CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

220018Orig1s000
220020Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 153858
Request Receipt Date	8/23/2024
Product	Lenacapavir (LEN, GS-6207)
Indication	Pre-exposure prophylaxis of HIV-1 infection
Drug Class/Mechanism of Action	HIV-1 capsid inhibitor
Sponsor	Gilead Sciences, Inc
ODE/Division	OID/DAV
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	10/22/2024

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and** will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

Lenacapavir (LEN) is being developed for the indication of pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection in at-risk adults and adolescents.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Although there have been tremendous advancements in the treatment of HIV in the past several decades, there remains no cure or vaccine for HIV, and HIV infection continues to have significant long-term health sequelae. According to the Centers for Disease Control and Prevention (CDC), in 2022 there were 31,800 new HIV diagnoses in the United States.

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

According to the Department of Health and Human Services Ending the HIV Epidemic (EHE) and the U.S. National HIV/AIDS Strategies (NHAS) initiatives, pre-exposure prophylaxis (PrEP) is an important means of reducing new HIV infections in the United States.

Currently, there are three products approved for HIV-1 PrEP: emtricitabine/tenofovir disoproxil fumarate (F/TDF, Truvada), emtricitabine/tenofovir alafenamide (F/TAF, Descovy), and long-acting injectable (LAI) cabotegravir (CAB, Apretude). F/TDF and F/TAF are oral regimens administered once daily. Following an optional oral lead-in (if chosen), CAB is administered by intramuscular (IM) injection with two monthly doses followed by IM injections every 2 months thereafter. In order to be effective in preventing HIV-1 acquisition, these products must be used correctly and consistently. Uptake of these available HIV-1 PrEP regimens in the United States has been increasing over recent years, but remains suboptimal. According to www.prepwatch.org, there are an estimated 522,769 cumulative PrEP initiations in the United States through 2024. As noted, adherence is vital to the effectiveness of PrEP. A metanalysis of HIV PrEP trials found that treatment adherence >70% was associated with greater efficacy in the reduction of new infections. Additionally, while adherence with oral PrEP is associated with decreased risk of HIV-1 infection compared with placebo, LAI CAB was associated with decreased risk of HIV-1 infection versus F/TDF in men who have sex with men (MSM) or transgender women and women at higher risk for HIV-1 infection.[3]

Lenacapavir (LEN) is the first investigational agent in a new class of antiretrovirals (ARVs) and has a pharmacokinetic (PK) profile that can support twice-yearly subcutaneous (SC) administration after initiation dosing in combination with LEN oral tablets. LEN's mechanism of action includes inhibition of HIV-1 at multiple points in the viral lifecycle, such as interfering with capsid-mediated nuclear uptake of pre-integration complexes and impairing virion production and proper capsid core formation. In May 2019, Gilead was granted a Breakthrough Therapy Designation (BTD) for LEN for the treatment of HIV-1 infection in heavily treatment experienced (HTE) patients with multi-drug resistance. In 2021, Gilead submitted a Breakthrough Therapy Designation Request (BTDR) for LEN for PrEP which was denied due to lack of clinical evidence of substantial improvement over therapies available at that time. LEN was approved December 21, 2022, for the treatment of HIV-1 infection in HTE adults with multidrug-resistant (MDR) HIV-1 infection failing their current ARV regimen due to resistance, intolerance, or safety considerations.

LAI PrEP products, like LEN, have several advantages over daily oral PrEP. Evidence from the Phase 3 HIV-1 PrEP trials for both LEN and CAB (the approved LAI PrEP product) suggest that LAI PrEP products may address adherence challenges encountered with daily oral PrEP. Topline data from the PURPOSE 1 study (GS-US-412-5624), a Phase 3, double-blind, randomized study, evaluating the safety and efficacy of twice-yearly, subcutaneous LEN for PrEP and once-daily oral F/TDF or F/TAF in more than 5,300 cisgender women and adolescent girls aged 16 to 25 across 25 sites in South Africa and three sites in Uganda, found 0 incident cases of HIV-1 infection among 2,134 women in the lenacapavir group (incidence 0.00 per 100 person-years [PY]). There were 16 incident cases among 1,068 women in the F/TDF group (incidence 1.69 per 100 PY). Though LEN was not formally compared to F/TAF, the observed HIV-1 incidence with F/TAF (2.02 per 100 PY) was similar to F/TDF. Topline data from the PURPOSE 2 study (GS-US-528-9023), a similarly designed study conducted in cisgender men (CGM), transgender women (TGW), transgender men (TGM), and gender nonbinary people who have sex with partners assigned male at birth demonstrated similar results with 2 HIV-1 infections in the LEN group (0.10 per 100 PY) compared to 9 in the F/TDF group (0.93 per 100 PY). Additionally, LAI PrEP may also provide a better option for people at risk who are concerned about stigma by eliminating the need to obtain, possess, and take pills, which could be found by sexual partners, family members, or friends.

LEN has several potential advantages over the approved LAI PrEP product CAB. First of all, it is administered every 6 months rather than every 2 months, which decreases the need for clinic visits. Although there have been no head-to-head comparisons of LEN versus CAB, this reduced dosing frequency could theoretically decrease the likelihood of missed doses. Secondly, CAB used for PrEP has the potential to compromise first-line integrase strand transfer inhibitor (INSTI)-based HIV-1 treatment regimens when HIV-1 infections occur (either in patients with undiagnosed infections who begin CAB for PrEP, as a rare PrEP failure, or in patients who previously took CAB for PrEP and have residual subtherapeutic exposures at the time of infection) due to the development of INSTI resistance. As LEN is currently only approved for the treatment of HIV-1 infection in HTE adults with MDR HIV-1 infection, and as LEN has a unique resistance profile, development of LEN resistance would not impact existing first-line HIV-1 treatment regimens.

[3] Chou R, Spencer H, Bougatsos C, et al. Pre-Exposure Prophylaxis for the Prevention of HIV Infection: A Systematic Review for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2023 Aug. (Evidence Synthesis, No. 228.)

8. Information related to endpoints used in the available clinical data:

Study GS-US-412-5624 (PURPOSE 1):

Criteria for the final efficacy analyses:

- Primary Analysis (*there is a second primary analysis unrelated to LEN to evaluate F/TAF vs background rate):
    - Endpoint: the ratio of the HIV-1 incidence (new HIV-1 infections per 100 PY of follow-up) for LEN vs background incidence rate (calculated based on recency assay).
    - The success criteria for the U.S. FDA regulatory review, per prior agreement, are if the upper bound of the 95% CI for the incidence rate ratio of the LEN arm to the background HIV-1 incidence rate (bHIV) < 0.8 with the point estimate being < 0.5 (1-sided alpha of 0.025 without any alpha-spending at the interim analysis).
- Key Secondary Analysis
    - Endpoint: the difference of the HIV-1 incidence between LEN arm and F/TDF arm.
    - The success criteria for the U.S. FDA regulatory review, per prior agreement, is to show comparability between LEN and F/TDF, is if the upper bound of the 95% CI for the incidence risk difference (LEN – F/TDF) is < 0.8/100 PY (1-sided alpha of 0.01 without any alpha-spending at the interim analysis).

Criteria for the interim analyses (which are different from the final efficacy analyses):

- Primary Analysis:
    - The success criteria for the U.S. FDA regulatory review, per prior agreement, are if the upper bound of the 95% CI for the incidence rate ratio of the LEN arm to the background HIV-1 incidence rate (bHIV) < 0.8 with the point estimate being < 0.5 (1-sided alpha of 0.0026).
- Key Secondary Analysis:
    - The success criteria for the U.S. FDA regulatory review, per prior agreement, is to show superiority of LEN over F/TDF using the rate ratio metrics (1-sided alpha of 0.0026).

Study GS-US-528-9023 (PURPOSE 2):

Criteria for the final efficacy analyses:

- Primary Analysis:
    - Endpoint: the ratio of the HIV-1 incidence (new HIV infections per 100 PY of follow-up) for LEN arm vs background incidence rate (calculated based on recency assay).
    - The success criteria for the U.S. FDA regulatory review, per prior agreement, is if the upper bound of the 95% CI for the incidence rate ratio of the LEN arm to bHIV < 0.8 with the point estimate being < 0.5 (1-sided alpha of 0.025 without any alpha-spending at the interim analysis).

- Key Secondary Analysis:
    - Endpoint: the difference of the HIV-1 incidence between LEN arm and F/TDF arm.
    - The success criteria for the U.S. FDA regulatory review, per prior agreement, is to show comparability between LEN and F/TDF, is if the upper bound of the 95% CI for the incidence risk difference (LEN - F/TDF) is <0.8/100 PY (1-sided alpha of 0.025 without any alpha-spending at the interim analysis).

Criteria for the interim analyses (which are different from the final efficacy analyses):

- Primary Analysis:
    - The success criteria for the U.S. FDA regulatory review, per prior agreement, are if the upper bound of the 95% CI for the incidence rate ratio of the LEN arm to the background HIV-1 incidence rate (bHIV) < 0.8 with the point estimate being < 0.5 (1-sided alpha of 0.0026).
- Key Secondary Analysis:
    - The success criteria for the U.S. FDA regulatory review, per prior agreement, is to show superiority of LEN over F/TDF using the rate ratio metrics (1-sided alpha of 0.0026).

LEN reduced the incidence of HIV-1 infection compared to both estimated background rates using the recency assay and also against the active comparator, F/TDF (see Section 11 below). These endpoints and analyses were agreed to by the division and are considered clinically significant.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

As noted above, F/TDF, F/TAF, and CAB are currently approved for HIV PrEP. Of note, TAF and TDF are both prodrugs of tenofovir (TFV). Please see the table below for a summary of each of these approved therapies for HIV-1 PrEP.

Table 1. Therapies Currently Approved for HIV PrEP

Therapy	Approved PrEP Indication	Efficacy Endpoint	Comments
F/TDF (Truvada)	For use in combination with safer sex practices for HIV-1 PrEP to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg	The incidence of documented HIV-1 seroconversion: • iPrEx Trial: Among high risk MSM and TGW, F/TDF resulted in a 42% (95% CI: 18-60%) reduction in risk compared to PBOPartners PrEP Trial: Among HIV serodiscordant heterosexual couples, F/TDF resulted in a risk reduction of 75% (95% CI: 55-87%) compared to PBO	In iPrEx, based on a posthoc case control study of plasma and intracellular drug levels, efficacy appeared to strongly correlate with adherence
F/TAF (Descovy)	For use in at-risk adults and adolescents weighing at least 35 kg for PrEP to reduce the risk of HIV-1 infection from	The incidence of documented HIV-1 infection per 100 PYs • DISCOVER Trial: Among MSM and TGW, F/TAF was noninferior to F/TDF in	Label includes the following Limitation of Use: The indication does not

	sexual acquisition, excluding individuals at risk from receptive vaginal sex.	reducing the risk of acquiring HIV infection (rate of HIV infection per 100 PYs was 0.16 and 0.34 in the F/TAF and F/TDF arms, respectively; rate ratio = 0.468 (95% CI: 0.19-1.15)).	include use of F/TAF in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated.
CAB (Apretude)	For use in at-risk adults and adolescents weighing at least 35 kg for PrEP to reduce the risk of sexually acquired HIV-1 infection.	The incidence of HIV-1 infections among participants: • HPTN 083: Among HIV-1 uninfected cisgender men and transgender women who have sex with men and have evidence of high-risk behavior for HIV-1 infection, CAB was superior to F/TDF with a 66% reduction in risk of acquiring HIV-1 infection, hazard ratio (95% CI) 0.34 (0.18, 0.62). HIV-1 infections per 100 PY were 0.37 in the CAB group versus 1.22 in the F/TDF group. • HPTN 084: Among HIV-1 uninfected cisgender women at risk for acquiring HIV-1 infection, CAB was superior to F/TDF with an 88% reduction in in the risk of acquiring incident HIV-1 infection, hazard ratio (95% CI) 0.12 (0.05, 0.31). HIV-1 infections per 100 PY were 0.15 in the CAB group versus 1.85 in the F/TDF group.	Failures are rare with CAB PrEP, however these failures can be associated with the development of INSTI resistance with the potential to compromise first-line INSTI-based treatment regimens.

Abbreviations: CAB, cabotegravir; CI, confidence interval; CGM, cisgender men; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; PBO, placebo; PrEP, pre-exposure prophylaxis; TGW, transgender women.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[4].

The following tables summarize the investigational drugs that are being studied for HIV-1 PrEP. Table 2 includes dapivirine vaginal ring, which was denied BTD due to lack of demonstrable improvement in efficacy over existing therapy. CAB is not listed in this Table as it has now been been approved; it did receive BTD for HIV-1 PrEP in 2020. As previously mentioned, in 2021, Gilead submitted a BTDR for LEN for PrEP with nonclinical proof of concept PrEP data from an animal model, which was not enough to support the approval for a BTDR. As there was no clinical evidence of substantial improvement over therapies available at that time, the request was denied.

Table 2. Investigational Therapies Denied for Breakthrough Therapy Designation for (b) (4)

(b) (4)

[4] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

[redacted]

11. Information related to the preliminary clinical evidence:

Table 3 below displays data from the two clinical trials supporting the BTDR for LEN, studies GS-US-412-5624 (PURPOSE 1) and GS-US-528-9023 (PURPOSE 2). Both trials conducted are Phase 3, randomized, double-blind, global, multi-center studies designed to evaluate the safety and efficacy of LEN for HIV-1 prevention. Both trials employ a novel counterfactual background HIV-1 incidence (bHIV), defined as the estimated HIV-1 incidence in the screened population, and have F/TDF serving as the internal active control. Additionally, both studies included a cross-sectional study (Incidence Phase), a Randomized Blinded Phase, a LEN Open-Label Extension (OLE) Phase, and a PK Tail Phase, displayed in Figures 1 and 2. While the primary and key secondary analyses agreed to by FDA for regulatory review are described above in Section 8, primary endpoints are the HIV-1 incidence reported per 100-person years of follow-up. Secondary endpoints include the HIV-1 incidence among participants while adherent to study drug, percentage of participants experiencing treatment-emergent adverse events, and percentage of participants experiencing clinically significant laboratory abnormalities. Both trials were stopped after the interim analyses due to efficacy, so the interim analyses will serve as the primary analyses.

Figure 1. Study Design, GS-US-412-5624

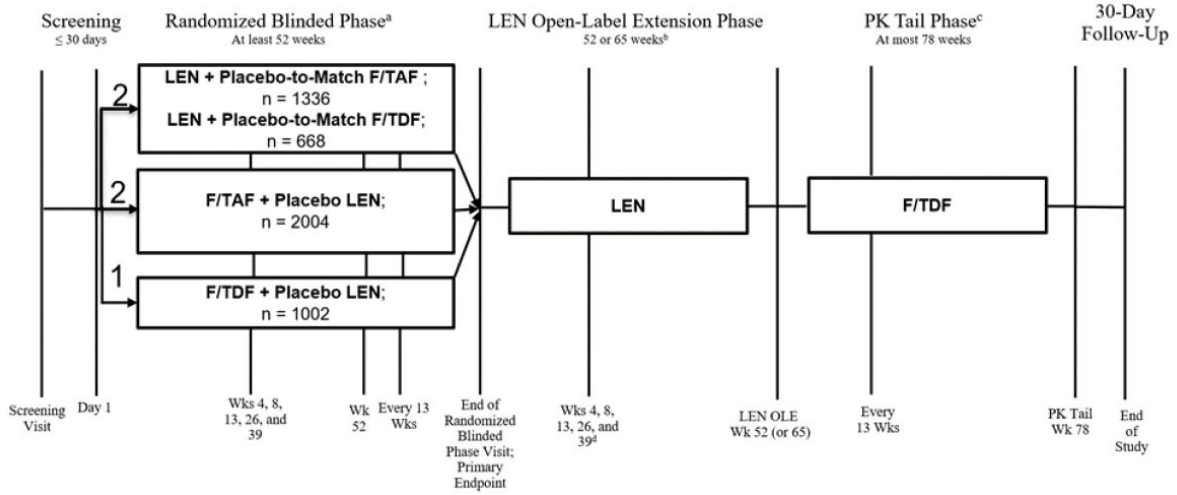

Figure 2. Study Design, GS-US-528-9023

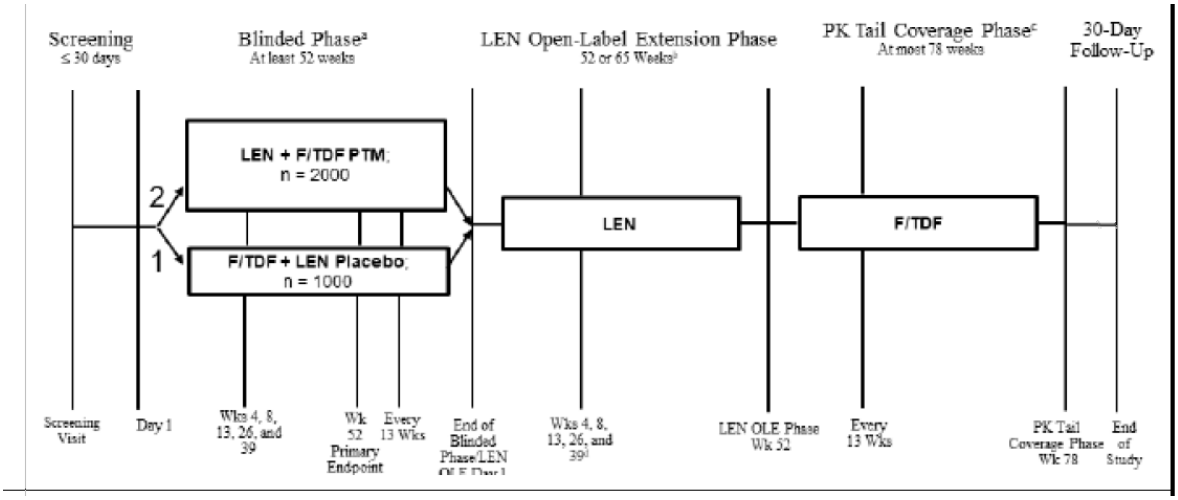

Table 3. Clinical Trials Supporting BTDR for LEN

Study ID	Patient Population	Primary Efficacy Analysis: LEN vs bHIV	Secondary Efficacy Analyses: LEN vs F/TDF
GS-US-412-5624 (PURPOSE 1)	AGYW who have sex with male partners and would benefit from PrEP	LEN: 0 of 2134 participants; 0.000 infections per 100 PY (95% CI: 0.000 to 0.190) bHIV: 2.407 per 100 PY (95% CI 1.815, 3.191) Rate ratio (LEN/bHIV) was 0.000 (95% CI 0.000, 0.042), p value <0.0001 LEN met the criteria for superiority over bHIV	F/TDF: 16 of 1068 participants; 1.685 infections per 100 PY (95% CI: 0.963 to 2.737) Rate ratio for HIV-1 incidence (LEN vs F/TDF) was 0.000; 95% (CI: 0.000 to 0.101; P < 0.0001), which demonstrated that LEN is superior to F/TDF.
GS-US-528-9023 (PURPOSE 2)	CGM, TGW, TGM, and gender nonbinary people who have sex with male partners and who would benefit from PrEP	LEN: 2 of 2180 participants; 0.10 infections per 100 PY (95% CI: not provided) bHIV: 2.37 per 100 PY (95% CI, 1.65 to 3.41) Rate ratio (LEN/bHIV) was 0.04; 95% CI, 0.01, 0.18; p value < 0.0001)	F/TDF: 9 of 1087 participants; 0.93 infections per 100 PY (95% CI: not provided) Rate ratio for HIV-1 incidence (LEN vs F/TDF) was 0.11 (95% CI, 0.02 to 0.51; P = 0.0025), which demonstrated that LEN is superior to F/TDF

Abbreviations: AGYW, Adolescent girls and young women; bHIV, background HIV-1 incidence; CI, confidence interval; CGM, cisgender men; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; PrEP, pre-exposure prophylaxis; PY, person-years; TGM, transgender men; TGW, transgender women.

Based on the results of PURPOSE 1 and PURPOSE 2, LEN is statistically superior to F/TDF for the prevention of HIV-1 infection. In PURPOSE 1, no participant in the LEN group had incident HIV-1 infection during the Randomized Blinded Phase (0.000 infections per 100 PY; 95% CI: 0.000 to 0.190), with the efficacy of LEN superior to both the bHIV incidence (rate ratio: 0.000; 95% CI: 0.000 to 0.042; P < 0.0001) and F/TDF (rate ratio: 0.000; 95% CI: 0.000 to 0.101; P < 0.0001). The other investigational drug in PURPOSE 1 is F/TAF (Descovy). Although LEN was not formally compared to F/TAF, the observed incidence in the F/TAF group was similar to F/TDF, and substantially higher than LEN (2.02, 95% CI 1.44-2.78). In PURPOSE 2, two of 2180 participants had incident HIV-1 infection (0.10 infections per 100 PY; 95% CI: not provided) in the LEN group. The efficacy of LEN was superior to both the bHIV incidence (Rate ratio 0.04; 95% CI, 0.01, 0.18; P < 0.0001) and F/TDF (rate ratio: 0.11 (95% CI,0.02 to 0.51; P = 0.0025). A reasonable conclusion is that SC injectable LEN has superior efficacy compared to the available oral PrEP options.

In the PURPOSE 1 and PURPOSE 2 studies, the main safety finding was injection site reactions (ISRs). In PURPOSE 1, ISRs were reported in 1472 of 2140 participants (68.8%) who received LEN and 1116 of 3204 participants (34.8%) who received active comparator (F/TDF or F/TAF) plus placebo injections. The majority of the ISRs were Grade 1 or 2 in severity, with Grade 3 ISRs reported in 4 participants (0.2%) who received LEN and 4 participants (0.1%) who received placebo injections. None of the ISRs are reported as serious adverse events (SAEs), with 4 participants (0.2%) who received LEN prematurely discontinued due to ISRs. In PURPOSE 2 ISRs were reported in 1816 of 2184 of participants (83%) who received LEN and and 757 of 1089 of participants (70%) who received F/TDF plus placebo injections. The majority of ISRs were Grades 1 and 2, with immediate injection pain and subcutaneous nodules the most commonly reported ISRs. 1.2% participants in the LEN group and 0.3% in the F/TDF group discontinued due to ISRs. Of note, the Sponsor reports that the incidence of ISRs decreased with subsequent injections in both PURPOSE 1 and PURPOSE 2 studies.

When ISRs are excluded, adverse events (AEs) were reported with similar frequencies in the LEN versus F/TDF groups in both PURPOSE 1 and PURPOSE 2. In PURPOSE 1, the percentages of participants with AEs considered related to study drug were similar between the study drug groups (LEN 23.3%, 498 participants; F/TDF 29.5%, 316 participants). There was a higher incidence of nausea and vomiting in the F/TDF group, with 13.3% and 10% in the F/TDF group compared to 6.7% and 5.8% in the LEN group. The percentages of participants with Grade 3 or higher AEs, SAEs, and AEs leading to premature discontinuation of study drug are also similar between groups, and there were no deaths. In PURPOSE 2, the percentage of AEs considered related to study drug were similar between the study drug groups for Grade 2 or higher (LEN 53.7%, 1173 participants; F/TDF 54.4%, 592 participants). The rates of participants with Grade 3 or higher AEs, SAEs, AEs leading to premature discontinuation, and deaths were also similar between study groups. There were 4 deaths among 2184 LEN recipients and 2 deaths among 1089 F/TDF recipients, and no deaths were deemed related to study drug.

No head to head comparisons of LEN versus CAB have been performed; however, based on data from the CAB PrEP trials 201738 (HPTN 083) and 201739 (HPTN 084), it appears that LEN has at least similar efficacy to CAB (see Table 1 and Table 3). Although substantial improvement in efficacy of LEN over CAB cannot be concluded, there are other areas where LEN may represent a substantial improvement in effectiveness or safety over CAB. LAI products require clinic visits for each dose; LEN's decreased dosing frequency (twice per year) compared to CAB (six times per year) may improve adherence as well as potentially reducing the frequency of ISRs. Furthermore, LEN used for PrEP would be less likely to compromise future HIV-1 treatment regimens compared to CAB. CAB has the potential to compromise first-line INSTI-based HIV-1 treatment regimens when HIV-1 infections occur (either in patients with undiagnosed infections who begin CAB for PrEP, as a rare PrEP failure, or in patients who previously took CAB for PrEP and have residual

subtherapeutic exposures at the time of infection) due to the development of INSTI resistance. Development of LEN resistance would not impact existing first-line HIV-1 treatment regimens.

12. Division's recommendation and rationale (pre-MPC review:

☒ GRANT:

BTD should be granted for LEN for HIV-1 PrEP for individuals at high risk of HIV-1 acquisition. LEN represents a substantial improvement in effectiveness over the available oral PrEP options. In two clinical trials, GS-US-412-5624 and GS-US-528-9023, LEN was shown to be superior to F/TDF in the prevention of HIV-1 acquisition in adolescent girls and young women who have sex with male partners, as well as in cisgender men, transgender women, transgender men, and gender nonbinary people who have sex with male partners and who would benefit from PrEP.

In addition, LEN may represent a substantial improvement in effectiveness or safety over the currently approved LAI HIV-1 PrEP product, CAB. While not compared directly to CAB in clinical trials, LEN may represent a substantial improvement over CAB for those needing PrEP for the following reasons:

- LEN used for PrEP would be less likely to compromise first-line INSTI-based HIV-1 treatment regimens compared to CAB. LEN has a unique resistance profile; therefore development of LEN resistance on the rare occasion that a PrEP user experiences a failure of PrEP, has residual subtherapeutic exposures at the time of HIV-1 infection due to prior PrEP, or has undiagnosed HIV-1 infection at the time of PrEP use, would not impact existing first-line HIV-1 treatment regimens.
- The reduced dosing frequency (twice a year vs six times per year), may result in improved adherence and a lower frequency of ISRs, the primary AE associated with LAIs

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

The Sponsor intends to submit an NDA for LEN for HIV-1 PrEP in late 2024 (December for the final portion). The Division has been and will continue to work closely with the Sponsor to determine the best path forward for the NDA. Both parties are committed to bringing the drug to the market as expedititiously as possible given the efficacy findings in both GS-US-412-5624 and GS-US-528-9023.

14. List references, if any:

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

Revised 2-26-2024 /M. Raggio

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

URSULA M KELLY
10/08/2024 03:58:06 PM

STEPHANIE B TROY
10/08/2024 03:59:22 PM

WENDY W CARTER
10/08/2024 04:19:07 PM

IND 153858

MEETING PRELIMINARY COMMENTS

Gilead Sciences, Inc.
Attention: Jamie Lam, MBS
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Jamie Lam:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for lenacapavir.

We also refer to your July 23, 2024, correspondence, requesting a meeting to discuss proposed NDAs for lenacapavir tablet and injection for HIV-1 preexposure prophylaxis (PrEP), including key aspects related to the content and format of the NDAs.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, an electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, contact me, at 301-837-7467 or Kevin.Allen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Kevin Allen, MS
Regulatory Project Manager
Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Preliminary Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: B

Meeting Category: Pre-NDA

Meeting Date and Time: 3:30-5:00 PM ET, September 19, 2024

Meeting Location: Zoom Meeting

Application Number: 153858

Product Name: lenacapavir

Indication: HIV-1 Pre-exposure Prophylaxis (PrEP)

Sponsor Name: Gilead Sciences, Inc.

Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 19, 2024 from 3:30 to 5:00 pm ET on Zoom between Gilead Sciences, Inc. and the Division of Antivirals. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Lenacapavir is a first-in-class, multistage selective inhibitor of HIV-1 capsid function that is being evaluated for PrEP of HIV-1 and has been approved for the treatment of multi-drug resistant HIV-1 in heavily treatment experienced people with HIV. The Sponsor is conducting two phase 3, randomized, double-blind, global, multicenter studies to evaluate the safety and efficacy of lenacapavir for HIV prevention. Study GS-US-412-5624 [PURPOSE 1] is being conducted in adolescent girls and young women (AGYW) who have sex with male partners and would benefit from PrEP, and Study GS-US-528-9023 is being conducted in cisgender men, transgender women, transgender men, and gender nonbinary people who have sex with male partners and who would benefit from PrEP.

The purpose of this meeting is to discuss the proposed NDAs for lenacapavir tablet and injection for HIV-1 preexposure prophylaxis (PrEP), including key aspects related to the content and format of the NDAs.

2.0 DISCUSSION

2.1. Clinical/Safety

Question 1: Does the Agency agree that the proposed indication for LEN is supported by the clinical studies described in Table 2?

FDA Response to Question 1: Determination of the labeled indication will depend on the review of both clinical trials.

Question 2: Does the Agency agree with Gilead's plan to present the pool efficacy and safety analyses from each of the registrational studies separately?

FDA Response to Question 2: We agree that the data from the two populations enrolled in the two trials should not be pooled for efficacy assessment. We also agree that the primary safety analyses should be separate for the individual PURPOSE studies; however, safety data from both PURPOSE 1 and PURPOSE 2 should be pooled as a supplementary analysis in the integrated summary of safety (ISS) to assess for rare safety findings and to assess for differences among subgroups. Please include a combined dataset for the ISS in the NDA submission.

Question 3: Does the Agency agree with the planned analysis in pregnant and lactating women?

FDA Response to Question 3: Your planned analysis in pregnant and lactating women is acceptable with the following additional considerations.

- Please provide a comprehensive review of pregnancy outcomes and comparison of adverse outcomes between study arms and versus estimated background rates in the relevant populations.

- With respect to the anticipated and observed variability in LEN exposure pharmacokinetics of LEN in pregnant and lactating women, which is at least in part due to varying degrees of timing following the last dose, various approaches should be leveraged to characterize the PK of LEN during pregnancy. This includes, but is not limited to, descriptive comparison of PK in the same participants (pre-, during, and post-pregnancy) and comparison to all nonpregnant participants at matching post-dose time points. Also, we strongly recommend that you utilize a population pharmacokinetic approach to determine the effects of pregnancy on LEN PK and submit it as part of your NDA.

Question 4: Does the Agency agree with the proposed list of studies and cutoff dates for additional safety data to be included with the required NDA Safety Update?

FDA Response to Question 4: We agree with the proposed list of studies and proposed timeline of NDA Safety Update submission as referenced under 21 CFR 314.50(d)(5)(vi)(b). However, the determination of priority or standard review timeline will be made once the NDA is submitted.

2.2. NDA Structure and Content

Question 5: Does the Agency agree with the proposed approach to submit LEN for PrEP data to the NDA for Injection and NDA for Oral Tablets by way of cross-reference letters as described below and as proposed in the draft Table of Contents (TOC)?

FDA Response to Question 5: In general, we agree. The proposed approach to submit product quality data for lenacapavir for PrEP indication to the NDA for Injection and NDA for Oral Tablets by way of cross-reference letters (LOAs) appears reasonable. Please ensure that your outline in Module 1.4.4 details only the quality information and data relevant to the new NDA, particularly for the container closure system. The adequacy of the approach will be determined at the time of NDA filing and NDA review based on the totality of the information submitted.

Question 6: Does the Agency agree with the provision of the documentation and datasets in the LEN for PrEP NDAs Modules 1 through 5 as outlined below and in the draft TOCs?

FDA Response to Question 6: We generally agree with your proposed documentation approach for Modules 1 and 2 with the following additional considerations:

- An Environmental Analysis or Claim of Categorical Exclusion should be submitted to each NDA.

- The Debarment Certification should be submitted to each NDA.

- Submit to m1.9.6 a copy of the most recent Pediatric Study Plan – Amended Agreement (dated March 22, 2024).

For Module 5, we strongly encourage you to reconsider participation with Bioresearch Monitoring (BIMO) Item III, as this will help facilitate our review process and appropriate selection of sites for inspection.

Question 7: Does the Agency agree [redacted] (b) (4)

FDA Response to Question 7: We do not agree. [redacted] (b) (4)

Additionally, to support labeling recommendations for oral bridging with the PrEP indication, we recommend submitting a similar analysis of clinical data from PURPOSE 1 and PURPOSE 2 to the analysis that was used to support labeling for oral bridging for the treatment indication, including justification for recommendations with missed weekly oral doses.

2.3. Clinical Virology

Question 8: Does the Agency agree the proposed virology data package?

FDA Response to Question 8: We agree.

2.4. Regulatory

Question 9: Based on the rationale provided below, does the Agency agree that the Amended Agreed initial pediatric study plan (iPSP) for LEN for PrEP issued on 22 March 2024 by FDA (under IND 153858) along with the under review iPSP for LEN oral bridging regimen for HIV treatment (IND 136260, SN 0295) fulfill the PREA requirement and will be adequate to support the upcoming LEN for PrEP marketing applications with the planned twice yearly and oral bridging regimen?

FDA Response to Question 9: Submission to the marketing applications of your Amended Agreed iPSP dated March 22, 2024, will be adequate.

Question 10: Does the Agency agree that the currently available safety information for LEN does not warrant inclusion of a Risk Evaluation and Mitigation Strategy (REMS)?

FDA Response to Question 10: At this time, we have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to

ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your applications.

Question 11: Does the Agency agree with the Sponsor's proposed strategy and rationale to seek a priority review designation for the planned LEN for PrEP NDAs?

FDA Response to Question 11: Final determination for a priority review designation will be made upon receipt and review of the NDA submissions.

Question 12: Gilead is submitting the Breakthrough designation (BTD) request for LEN for PrEP in conjunction with the briefing package submission. Assuming the Agency supports the request for BTD for the LEN for PrEP, does the Agency anticipate an expedited review of the LEN for PrEP marketing applications?

FDA Response to Question 12: Your BTD request has been received and determination is pending. We will endeavor to review your NDA packages as efficiently as possible given the justifications provided.

Question 13: Does the Agency agree with reviewing portions of the application under a rolling review to support an expedited review, as outlined below, before submission of the complete NDA?

FDA Response to Question 13: We agree with a rolling review approach in principle; however, the review clock will not officially begin until all modules are completely submitted. We disagree with the partial module submissions that you have proposed in Tables 5-8 and request that you submit complete sections only. As an exception, you may submit a complete study report with PURPOSE 1 results early and submit the remainder of the clinical section when complete PURPOSE 2 results are available. Please refer to FDA Guidance Expedited Programs for Serious Conditions | Drugs and Biologics May 2014: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics.

Question 14: Based on the nonclinical and clinical data provided to IND 153858, does the Agency expect an FDA Advisory Committee Meeting?

FDA Response to Question 14: Determination of the need for an Advisory Committee Meeting will be made after we receive the NDA submissions.

3.0 Additional Comments

Biometrics

1. Please submit all executable programs used for generating integrated ADaM datasets from SDTM datasets for all included individual studies and integrated

analysis datasets.

2. Please submit all executable programs used for generating the primary, key secondary efficacy endpoint, and safety analyses for all submitted individual studies and integrated analyses.

3. Please provide study data reviewer's guide and analysis data reviewer's guide along with the clinical datasets.

Combination Products

4. As stated in the briefing package, the proposed kit that contains the lenacapavir drug vial and the delivery devices (i.e., 18G needle/(b) (4), syringe/(b) (4) and 22G injection needle/(b) (4)) remains a co-packaged combination product per 21 CFR 3.2(e)(4). Please note that Part 3 combination products are subject to 21 CFR Part 4.A "Current Good Manufacturing Practice Requirements for Combination Products" accessible at: https://www.federalregister.gov/documents/2017/01/11/2017-00411/current-good-manufacturing-practice-requirements-for-combination-products-guidance-for-industry-and.
Related guidance is available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-manufacturing-practice-requirements-combination-products.

5. In your future IND submission, Form 1571 should identify your product as a combination product (see form field 13). In your future NDA submission, Form 356h should identify your product as a combination product (see form field 24); the combination product Type will depend on the final to-be-marketed configuration. Also, on the 356h form, identify all facilities involved in the manufacturing of the combination product, including all facilities involved in the manufacturing of each constituent part and all facilities responsible for the disposition (e.g., release) of the combination product.

6. For information on the location of device related information, see Section 5 of the Agency eCTD Technical Conformance Guide: Technical Specifications Document: Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" November 2022, accessible at: https://www.fda.gov/media/93818/download.

7. Part 3 combination products are subject to post-market reporting safety requirements per 21 CFR Part 4.B. For more information on post-market safety reporting requirements for combination products, see: https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products.

8. Please note FDA has published the draft guidance "Essential Drug Delivery Outputs for Devices Intended to Deliver Drugs and Biological Products" that is open for comment through September 30, 2024. In this draft guidance Essential Performance Requirements are referred to as Essential Drug Delivery Outputs. See: https://www.fda.gov/media/179545/download

4.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

5.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing

[1] https://www.fda.gov/media/86340/download
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

6.0 MANUFACTURING FACILITIES

[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[5] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[6]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for

[5] https://www.fda.gov/media/84223/download
[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

commercial production and those used for product and manufacturing process development.

7.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[7]

[7] https://www.fda.gov/media/85061/download

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KEVIN L ALLEN
09/16/2024 03:19:46 PM

IND 136260

MEETING PRELIMINARY COMMENTS

Gilead Sciences, Inc.
Attention: Grace Gill, PharmD
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Lawrence:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for lenacapavir (GS-6207).

We also refer to your May 29, 2020, correspondence, received May 29, 2020, requesting a meeting to discuss and obtain FDA agreement on the proposed Phase 3 pre-exposure prophylaxis (PrEP) study design to support the registration of the PrEP indication for lenacapavir.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (240) 402-5708 or the mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Andrew Gentles, PharmD, BCPS AQ-ID
Senior Regulatory Project Manager
Antivirals Group
Division of Regulatory Operations for Infectious Diseases
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	End of Phase (EOP) 2
Meeting Date and Time:	September 10, 2020 3:00-4:30 PM
Meeting Location:	TCON
Application Number:	136260
Product Name:	Lenacapavir (GS-6207)
Indication:	Pre-exposure prophylaxis (PrEP) in at-risk individuals to reduce the risk of HIV-1 infection from sexual acquisition
Sponsor/Applicant Name:	Gilead Sciences, Inc

FDA ATTENDEES

John Farley, MD, MPH, Director, Office of Infectious Diseases
Debra Birnkrant, MD, Director, Division of Antivirals (DAV)
Jeffrey Murray, MD, MPH, Deputy Director, DAV
Poonam Mishra, MD, Deputy Director for Safety, DAV
Kim Struble, PharmD, Clinical Team Lead, DAV
Benjamin Lorenz, MD, Clinical Reviewer, DAV
Hanan Ghantous, PhD, DABT, Director, Division of Pharmacology/Toxicology for Infectious Diseases (DPT-ID)
Deacqunita Diggs, PhD, Pharmacology/Toxicology reviewer, DPT-ID
Karen Winestock, Chief Project Management Staff, Division of Regulatory Operations for Infectious Diseases, DROID
Andrew Gentles, PharmD, BCPS AQ-ID, Senior Regulatory Project Manager, DROID
Julian O'Rear, PhD, Lead Clinical Virology, DAV
Damon Deming, PhD, Virology Reviewer, DAV
Lisa Naeger, PhD, Virology Reviewer, DAV
Vikram Arya, PhD, Clinical Pharmacology Team Lead, Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP), Division of Infectious Disease Pharmacology (DIDP)
Jenny Zheng, PhD, Pharmacology Reviewer, OTS/OCP/DIDP

Thamban Valappil, PhD, Biometric Team Lead, OTS, Office of Biometrics, Division of Biometrics IV (DBIV)
Hengrui Sun, PhD, Biometrics Reviewer, DBIV
Erika Englund, PhD, Acting CMC Team Lead, OPQ

SPONSOR ATTENDEES

Diana Brainard, MD (Senior Vice President, Virology Clinical Research)
Moupali Das, MD, MPH (Executive Director, Virology Clinical Research)
Lijie Zhong, PhD (Executive Director, Biostatistics)
Jan de Jong, PhD (Senior Director, Clinical Pharmacology)
Anne Chester, PhD, DABT (Executive Director, Nonclinical Safety and Pathobiology)
Anna Chiu, PhD (Senior Director, Process Development)
Mae J. Lai, BS (Executive Director, Regulatory Affairs)
Grace Gill, PharmD, Associate Director, Regulatory Affairs
Garland Lee, PharmD (Senior Manager, Regulatory Affairs)
Kate Lawrence, PhD (Manager, Regulatory Affairs)

Introduction

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 10, 2020 between Gilead Sciences, Inc and the Division of Antivirals. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Gilead Sciences, Inc has developed lenacapavir, a novel, first-in-class, multistage, selective inhibitor of HIV-1 capsid for the treatment of HIV-1 infection. Lenacapavir inhibits the proper assembly of mature capsid protein in extracellular HIV-1 particles in

the late stage of HIV-1 replication cycle and at the same time also reduces virus production through specific binding interactions with the capsid domain of intracellular p24 and gag/gag-pol precursor proteins in the early stage of HIV-1 replication. Gilead is currently conducting studies to evaluate the potential of lenacapavir in becoming part of a highly effective HIV treatment regimen for highly treatment experienced (HTE) people living with multi-drug resistant HIV-1 infection. In addition, Gilead plans to support the registration of lenacapavir as a single agent for the PrEP indication with two registrational Phase 3 clinical trials, one in men who have sex with men and transgender women (MSM/TGW) and the other in cisgender adolescent girls and young women (AGYW). On May 29, 2020, Gilead submitted a meeting request for a Type B (EOP), Pre-Phase 3 meeting to seek agreement on the proposed study designs for it's two Phase 3 registrational trials for PrEP in MSM/TGW and cisgender AGYW. The Agency granted the request on June 12, 2020 and Gilead submitted a meeting package on June 26, 2020.

DISCUSSION

Your questions are in *italics* and DAV comments are in standard font.

Question 1: Proposed Phase 3 Study in MSM/TGW

Does the Agency agree that the proposed Phase 3 study design in MSM/TGW would support a PrEP indication for lenacapavir in this population?

FDA Response to Question 1: We acknowledge the challenges involved with PrEP clinical trial design in MSM/TGW, and we agree with the general approach you have proposed. As you move toward developing the final protocol, we have the following comments or recommendations.

- Please provide an update regarding the dose rationale for Phase 3 trials. Phase 3 trials should not be initiated until sufficient safety data are available at the dose and dosing interval you plan to study. Depending on the amount of safety data available and risk assessment, additional data or revisions to the trial may be needed before enrolling the large number of subjects needed for the Phase 3 trial. We note that you have an interim safety review planned after the first 300 subjects in the LEN arm have completed their Week 8 visit; however, it is not clear if there will be an enrollment pause during this interim review and how this review will determine whether enrollment will continue or not.

- We understand that the COVID-19 pandemic may have impacted estimated completion dates for many studies. Please provide an update regarding the progress of recruitment in each of your ongoing LEN studies, specifically including the number of subjects with safety data available at the dose (or higher) and dosing interval that will be studied in your proposed Phase 3 PrEP trial.

- Please provide additional details regarding the methods for estimating concurrent background HIV-1 incidence rates. Inclusion of the performance characteristics of the proposed recency assay will help to determine the acceptability of the estimates.

- We recommend the primary analysis be conducted using LEN versus background incidence rates based on the recency assays. Comparison between LEN and F/TDF should also be considered and this can be a secondary efficacy endpoint.

- Please address the PK tail for LEN and likelihood of acquiring resistance due to subtherapeutic levels or LEN monotherapy if HIV-1 transmission occurs following cessation of PrEP.

Question 2: Proposed Phase 3 Study in Cisgender AGYW

a) Does the Agency agree that the proposed Phase 3 study design in cisgender AGYW would support a PrEP indication for lenacapavir and F/TAF in this population?

FDA Response to Question 2a: We acknowledge the challenges involved with PrEP clinical trial design in cisgender AGYW, and we agree with the general approach you have proposed. In addition to the comments we provided above for your proposed MSM/TGW trial, as you move toward developing the final protocol for cisgender AGYW, we have the following comments or recommendations:

- Please comment on the availability of a sufficient number of subjects at the proposed sites, especially if additional PrEP trials may be recruiting in these regions.

We recommend the primary analyses be conducted using LEN versus background incidence rates based on the recency assays, and F/TAF versus background incidence rates based on the recency assays. Comparisons between LEN versus F/TDFand F/TAF versus F/TDF should also be considered and they can be secondary efficacy endpoints.

b) Does the Agency agree that the benefit of preventing HIV infection during pregnancy with a long-acting agent that is not dependent on adherence and the assuring preclinical safety data support allowing women who are randomized to lenacapavir and who become pregnant the choice to continue lenacapavir after providing additional informed consent?

FDA Response to Question 2b: In general, the nonclinical safety data appears to support continuation of LEN in women who become pregnant. According to the information in your iPSP, the pre- and postnatal development study is on-going. Please submit interim and/or draft study reports (in lieu of final audited reports) of available data

of this study. When submitting final audited study reports, please include a description of all changes made to the interim and/or draft reports.

In your protocol synopsis you noted that “breastfeeding information” would be collected. Please expand on the available data to inform risk assessment for breastfeeding mothers and their infants, particularly given extended exposures anticipated with LEN.

Question 3: Data to Support Initiation of PrEP Phase 3 Trials

Does the Agency agree that Gilead may proceed with conduct of the two Phase 3 PrEP trials based on the totality of all available safety and efficacy data from Studies GS-US-200-4625 and GS-US-200-4334?

FDA Response to Question 3: We do not agree. We would need to address the concerns raised in our responses to Questions 1 and 2 before assessing the totality of data needed to proceed. The safety experience with LEN has not been sufficiently described at the dose and dosing interval likely to be proposed (we assume you will likely use the subcutaneous dose of 900mg every 6 months); however, it is also not clear what long-term PK and safety experience will be available, including results of the thorough QT study.

Additional Comments

Statistics:

1. Please provide details about the recency assay regarding what assay will be used and how it will estimate the background incidence rates for the two PrEP trials.

Clinical Pharmacology:

1. Please clarify why eGFR criteria are different for subjects at least of 18 years of age and less than 18 years of age.

2. Please clarify what PK criteria will be used to assess adherence to LEN.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANDREW A GENTLES
09/05/2020 07:30:47 AM