yes. Mirroring some of the prior comments, I think that the data presented in the DISCOVER trial are very strong for supporting the noninferiority of Descovy for pre-exposure prophylaxis in men who have sex with men. I do want to state again the importance of selling this as a noninferiority both from efficacy and safety.

I think overselling the safety here could create an environment where drug switches are done in a way that don't reflect the data and may also create significant disparities in various populations of men who have sex with men.

My expectation of this approval is that it should be marketed responsibly from the perspective of not creating these disparities and having

Truvada be a drug for poor people and Descovy be a drug for rich people, or for insured versus uninsured. So I think it's really important that we don't oversell the elements of noninferiority.

From the perspective of transgender individuals, and I'm including transwomen and transmen who have sex men on that list, I think more data are necessary. I think that in the same breath that we're going to probably discuss women, we should also discuss transwomen and transmen and the need and responsibility to actually get more robust data.

Historically, the answer it's hard to do has created a lot of disparity and mistrust of both public health and research among transgender individuals, so we need to work with strategies to go beyond that rather than to stay with that. Ultimately, then I think with the caveat of work to do in the transgender population, I stand by my vote of yes for noninferiority men who have sex with men.

DR. GIORDANO: Tom Giordano. I voted yes

largely for the reasons that have already been stated. I agree completely with the comments already made. I will comment that I am not convinced that we have enough data to say anything about transgender women.

However, I did vote yes on that, including that language, mainly because the biological similarities is anal receptive sex primarily is the risk factor. So I agree that there's sufficient evidence, that that population probably would be protected with this noninferior drug.

DR. DODD: Lori Dodd, and I voted no because the question had the term "men and transgender women," so my concern is really related to transgender women. I agree with the comments said previously, so I won't articulate further.

DR. BADEN: Dr. Walker?

DR. WALKER: Dr. Walker here. I voted no for all the reasons that were expressed. According to the CDC, more than 290,000 African Americans with stage 3 HIV have died since the inception of the HIV epidemic. As African Americans remain

disproportionately at risk for HIV, with gay and bisexual men and heterosexual women being affected more than any other race ethnicity, there was not substantial or compelling evidence to indicate the safety and effectiveness of Descovy for PrEP to reduce HIV infection among this population. So that's why I voted no.

As a public health researcher and a community advocate, and an African American heterosexual woman, I have alarming concerns regarding the safety of Descovy, as well as the sexual behaviors that will result from individuals taking this drug. There was a lost opportunity to provide data, substantial data, that is reflective of the community in which its greatly impacted by HIV. Furthermore, the data from the DISCOVER trial failed to enough data on the prevention of HIV in cisgendered women.

DR. BADEN: Thank you. Dr. Le?

DR. LE: I voted yes for this, for the reason that the drug combination has demonstrated noninferiority to Truvada and offers an alternative

for PrEP, which is critical in light of data showing that only 7 percent of CDC's estimate of 1.1 million people in the United States with PrEP indication actually received PrEP. Also, Descovy may offer potential advantages of reduced bone and renal toxicity. Despite voting yes, I do agree that we need more information on transgendered women.

DR. BADEN: Thank you. Dr. Burgess?

DR. BURGESS: Tim Burgess. I voted yes. I think that data from the DISCOVER trial met the noninferiority to Truvada, and just that, in men who have sex with men.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: Igho Ofotokun. I voted yes for the same reasons that have been expressed by my fellow committee members. I am convinced that Descovy is noninferior to Truvada, and I think it should be emphasized that this is a noninferiority study.

Even though I voted yes, I am particularly very concerned about the low number of non-white

participants in this study, and that should be noted. I think if this moves forward, the agency should strongly recommend a postmarketing study that really include all this population, especially men who have sex with men, black men who have sex with men, who are most affected by this epidemic in the U.S.

Again, I think, as has been expressed, there's not enough transgender women to be able to make a strong recommendation, but I believe, based on the data, that it will be effective. And again, this is another population that should be studied should this approval move forward.

I think we should also emphasize the side effects related to Descovy. It's sold as a safer drug. I may be safer in some aspects, but there are other aspects. For instance, the lipid profile of Descovy is definitely something that should be emphasized, and I am still concerned that the jury is not yet out on the weight gain issue with TAF. Thank you.

DR. BADEN: Thank you.

Lindsey Baden. I voted yes. We'll just highlight some key issues. The continuum of the body of evidence from the prior studies with Truvada, with DISCOVER, it's a continuous set of data that work well together and are very reassuring that in MSM, it works very well.

I share the concerns in the population studied, that's where we have the data. Transgender were a very small subset, and then other ethnic and racial backgrounds also have limited representation, so that will just have to be part of the consideration to grow the data set.

I think the weight and the lipids are not trivial issues and can become significant over years of treatment and perhaps consequence or not, but that's where data and follow up will be required.

Dr. Weina?

DR. WEINA: Peter Weina. I voted yes. I believe there is substantial evidence of the safety and effectiveness to reduce the risk of sexually-acquired HIV in the indicated population.

Ignoring all the background politics, potential gamesmanship, market pressures, whatever, this is another approved product in our toolbox that gives clinicians an option that we didn't previously have.

While no package is ever ideal for all potential patient populations, it actually was nice to see a trial that was reasonably powered given the targeted population, and in time when even more is known about it, available to all patient populations.

DR. BADEN: Dr. Green?

DR. GREEN: Michael Green. I voted yes. I thought the data as presented clearly met the criteria for noninferiority and have an equivalent, if not superior, safety profile, though the impact on lipid metabolism and weight gain might balance out the bone density and renal benefits if they are real. With the caveat that the study did not include enough transgender women to allow subset analysis, the study was generally well designed, including a large cohort and robust follow-up.

If approved, the label should clearly highlight the noninferiority performance of F/TAF and not infer superiority. Safety claims should highlight not only the potential benefits in terms of renal and bone density but also the potential increased risk related to lipid metabolism and weight gain and obesity. Thank you.

DR. BADEN: Thank you. Not yet, Dr. Gripshover. We have Dr. Lupole on the phone. Do you have?

MS. LUPOLE: [Inaudible - distortion]

DR. BADEN: We're having trouble hearing you. Now we can hear you.

MS. LUPOLE: All right. Can you hear me now? [Inaudible - distortion].

DR. BADEN: That may not be working well. Mute your computer while you speak is the advice I'm given.

MS. LUPOLE: I'm sorry. What, sir?

DR. BADEN: That sounds good. What you just did worked.

MS. LUPOLE: Okay, good. I voted yes. I

have concerns for transgender. I think more data needs to be collected, but yes is the answer to the question the way it was presented.

DR. BADEN: Thank you. Dr. Gripshover?

DR. GRIPSHOVER: I also voted yes. I believe the DISCOVER trial showed the efficacy and safety of Descovy to reduce the risk of HIV acquisition in men. I think it's a little bit of a stretch for transgender women, but I also agree it's the same biologic, at least method, of acquisition. But I think a small amount, but statistically significant improvements in bone mineral density and renal tubular function in TAF versus TDF may be important in young adults building bone and older ones losing it, or those with other comorbidities and renal function.

However, for the vast majority of people, TDF/FTC is safe, and I would not want those without access to TAF due to geography or cost to forego its benefit as PrEP, and I think we need to emphasize that this was a noninferiority study.

DR. BADEN: Dr. Siberry?

DR. SIBERRY: George Siberry. I voted yes. Like many before me, I think the trial adequately provided evidence for a claim for noninferiority as an alternative, both from an efficacy and a safe clinically meaningful safety standpoint. I'd add that the claim would include adolescence. I strongly support the use of weight without age down to 35 kilos and accept the ability to extrapolate for adolescents in that claim. Thank you.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: Yes. I agree that there was evidence of noninferiority as far as the efficacy in MSM, but that the numbers were insufficient to draw a clear conclusion about transgender women.

Nevertheless, because I think the number of variables that would have to be controlled for the number of patients that would have been required to be enrolled wouldn't really been feasible, and I agree that it may have to depend on postmarketing evaluations. But the way the question was phrased, I agree that they did provide substantial evidence

of efficacy.

DR. BADEN: Dr. Cheever?

DR. CHEEVER: Laura Cheever. I voted yes, and I think there is adequate evidence through the DISCOVER trial for noninferiority. I am disturbed that this far into the epidemic and this many clinical trials, we still can't do trials in the people most at risk in this country, representatively, and that we really do need to be looking at African Americans.

I echo other people talking about the lack of transgender women really represented in this trial. Once again, that needs to be looked at to better understand the efficacy or noninferiority in that population.

DR. BADEN: Thank you.

For question 1, it was 16 to 2, but even those who voted no, there was a large consensus in viewpoint that the data do support efficacy. However, it's in the population studied, and there was limited power in transgender and other key populations, as well as some safety signal in

weight and lipids.

Those will all have to be carefully followed and monitored in a postmarketing setting. The database expanded in the key at-risk populations, especially the transgender, and it's a noninferiority, not superiority, on either of the key issues.

Now we can move to question 2. Do the data from the DISCOVER trial, in combination with the available pharmacokinetic data and other previous HIV-1 prevention trials with Truvada in cisgender women, allow for the expansion of the DISCOVER PrEP indication to include cisgender women?

If yes, please provide your rationale. If no, please provide your rationale and list what additional studies/trials are needed. Also comment on the trial designs that would be adequate to expand the indication. Please provide any additional comments or thoughts on your vote.

Any questions about the question?

Dr. Siberry?

DR. SIBERRY: It's not simply asking whether

we would support expanding the indication, but specifically saying do we think that the data are the reason that we would expand it? Am I reading that right? Because it's a little nuance there, I think.

DR. BADEN: My read of this -- and the agency can please correct me -- is do we believe there are data establishing substantial efficacy and safety in this population, which is cisgender women, given the totality of the information provided.

Is that the intent of the question?

DR. MURRAY: Yes.

DR. BADEN: Does that answer your question?

DR. SIBERRY: Yes.

DR. BADEN: If no other questions, then let's vote.

(Voting.)

DR. HOTAKI: The online voter is being handled; all done.

One more person needs to vote, so if everyone can press theirs again.

DR. BADEN: Everyone repress your button.

(Pause.)

DR. HOTAKI: For the record, the vote is 8 yes, 10 no, zero abstention, zero no voting.

DR. BADEN: Please state your name and your vote into the record. We'll start with Dr. Cheever.

DR. CHEEVER: Laura Cheever. I voted no. I really think that the company's demonstrated difference in metabolism in TDF and TAF, and we really do not know the protective factors for PrEP, exactly how it works in the mechanisms. I know that we do know that we have differences in immunologic milieu between the vagina and the rectal mucosa, so I have real concerns there about what has been shown.

That said, I wanted to vote yes because the thought of not having this indicated for women I think will only further inhibit the implementation of PrEP among women. So from a public health perspective, I think there's probably more harm than good not approving it for this indication, but

that wasn't the question that was asked.

So that's sort of how I split that. We've talked about it all day long. The failure to implement PrEP in women is huge. We keep glossing over it and trying to just get to the adherent women and throwing out all the rest, and I think that is the wrong conversation to be having.

It's really about why women and why transgender persons in youth and what we can do to better get them to have protective effects of PrEP, and whether that's different modalities or whatever is part of that larger discussion that we weren't having today.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: I voted no because -- I'll just go through the reasons here. I think as far as the question as to what the data allowed you to conclude is what's key here. The cells that are being infected in the vagina and cervix versus those in the rectal or penile mucosa are not clearly defined.

So although virus transcytosed in the

mucosal epithelium must infect dendritic or CD-4 cells resident in all tissues, the resident target cell population at the time of exposure is the local pool of T lymphocytes. This pool is known to be relatively static, and more so in vaginal tissues than in the GI tract. They are also long-lived and replenished by local expansion.

Thus, the PK and PD in these lymphocytes may not be the same as those in the peripheral blood or other anatomic sites. We just do not know. Thus, the relative efficacy of TAF and TDF may differ between rectal and vaginal tissues and between MSM and cisgender women.

Measurements of tissue drug levels in this context is not particularly relevant. As unlike with PBMCs, the levels are not being measured primarily in cells that are infected but by rather in bulk populations of extremely heterogeneous cells from biopsies. And while there's evidence that the safety profile of TAF may be superior, particularly for long-term use, this has to be balanced against the possibility of inferior

efficacy.

In this situation, a relative lack of efficacy may translate into a currently incurable infection. Thus, one has a potential choice between long-term morbidity versus immediate risk. Nevertheless, I do not believe that we can state with scientific validity that TAF/FTC is as effective as TDF/FTC in cisgender women for PrEP. Extrapolation from one group to another is defensible if there is no scientific reason to believe that there could be pharmacokinetic or pharmacodynamic differences between the two groups.

That is not the case here, and therefore the basis for extrapolation from TDF to TAF in cisgender women is not obvious. The absence of actual clinical data in this group combined with the potential difference in the site of exposure, and other potential gender-based biological co-factors, do not allow me to recommend labeling this drug as effective in cisgender women.

I do not believe the drug should be approved or labeled without adequate evidence merely because

doing the necessary clinical studies would be challenging. The alternative is to potentially expose segments of the population who are underrepresented in studies to ineffective therapy.

DR. BADEN: Dr. Siberry?

DR. SIBERRY: George Siberry. I voted no. I think that there's good evidence of a biologic correlate of adherence. I remain unconvinced that we have a good biologic correlate for protection. For the reasons Dr. Swaminathan said, I think it is inappropriate to extrapolate to women. However, I feel like we have failed women by letting this application come in without data from women to begin with, and I fear we're failing them again by having approval for use in men and not women.

That's why I asked for that clarifying question about the question because I think these are two different things, and I would be supportive of an indication that includes women with a strong postmarketing requirement for clinical evaluation in women. Thank you.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: Hi. Barb Gripshover. I also voted no. I do not believe the data support TAF/FTC efficacy as PrEP for women, as it's not been studied in that population, and I don't think it's clear that just the level of tenofovir diphosphate in PBMCs is the sole determinant of efficacy in women at risk for cervical vaginal infections or the reasons the gentlemen have just said.

I believe there is a large unmet need of women at risk of acquiring HIV worldwide that should be able to engaged in studies to answer this question; maybe using matched geographic demographic incidence rates as a control or incidence in screening that has been suggested.

While I do not like the idea of approving a drug for a single population, as it does look effective in MSM, I also think we are obligated to base our recommendations for use of a drug based on data. Women in underserved populations deserve our best efforts to make sure drugs are effective and safe for them as well before we start recommending

it in lieu of one that has demonstrated safety and efficacy.

So if the drug is approved for MSM, then I would absolutely require a strict efficacy setting in women as part of the agreement.

DR. BADEN: Wait, Dr. Green. Dr. Lupole?

(No response.)

DR. BADEN: You're on mute if you are talking.

(No response.)

DR. BADEN: Okay. We may have lost the connection. We can try to bring Dr. Lupole on.

MS. LUPOLE: Can you hear me now?

DR. BADEN: We can hear you now.

MS. LUPOLE: Okay. Sorry about all this.

I voted no as well. The lack of data, the lack of study participants, conflicting data, it's my recommendation that the trial for this drug in cisgender women and juveniles be redesigned to examine the impact because it's clear it's not been presented to me that it would be safe and effective. Thank you.

DR. BADEN: Thank you. Dr. Green?

DR. GREEN: Michael Green. I voted yes, but I almost abstained and I almost voted no.

(Laughter.)

DR. GREEN: With regards to extension of approval to cisgender women, the key concern of the FDA appeared to have been relating to the tissue level in vagina and cervix, and that those associated with TAF were lower than TDF. Therefore, the absence of a trial in cisgender females directly to confirm efficacy, they're asking us if we can extrapolate to extend approval based on the DISCOVER population.

However, the data that was presented suggest that TDF also has low levels, both at 4 four hours, and at 24 hours, and 48 hours, and yet F/TDF carries an approval in men, women, and adolescents for pre-exposure prophylaxis against HIV and is considered effective in these populations if those taking it are compliant.

Accordingly, it's not clear that low tissue levels had any impact on the effectiveness of

Truvada, and it seems unlikely, at least to me, that it would for Descovy. Clearly, there is not a concern that intracellular levels in PBMCs would be different between men and women. We've also heard the agency state that they feel challenged by developing design for noninferiority studies, and that there's no reason to expect a positive outcome in a superiority trial, and that a comparison to placebo would be unethical.

Given these issues, I felt it was appropriate to include cisgender women in the indication, especially given the equity issues that have been discussed during this committee hearing. Having said that, it would be important to mandate postmarketing studies and this indication be undertaken by the sponsor. And if these subsequent studies did not bear out efficacy in cisgender women, that the label be modified to reflect this if not having the indication removed. Thank you.

DR. BADEN: Dr. Weina?

DR. WEINA: Peter Weina. I voted yes, but the answer is really maybe. The reality is that we

really don't have a clue which is the appropriate surrogate marker to use. Is it the tissue level? Is it potentially PBMC levels? Is it adherence that's the key? Or is it more likely something we haven't even considered yet because we haven't bothered to count it, and some revelation years from now is finally going to give us that insight?

Right now, it seems like the surrogate marker selected depends upon which opinion you'd like to have supported, and the science behind it is whichever you select, and that seems very whimsical. So I reach back to the FDA's mission statement, and the mission statement is to promote and protect the public health by helping safe and effective products reach the market in a timely manner and monitor the products for continued safety after they are in use.

This product is already out there for treatment. It's already being demanded by patients who are subjected to social media pressures, and this is only going to accelerate. I have absolutely no doubt that this is already being used

in cisgender women somewhere here in the United States, and it's not being followed.

We should follow the FDA's mission statement to get this to the market for the broadest population possible and reasonable, and then monitor the product for continued safety. Here of course, I'm referring also to the efficacy because if it doesn't work, then it's putting the users at risk.

If approved for MSM and transgender women, it's definitely going to be used either off label or on label in adolescents and in cisgender women just because of the perception of better safety. We may as well carefully guide the postmarket surveillance of this product and how well it works. Clearly, we need carefully prescribed and intensive postmarketing required trials.

DR. BADEN: Dr. Baden. I voted no. The question was do we have substantial evidence of safety and efficacy? There are no efficacy data presented, and the historical efficacy data are too strong to allow a placebo trial, but too weak to

allow a noninferiority margin. So one is choosing which pieces of data to use to say that we cannot study this population.

I share the open public hearing speakers, as well as Dr. Siberry's comments we have failed women. To be at this point and not have the data to guide decision making is a shame on all of us. I feel like Arrowsmith. "We are in a desperate situation, therefore let's do something because we can do something."

There are side effects to our interventions. Our interventions are not benefit with no risk, and the presumption that we can benefit and not have risk is also shame on us. We need to generate some data to guide the risk-benefit ratio, and the road traveled for prevention in women is uneven with high-quality large studies done. So for us to presume that the good data are the ones we should hang our hat on is presumptuous.

I think that given the mixed historical data, the absence of data with this particular agent, I cannot support an indication which has

efficacy. On the other hand, there should be a mandated study. Whether it's mandated as part of an approval or mandated in order to get approval, both can be done, but it should be mandated.

I think once there's an approval, it's impossible to undo even if there's no benefit shown. If there's no approval, then the pressure is to do the study, but then there are women at risk who don't have opportunity to access this medication. Hence, we have failed this population. But I voted no because there were no data in the population in question.

Dr. Ofotokun?

DR. OFOTOKUN: Igho Ofotokun. I voted yes. Taking a look at the data as a whole, the Descovy data and the historical data from Truvada, based on data in HIV-infected individuals who are treated with Descovy, I am convinced that the product is just as safe in men and in women, and the big question is that of the efficacy in ciswomen.

I tend to have some confidence in the pharmacokinetic data and the correlate of Truvada

efficacy. The tenofovir diphosphate correlates with protection, I seem to believe that that in itself provides strong compelling data that TAF would be just as efficacious in ciswomen.

I agree that it's a terrible failure that the agency as well as the sponsor would come to this committee with lack of data for women in this hearing. I strongly believe, like others have expressed, that there should be a mandated study to look at women, ciswomen, either as part of the approval process or before the approval of this agent.

I also believe that approving Descovy for PrEP in men who have sex with men alone would create a two-tier system. It will just accentuate this equity, the equity issue that already exist; that either you're going to approve it for indication for prep in men and women, or you're not going to move forward with it.

I think creating a two-tier prevention treatment will not be helpful, and we should remind ourselves there are more women living with HIV in

the world than there are men, and that the risk of new infection is significantly higher among women if we look at this globally.

So I will stop there, and thank you.

DR. BADEN: Thank you. Dr. Burgess?

DR. BURGESS: Tim Burgess. I voted yes, but as some others have said, I very nearly voted no and very nearly abstained. I share concerns about what we think we understand about the putative mechanism of protection depending on route of exposure.

My overarching concern was about the public health impact of an indication in one population and not in another population. Coupled with the fairly compelling articulation of levels in PBMCs as the primary, if not total component of the likely mechanism of protection, led me to vote yes. I, like others, articulate a strong recommendation for, compelled postmarketing surveillance, focusing on effectiveness in women.

DR. BADEN: Dr. Le?

DR. LE: My vote for approval in cisgender

woman was largely based on three factors: one, data pertaining to vaginal tissue and PBMC as presented earlier by Dr. Read; two, some safety data but from other studies; and three, making this drug combination available as an option for women, not just for men, despite the lack of efficacy data.

However, my vote for yes is contingent upon full commitment from the applicant to incorporate a robust package labeling, stating that efficacy and effectiveness have not been established in cisgender women with the use of this product, and that vaginal tissue penetration was low, and that the approval was based on extrapolation of existing data in other populations.

Also, the applicant should commit to conduct robust postmarketing studies to allow for us to better understand efficacy and more effectiveness, as well as incorporating safety monitoring for weight gain, renal function, and on fasting plasma lipid levels.

DR. BADEN: Thank you. Dr. Walker?

DR. WALKER: Dr. Roblena Walker. It was a strong no for me, no wavering on the fence. I'm almost highly appalled. There's about 8 women on the committee, and that the agency and the applicant would present insufficient data to support the prevention of Descovy amongst cisgendered women, or heterosexual women, or just women in general, I was highly appalled that more dedication and passion wasn't put into the study.

DR. BADEN: Dr. Dodd?

DR. DODD: So I voted no, and I was not on the fence on this, unlike the last one. My concern is about confusion or a lack of trust that might be generated by an approval that wouldn't be supported by strong science. We can't approve something just because there's a need.

I also want to commend the agency for their good discussion about surrogacy. I think this is often a confusion in reviews of studies. There are lots of reasons why a good correlate of protection may fail as a surrogate endpoint for the clinical benefit endpoint. In this case, the clinical

benefit endpoint is protection.

A correlate does not a surrogate make, and we've seen data to support PBMCs as a good marker of protection and women -- or we've not seen the data; excuse me. And I thought the agency did a good job of providing some reasonable arguments about why PBMCs may not be a good marker of a clinical benefit endpoint.

I think there probably should be both data related to the biological mechanism supporting additional surrogacy studies -- this looks like more studies on tissue concentrations -- and additionally, studies in ciswomen with an actual clinical benefit endpoint of protection.

I'm not convinced that there's not a study design out there that could be considered that would support this. I don't know that it would have to be something as large as a 20,000 participant study, but I think it's time to put some creative heads together and think of some feasible designs.

DR. BADEN: Dr. Giordano?

DR. GIORDANO: Tom Giordano. I voted no. It pains me to say that. I really wanted to vote yes because I believe there is the potential for creating two systems, and one drug for the rich, one for the poor, one for men, and one for women, I think that's a horrible precedent.

Nonetheless, the FDA's approval, to me, means we know this drug is safe and effective. I'm convinced we know this drug is safe in women, no doubt about that, but is it effective? That remains a hypothesis. And given that there's different biology involved between men and women and the acquisition of HIV in men and women, I think you need efficacy data, and it just boils down to that for me.

I think that we're in this position is absolutely horrible, but that's the position we're in. So I don't envy the agency's ultimate decision, but, to me, there is no way you can say this drug has efficacy in cisgendered women. And who's to blame for that? That's not my decision.

DR. BADEN: Dr. Daskalakis?

DR. DASKALAKIS: Demetre Daskalakis. I voted yes. I think that there are a couple of reasons. First, we have limited success with topical agents that we know of to prevent HIV, and I think we've seen data that intracellular levels of drug seem to be protective, so that in combination with what I thought was a pretty convincing explanation for the role of a PBMC level, intracellular level, and prevention made me feel that I had enough evidence to recommend that you consider approval for this drug for cisgender women.

Now, I would put the caveat that labeling would be very critical if it does come out like this, so I think it would need to be an alternative agent for women in certain clinical scenarios. And I also think that it would be important to state that there has not been an efficacy study done. Now, from the safety perspective, I agree with what everyone else has said, that I think safety has been demonstrated by other studies, and that's not really much of a debate.

I also want to say that I don't think the approval of this drug would increase PrEP uptake among women. So bottom line is that's not the problem, at least in the U.S. The size of the pill and the marginal improvement in bone and kidney outcomes, not the problem.

The problem is that patients and providers are unable to do appropriate assessment of who needs PrEP, and I'm just concerned that creating the tiered system that we may be creating if we don't approve the drug for women will create even more confusion with providers and poor advice to their female patients who are considering PrEP, so that makes me very concerned.

I think a mandatory study, no matter what, whether it is after approval or preapproval, requiring that is critical, and that needs to help answer this question about intracellular level versus mucosal level. So really good science that looks at the role of mucosal levels of tenofovir in women will be critical.

I also recommend thinking about coupling the

transgender female study with a women's study since they are women, and that probably is a better way to actually convince folks to enter the study. I bet you one reason you can't recruit a transgender study is because it says MSM, and that's not going to work.

Another thing I just want to bring up briefly is the precedent for extrapolating data. We have U.S. preventative health services recommendations that PrEP is an A recommendation, and there is a line in there that says that tenofovir could potentially be used as monotherapy to prevent PrEP in women and heterosexual males and females, and injection drug users.

I do not see us having a conversation about using a generic, cheaper agent and extrapolating that data to men who have sex with men, so we could actually pour PrEP onto the entire country and be less concerned about cost. So as we're having this conversation about an expensive new drug, I would encourage the agency to consider looking back at the Bangkok PrEP study, at TDF2, at Partners PrEP,

and ask the question, should we be asking the same thing about a drug that could cost as less as $5 a month? Thank you.

DR. BADEN: Thank you. Dr. Read?

DR. READ: Sarah Read. I voted yes, but with a lot of the same hesitations that have been expressed by the other members who voted yes. Just to be clear, I also agree that it's extremely disappointing to be in a situation in which there are no clinical efficacy data in cisgender women, a population clearly in need of more effective prevention choices and in whom much remains to be learned regarding acceptability and preferences for prevention choices. However, I felt in this case that it was reasonable to extrapolate data from the DISCOVER trials as well as previous prevention trials with Truvada.

In terms of safety, although cisgender women were not included in the DISCOVER trial, I think it's reasonable to extrapolate safety from the study participants, as well as the large experience in treatment of women with HIV. And based on

treatment experience, I think that it's unlikely that the safety profile will differ in cisgender women relative to men.

In the absence of clinical efficacy data in cisgender women and the question of the relevance of PK in different compartments being not entirely clear, extrapolation of the efficacy of cisgender women is certainly not straightforward.

Although the collective data regarding PK levels and correlation of clinical efficacy of oral PrEP contain mixed results, I think it's reasonable to extrapolate the clinical efficacy seen with Truvada and Partners PrEP in cisgender women on the basis of the data provided by the applicant, indicating higher levels of TDF diphosphate in PBMCs with F/TAF compared to Truvada.

PK data provided by the applicant on cervical vaginal tissue levels, however, is less clear given the number of samples that are unevaluable. However, it's also unclear what levels are required in this tissue. I therefore think these data should largely be disregarded.

I think it would be problematic to approve an indication in men who have sex with men alone without including women. Such a limited indication and subsequent delay in access for women for many years would be untenable and an unfair situation. Consideration, therefore, I think should be given either to the approval with a broader indication to include women or no approval at all until evidence of adequate efficacy can be achieved in that population.

If an indication to include cisgender women is approved, like others, I recommend strongly that the applicant be required to perform trials to collect both safety and effectiveness data in this population. Not only is the effectiveness important, but also the safety profile in this population needs to be further supported.

I think it's important that the company has attested and pledged that they will perform these trials, and I think it's up to the agency to require them to do so.

DR. BADEN: Thank you. Dr. Smith?

DR. SMITH: I feel like we're moving backwards from the 2012 meeting that approved Truvada, in which there was a lot of discussion and concern that we had data on African women and not on African American women. And now we don't have data on women at all. The decision has been made that we'll do the trial in MSM, and then we'll figure out what it means for women rather than studying women themselves.

I find that bad science, and that's why I voted no, but I also find it disrespectful and an issue of sort of research equity. Women deserve the same quality of data about the safety and efficacy of the drugs that they're exposed to that men get, and that's not the situation we find ourselves in at the moment.

I also think that because we have Truvada approved for women, we're not denying women access to PrEP, and it's important to remember that. What we are doing is saying that a second drug that is similar in risk and benefit is available to one population but not another, yet, based on the data

that we have. I think that's preferable to approving it, doing an efficacy study and somebody suggested maybe taking it back or modifying it if it doesn't work out as well.

That's a recipe for disaster among the African American community if we get ourselves into a situation where we're approving something and then saying, oh well, no, actually we weren't right; that didn't work, so I wouldn't even think about doing that.

I think the other thing is that even though we think about the fact that it may be hard to explain why this is for this group and not for that group, if the proper studies are done in the short term over the next three or four years to get the kinds of data that is missing, then we'll be in a position to say whatever is appropriate about women.

I think we are going to increasingly in the PrEP field have this situation of some things are for some people and other things are for other people. Whether that's the dapivirine ring, if

that becomes approved, that's surely not going to be for all populations. I know we're nervous about what that means when we suddenly have to start making decisions, but I think this is not the occasion in which that should overrule the absence of data on efficacy for women as the basis for our decision.

DR. BADEN: Dr. Goetz?

DR. GOETZ: Matthew Goetz. I did vote yes, and I think I'm like the other 8 people who voted yes. I do not hear a strong ringing endorsement from anyone of strong data. I read the statement, "allow for expansion" as a liberal statement, "allow for expansion."

I thought critically about what we know about surrogate markers, correlates of protection. I think "correlate" is the right word in many regards. The fact of the matter is that we will need a phase 4 mandated clinical trial to substantiate that this is I think an alternative, and in any guidelines, documents, that are produced by other societies, the strengths and weaknesses of

this, the conditional nature, and this is an alternative needs to be very clear.

I felt very strongly that I'm not sure that tissue markers are the surrogate either. As has been pointed out by many individuals, when we biopsy, first of all, we get very limited samples. It's not robust. Secondly, the cells that we sample are not likely the relevant cells. So we either need robust data showing across levels of different adherence, and we want everyone to be adherent of course.

Inevitably, some people are going to be less adherent, and we need to be able to correlate if we're going to substantiate in any way. PBMCs show that the correlate between PBMC and protection is similar across all the relevant risk groups, and I think that will go a long ways to demonstrating what we need to show here.

Perhaps finally -- I can go on for a lot long longer -- I think adherence is a crucial measure. What we have in this drug and the study we have in DISCOVER is a population that was

extraordinarily adherent. That's wonderful, but we need to be clear that we want to really emphasize adherence throughout. TAF may have a longer half-life than plasma in cells, but that is not to be taken as any opportunity to be less adherent; phase 4 studies absolutely mandated.

DR. BADEN: Thank you. There you have it, 8 to 10 vote. The three key principles as I hear it, because I will summarize the yes and the nos together, the correlate is unclear and perceived differently. The optics of approving for population A but not population B has many deleterious effects if done or not done. Everyone agrees there needs to be actual data.

So then the challenge -- and I'll be presumptuous, but I'll speak for the committee, and to the agency, and to the applicant -- can you please do the study as quickly as possible? And it'd be designed -- I don't accept that it's too hard, too big, too difficult.

There should be a way to do some type of study systematically in a reasonable amount of time

if there's collective will to generate data expeditiously, and that will be the best way to minimize the optics of some of the concerns raised. Many of us believe that this should work and will work, but we cannot have belief guide policy or regulatory pathway.

So that is the voting segment. We have run 15 minutes over. I would like to take 5 minutes to discuss the last question, and that will be an open discussion unless the agency advises me otherwise. The open discussion is please discuss whether the data from the DISCOVER trial are relevant to at-risk men who practice insertive vaginal sex with cisgender women.

I'll open the discussion and look for disagreement or augmentation. There are many aspects of insertive vaginal sex that have elements that are analogous to MSM in the sense of the biology of how the drug works and the nature of the exposure. We weren't able to extract out MSM with only insertive, but presumably there will be some of that in the population -- it was a large

population -- and the biology in the prior experience is such that I don't think it's unreasonable to think that it's likely to work in that population.

But I would like other comments from the committee as to if others agree that it should likely work in that population or if there are concerns as to why it may not.

DR. SWAMINATHAN: Just to make clear, we're talking about HIV, uninfected men having sex with a discordant partner, female partner.

DR. BADEN: Yes, and circumcision has not been addressed, but presumably the other preventive strategies will be maximally encouraged.

Dr. Siberry?

DR. SIBERRY: I agree with your general view that this can be extrapolated, but I do think that the data should be looked at more carefully from the DISCOVER trial. They enrolled people who had condomless anal sex, not just condomless receptive anal sex. So I think if they had collected information about practices, you may be able to

segregate those practices, predominantly insertive sex from those who didn't, look at it stratified by condoms, and see if there was a difference in the protective -- the levels of infection in the two arms.

Granted, the overall infection risks are probably lower in both arms of that group if you limit it to those, but I think we should ask for additional scrutiny of data.

DR. BADEN: And perhaps new data to actually look at that population.

DR. SIBERRY: Yes.

DR. BADEN: Dr. Gripshover?

DR. GRIPSHOVER: I'm sorry. I didn't realize there's still a vote, but I do think the fact that 44 percent were umcircumcised means that at least there was a group that had not yet even used that other protective mechanism, so that's I think helpful, too.

DR. BADEN: Dr. Weina?

DR. WEINA: Given the way the trial was enrolled, the data's just not there. So I'm not

sure that you can actually extrapolate anything from that trial.

DR. BADEN: So what is your view, then, on the applicability to men who have vaginal sex?

DR. WEINA: I think it's just like -- well, in my patient population, I have individuals that I have in my patient population that are at high risk, and in heterosexual relationships, and come to me and are actually on Truvada for preventive reasons, but the data is not really there to support it. It just makes sense based upon the data that is out there.

So there's an extrapolation because the individual is at very high risk, and everything that we can do to help prevent it is going to be something that's worthwhile as long as they're properly informed as to the risks associated with taking the medication as well.

DR. BADEN: Well, let me push you a little bit on that --

DR. WEINA: Sure.

DR. BADEN: -- in that if you have MSM who

have insertive and receptive, presumably the insertive risk would be similar to the insertive risk in non-anally receptive.

DR. WEINA: Agree.

DR. BADEN: So therefore, if data suggest that it works in that population, even those not specifically pulled out, that would be suggestive that it is likely to work in that population.

DR. WEINA: so again, just like I was talking about before, suggestive and correlates and surrogate markers and everything else are --

DR. BADEN: Although, I think it's a little different. These are human data --

DR. WEINA: True.

DR. BADEN: -- in men who are in study on drug and not getting infected.

DR. WEINA: True.

DR. BADEN: This is not extrapolating from assays that we're not completely sure what they tell us with a correlate, that we're not sure what it tells us in 5 people.

DR. WEINA: True. So given the potential

outcome of not putting the individual on Truvada, when they come to me with exceedingly high risky behavior with multiple unknown partners on a regular basis, I inform them of the risks associated with it and the potential benefits --

DR. BADEN: And the limitations of the data.

DR. WEINA: -- and allow them to make the decision.

Dr. Daskalakis?

DR. DASKALAKIS: Just fusing this issue a bit with the issue about the need for a study in women, it seems as if there's a need for another serodiscordant heterosexual study like a Partners PrEP but that uses this drug.

DR. BADEN: Although part of a challenge there is treatment as prevention.

DR. DASKALAKIS: Right, but still --

DR. BADEN: But still --

DR. DASKALAKIS: There's an environment where it's still feasible with lower edge retroviral uptake, so it wouldn't necessarily launch that study --

DR. BADEN: But generating the data makes sense.

DR. DASKALAKIS: But I think that there's other parts of the world where you can have serodiscordant couples and follow that, realizing that there will be -- that the sample size will probably have to be bigger and the effect may be smaller.

DR. WEINA: But the point is that there are parts of the world in which this could be done just like we do malaria studies in other parts of the world because we haven't got a whole lot of malaria here in the United States to get new drugs approved.

DR. BADEN: Dr. Swaminathan?

DR. SWAMINATHAN: I guess the difference to me is that there's a little bit more that you can extrapolate from. You have data in discordant couples where the woman is positive that tenofovir works, and MSM couples it works, and we have evidence that TAF works in MSM couples.

So now you're just sort of bringing in the

fourth variable or a mix of those two variables to say, well, TDF works for this situation and TAF works for this situation, and TDF also works for this situation, which is -- you can sort of extrapolate a little bit more from that, that you would expect the person who was protected by TDF in the Partners study to be protected by TAF in the future.

DR. BADEN: Dr. Goetz?

DR. GOETZ: I think another piece of supporting evidence is the incidence of gonococcal urethritis and other urethritis in the patient population, which I think was 15 to 20 percent thereabouts. So there was substantive exposure to -- evidence of insertive practices.

Yet, if I recollect the data properly, all the cases of infection were amongst those people who clearly had receptive anal intercourse. The presence of the urethritis I think is a strong piece of evidence in favor of the fact that there was risk in the patient population.

DR. BADEN: Dr. Smith?

(Dr. Smith gestures no.)

DR. BADEN: So I think that that touches on a lot of the key issues around this question. Are there any other issues the agency would like us to address?

(No response.)

DR. BADEN: If not, then I would like to thank the applicant for a tremendous amount of data being presented and entertaining a lot of discussion in a challenging area; the agency for sharing your views in the challenge here; the panel members for a robust, high energy day in covering a lot of complex issues; and the public as well for sharing your thoughts.

I'll see if the agency has any closing remarks.

DR. BIRNKRANT: Well, I, too, on behalf of our division and the agency, want to thank the committee for their thoughtful discussion and deliberations today. I also want to thank the speakers who commented during the open public hearing as well. I want to thank the company for

conducting the DISCOVER study and other pertinent research and for committing earlier in the day to conduct a trial, or trials, in women.

I also want to thank the trial participants as well. Lastly, I'd like to thank our staff for their dedication and diligence in conducting the reviews and preparing for this committee. I want to leave you with a couple thoughts before we end. Our review of this application continues. We have not made any final determinations as of today, and your comments and the discussions will greatly impact our final determination.

Lastly, I feel like we should dedicate our collective efforts to ensuring the availability of safe and effective medications for all populations so that the next time we meet, we can definitively state that the HIV incidence in the United States has substantially declined in all populations, and we are moving closer to defeating this epidemic. Thank you very much.

Adjournment

DR. BADEN: Thank you, and I will now

adjourn the meeting. Safe travels.

(Whereupon, at 4:54 p.m., the meeting was adjourned.)