GILEAD | Medical Information

# Sunlenca® (lenacapavir) Coadministration with ARVs

This document is in response to your request for information regarding Sunlenca® (lenacapavir [LEN]) and coadministration with other ARVs, including pharmacologic boosters such as ritonavir and COBI.

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**The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/sunlenca/sunlenca_pi.**

## Summary


### Product Labeling

LEN, a human immunodeficiency virus type 1 (HIV-1) capsid inhibitor, in combination with other antiretroviral(s), is indicated for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection whose current antiretroviral regimen is failing due to resistance, intolerance, or safety considerations.

In a study of LEN in combination with representatives from the major classes of anti-retroviral agents (INSTIs, NNRTIs, NRTIs, and PIs), no antagonism of antiviral activity was observed. Concomitant administration of LEN with strong CYP3A inducers is contraindicated due to decreased LEN plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to LEN. Concomitant administration of efavirenz, nevirapine, or tipranavir/ritonavir may result in loss of therapeutic effect and development of resistance. Concomitant administration with atazanavir/cobicistat, atazanavir/ritonavir, efavirenz, nevirapine, or tipranavir/ritonavir is not recommended.[1]

### Phase 2/3 Studies

CAPELLA (GS-US-200-4625) is an ongoing, phase 2/3, double-blinded, placebo-controlled clinical study designed to evaluate LEN as an add-on therapy to a failing regimen in heavily-treatment experienced people with HIV (PWH) with multidrug resistance.[2] CAPELLA study did not permit the use of ATV, ATV/c, ATV/r, efavirenz, etravirine, nevirapine and tipranavir in OBR.[3]

CALIBRATE (GS-US-200-4334) was a phase 2, randomized, open-label, active-controlled clinical study that evaluated LEN in combination with other ARVs in treatment-naïve PWH.[4]

### Phase 1 Studies

A drug interaction study in healthy volunteers evaluated the clinical effects of the coadministration of LEN with ARVs that are strong CYP3A, P-gp, and UGT1A1 inhibitors, CYP3A inducers and sensitive P-gp substrates.[5] Of the ARVs studied, coadministration with ATV/c or efavirenz is not recommended due to a clinically significant drug interaction.

# Product Labeling[1]

In a study of LEN in combination with representatives from the major classes of anti-retroviral agents (INSTIs, NNRTIs, NRTIs, and PIs), no antagonism of antiviral activity was observed. Concomitant administration of LEN with strong CYP3A inducers is contraindicated due to decreased LEN plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to LEN. Table 1 provides a listing of clinically significant ARV interactions with recommended prevention or management strategies, but is not all inclusive. The drug interactions described are based on studies conducted with LEN or are drug interactions that may occur with LEN.

## Effect of Other Drugs on LEN

Drugs that are strong or moderate inducers of CYP3A may significantly decrease plasma concentrations of LEN, which may result in loss of therapeutic effect of LEN and development of resistance. Concomitant administration of LEN with strong CYP3A inducers during LEN treatment is contraindicated. Concomitant administration of LEN with moderate CYP3A inducers during LEN treatment is not recommended. Combined P-gp, UGT1A1, and strong CYP3A inhibitors may significantly increase plasma concentrations of LEN. Concomitant administration of LEN with these inhibitors is not recommended (Table 2).

## Effect of LEN on Other Drugs

LEN is a moderate inhibitor of CYP3A. Due to the long half-life of LEN following subcutaneous administration, LEN may increase the exposure of drugs primarily metabolized by CYP3A initiated within 9 months after the last subcutaneous dose of LEN, which may increase the potential risk of adverse reactions. See the prescribing information of the sensitive CYP3A substrate for dosing recommendations with moderate inhibitors of CYP3A (Table 3).

## ARVs without Clinically Significant Interactions with LEN

Based on drug interaction studies conducted with LEN, no clinically significant drug interactions have been observed with: darunavir/cobicistat, cobicistat or tenofovir alafenamide.

**Table 1. ARV Drug Interactions with LEN**

| Antiretroviral Agents | Effect on Concentration[a] | Clinical Comment |
|---|---|---|
| atazanavir/cobicistat [b]<br>atazanavir/ritonavir | ↑ LEN (atazanavir/cobicistat, atazanavir/ritonavir) | Concomitant administration with atazanavir/cobicistat or atazanavir/ritonavir is not recommended. |
| efavirenz [b]<br>nevirapine<br>tipranavir/ritonavir | ↓LEN (efavirenz, nevirapine, tipranavir/ritonavir | Concomitant administration of efavirenz, nevirapine, or tipranavir/ritonavir may result in loss of therapeutic effect and development of resistance and is not recommended. |

[a] ↑ = Increase, ↓ = Decrease.
[b] Drug-drug interaction study was conducted.

**Table 2. Effect of Other ARVs on LEN[a,b]**

| Coadministered Drug | Dose of Coadministered Drug (mg) | Mean Ratio of LEN Pharmacokinetic Parameters (90% CI); No effect = 1.00 | |
|---|---|---|---|
| | | $C_{max}$ | AUC |
| Cobicistat (fed)<br>(Inhibitor of CYP3A [strong] and P-gp) | 150<br>once daily | 2.10<br>(1.62, 2.72) | 2.28<br>(1.75, 2.96) |
| Darunavir / cobicistat (fed)<br>(Inhibitor of CYP3A [strong] and inhibitor and inducer of P-gp) | 800/150<br>once daily | 2.30<br>(1.79, 2.95) | 1.94<br>(1.50, 2.52) |
| Atazanavir / cobicistat (fed)<br>(Inhibitor of CYP3A [strong] and UGT1A1 and P-gp) | 300/150<br>once daily | 6.60<br>(4.99, 8.73) | 4.21<br>(3.19, 5.57) |
| Efavirenz (fasted)<br>(Inducer of CYP3A [moderate] and P-gp) | 600<br>once daily | 0.64<br>(0.45, 0.92) | 0.44<br>(0.32, 0.59) |

[a] Single dose of LEN 300 mg administered orally.
[b] All interaction studies conducted in subjects without HIV-1.

**Table 3. Effect of LEN on Other ARVs[a,b]**

| Coadministered Drug | Dose of Coadministered Drug (mg) | Mean Ratio of LEN Pharmacokinetic Parameters (90% CI); No effect = 1.00 | |
|---|---|---|---|
| | | $C_{max}$ | AUC |
| Tenofovir alafenamide (fed)<br>(substrate of P-gp) | 25 single dose | 1.24<br>(0.98, 1.58) | 1.32<br>(1.09, 1.59) |
| Tenofovir [c]<br>(substrate of P-gp) | | 1.23<br>(1.05, 1.44) | 1.47<br>(1.27, 1.71) |

[a] All interaction studies conducted in subjects without HIV-1.
[b] Following 600 mg twice daily for 2 days, single 600 mg doses of LEN were administered with each coadministered drug, resulting in LEN exposures similar to or higher than those at the recommended dosage regimen.
[c] Tenofovir alafenamide is converted to tenofovir *in vivo.*

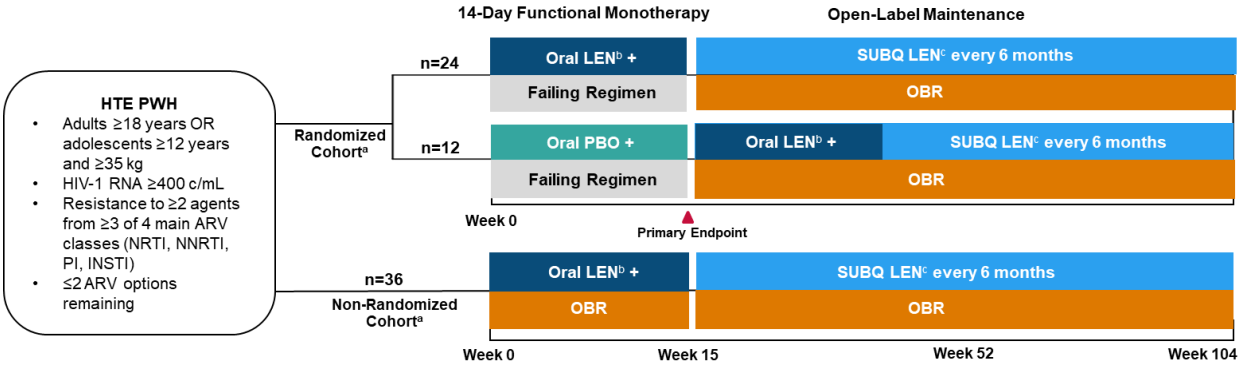
# Phase 2/3 Studies

## CAPELLA

### Study Design and Coadministered ARVs

CAPELLA (GS-US-200-4625) is an ongoing, phase 2/3, double-blinded, PBO-controlled clinical study designed to evaluate LEN as add-on therapy to a failing regimen in HTE PWH with multidrug resistance. According to the change in the HIV-1 RNA level between the screening and cohort-selection visits, participants were enrolled in either the randomized or non-randomized cohort. Participants in the randomized cohort were assigned to receive oral LEN or PBO in a 2:1 ratio for 14 days, in addition to continuing their failing regimen. The non-randomized cohort started LEN (2-week oral initiation then SUBQ) with an OBR (Figure 1). Both cohorts are part of the maintenance phase evaluating the safety and efficacy of SUBQ LEN administered every six months in combination with an OBR.[2,6,7] An overview of ARV drug classes/agents including IBA and fostemsavir used concomitantly with LEN in this study are provided in Table 4.[8]

**Figure 1. CAPELLA: Study Design**[2,6,7]




Note: ATV, ATV/COBI, ATV/ritonavir, efavirenz, etravirine, nevirapine, and tipranavir were not permitted for use in OBR.
[a]Participants with <0.5 $log_{10}$ decline in HIV-1 RNA and HIV-1 RNA ≥400 c/mL were enrolled in the randomized cohort; participants were enrolled in the non-randomized cohort if they had ≥0.5 $log_{10}$ decline in HIV-1 RNA and/or had HIV-1 RNA <400 c/mL or were enrolled after the randomized cohort was fully recruited.
[b]Oral LEN dosing schedule: Day 1, 600 mg; Day 2, 600 mg; and Day 8, 300 mg.
[c]Subcutaneous LEN dosing schedule: 927 mg (2× 1.5 mL) on Day 15 and then every 6 months.

**Table 4. CAPELLA: Drug Classes/Agents, Number of Fully Active ARV Agents, and OSS in Failing Regimens and OBR[8]**

| | Failing Regimen (n=72) | OBR (n=72) |
|---|---|---|
| Drug class/agent | | |
| NRTI, % | 82 | 85 |
| INSTI, % | 68 | 65 |
| PI, % | 63 | 63 |
| NNRTI, % | 31 | 33 |
| IBA, % | 19 | 24 |
| Maraviroc, % | 14 | 14 |
| Fostemsavir, % | 6 | 11 |
| T20, % | 6 | 7 |
| Number of fully active ARV agents, 0/1/≥2, % | 42/36/22 | 17/38/46 |
| OSS,[a] median | 1 | 2 |

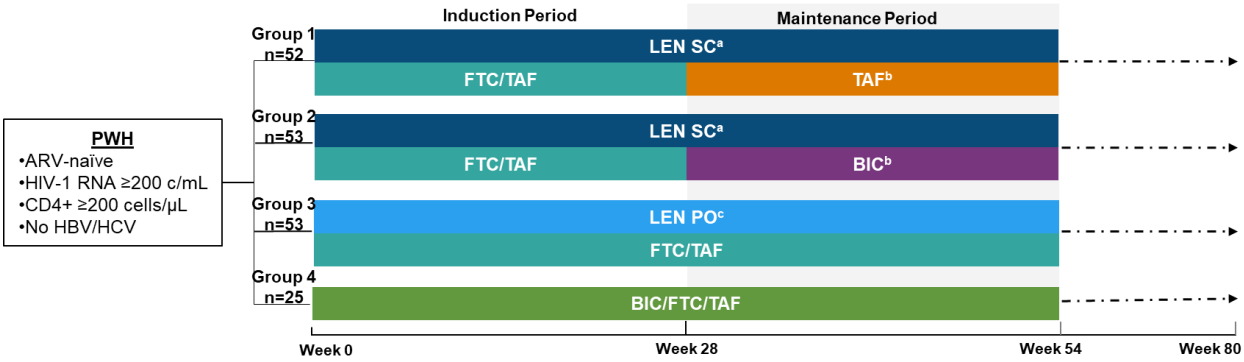
[a] OSS were calculated with a proprietary algorithm (Monogram Biosciences Inc.), and investigators provided data for scoring from historical resistance reports. An OSS of 1 indicated full susceptibility, 0.5 indicated partial susceptibility, and 0 indicated no susceptibility. The OSS of the OBR was the total sum of the individual scores.

# CALIBRATE

## Study Design and Coadministered ARVs

CALIBRATE (GS-US-200-4334) was a randomized, open-label, active-controlled phase 2 study that evaluated the safety and efficacy of LEN in combination with other ARVs compared with BIC/FTC/TAF in ARV-naïve PWH. Participants received LEN subcutaneously or orally, in combination with other oral ARV agents, or BIC/FTC/TAF (Figure 2).[9]

**Figure 2. CALIBRATE: Study Design[9]**




[a] The LEN SC dosing schedule includes an oral lead-in phase (Day 1: 600 mg; Day 2: 600 mg, Day 8: 300 mg), followed by LEN 927 mg SC (2 × 1.5 mL) on Day 15 and every 6 months (26 weeks) thereafter.
[b] Participants needed to have HIV-1 RNA <50 c/mL at Weeks 16 and 22 to initiate treatment with a two-agent regimen at Week 28. Those with HIV-1 RNA ≥50 c/mL will discontinue the study at Week 28.
[c] The LEN PO dosing schedule consists of the following: 600 mg on Day 1, 600 mg on Day 2, 50 mg on Day 3 and onwards.
Note: FTC/TAF (200/25 mg), TAF (25 mg), BIC (75 mg), and BIC/FTC/TAF (50/200/25 mg) are administered as oral daily doses. Please note, BIC 75 mg is not commercially available.

# Phase 1 Studies

## Drug Interactions Between PO LEN and Probe Drugs[5]

### Study Design

A study was conducted in healthy volunteers to evaluate the clinical effects of strong P-gp, CYP3A, and UGT1A1 inhibitors and inducers as well as increased gastric pH on LEN exposure. The clinical effects of LEN coadministration upon sensitive P-gp, BCRP, organic anion-transporting polypeptide, and CYP3A substrates were also evaluated.

### Effect of ARVs that are Strong P-gp, CYP3A, and UGT1A1 Inhibitors on LEN Exposure

With only CYP3A inhibition (VORI), a 30% increase in LEN AUC was observed. When P-gp was also inhibited (COBI, DRV/c) a larger increase in LEN exposure was observed (Table 5). This illustrated the role of P-gp in limiting the oral absorption of LEN. P-gp and UGT1A1 were found to play a more substantial role than CYP3A in the pharmacokinetics of LEN. CYP3A/P-gp/UGT1A1 inhibition (ATV/c) resulted in the largest increase in LEN AUC (Table 5). This supported glucuronidation as the primary elimination pathway for LEN.

The increases observed in LEN exposure when coadministered with DRV/c, COBI, and VORI were not considered to be clinically relevant based on current safety data and indicated that dose modifications are not required when LEN is coadministered with strong CYP3A and/or P-gp inhibitors. In the absence of additional data, coadministration of LEN and strong UGT1A1 inhibitors is not recommended.

### Effect of LEN on Sensitive P-gp Substrates

A small increase in TAF exposures (AUC=1.5× increase) support the administration of LEN with P-gp substrates (Table 5).

**Table 5. Effect of ARVs on LEN AUC (Lutz et al)[3,5]**

| | Concomitant Drug | Change in LEN AUC |
|---|---|---|
| **Potential for other ARVs to affect LEN** | | |
| Strong CYP3A4/P-gp inhibitors | DRV/c | +2.1-fold increase |
| | COBI | +130% |
| Strong CYP3A4/P-gp/ UGT1A1 inhibitors | ATV/c | +300% |
| Moderate CYP3A4 inducers | Efavirenz | -56% |
| Strong CYP3A4 inducers* | Rifampin | -85% |
| **Potential for LEN to affect other ARVs** | | |
| Sensitive P-gp substrates | TAF | – |

*ARVs that are strong CYP3A4 inducers should not be coadministered with LEN.

# References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# Abbreviations

ARV=antiretroviral
ATV=atazanavir
ATV/c=atazanavir boosted by cobicistat
ATV/r=atazanavir boosted by ritonavir
AUC=area under the curve
BIC=bictegravir
COBI=cobicistat
DRV=darunavir
DRV/c=darunavir boosted by cobicistat
FTC=emtricitabine
IBA=ibalizumab
INSTI=integrase strand transfer inhibitor
LEN=lenacapavir
NNRTI=non-nucleoside reverse transcriptase inhibitor
NRTI=nucleoside reverse transcriptase inhibitor
OBR=optimized background regimen
OSS=overall susceptibility scores
P-gp=P-glycoprotein
PI=protease inhibitor
PWH=people with HIV
PO=by mouth
SC=subcutaneous
T20=enfuvirtide
TAF=tenofovir alafenamide
UGT1A1=uridine diphosphate glucuronosyltransferase 1A1
VORI=voriconazole

# Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Sunlenca US Prescribing Information available at:
www.gilead.com/-/media/files/pdfs/medicines/hiv/sunlenca/sunlenca_pi

# Follow-Up

For any additional questions, please contact Gilead Medical Information at:

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FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or www.accessdata.fda.gov/scripts/medwatch

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