Drug-Drug Interaction Liability of BIC/LEN Compared With Representative Complex Antiretroviral Therapy Regimens in the Phase 3 Portion of ARTISTRY-1

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ARTISTRY-1

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Conclusions

- In the Phase 3 portion of ARTISTRY-1, the majority of participants were on a complex regimen (CR) containing a boosted protease inhibitor (PI) and/or integrase strand transfer inhibitor (INSTI)
- Potential drug-drug interactions (DDIs) identified for bictegravir/lenacapavir (BIC/LEN) were fewer compared with commonly prescribed CRs, all containing a pharmacokinetic (PK) booster
  - This is likely due to strong inhibition of cytochrome P450 3A (CYP3A) and P-glycoprotein (P-gp) by PK boosters cobicistat and ritonavir
- This analysis, along with ARTISTRY-1 Phase 2 efficacy and safety findings, highlights the potential of BIC/LEN as a single tablet regimen (STR) for treatment optimization in people with HIV (PWH) who are virologically suppressed (VS) on a CR

Plain Language Summary

- Some people who have human immunodeficiency virus (HIV) need to take several tablets each day for their HIV because existing single tablet treatments do not work for them, might not be safe for them to take, or cause side effects
  - Taking several treatments a day for the same disease is called a "complex regimen"
- People with HIV are likely to be taking medicines to treat other health problems, so it is important to know how HIV treatments affect these medicines
- The ARTISTRY-1 study looked to see if two HIV medicines, bictegravir (BIC) and lenacapavir (LEN), taken together are effective and safe for people with HIV who switch from a complex HIV regimen
- In this analysis, researchers looked at how complex regimens or BIC/LEN might interact with other medicines that are frequently taken by people in the US for other health problems
- Researchers found that BIC/LEN is expected to have fewer interactions with frequently used medicines than some of the other commonly used combinations of HIV medicines
- Taking a single tablet that combines both BIC and LEN once a day may be of benefit to some people with HIV because BIC/LEN has a lower chance of interacting with other medicines compared with complex regimens

Introduction

- Many PWH are unable to benefit from guideline-recommended STRs due to drug resistance, intolerance, contraindications, or DDIs, and are required to take complex antiretroviral therapy (ART) regimens comprising ≥ 2 core antiretroviral classes, ≥ 2 pills/day, and/or requiring more than once-daily dosing[1-5]
  - CRs commonly include PIs coadministered with PK boosters, which inhibit drug-metabolizing enzymes, including CYP3A[6]
- CRs can create numerous challenges for PWH, including pill burden, suboptimal adherence, and reduced quality of life[7-9]
- PWH also often take concomitant medications to treat comorbidities[10-12]
  - It is important to evaluate these medications for potential DDIs, which are frequently reported with boosted PIs, to avoid toxicity and maintain efficacy of all medications[6,13]
- ARTISTRY-1 (NCT05502341) is an ongoing randomized, open-label, multicenter, active-controlled Phase 2/3 study evaluating the safety and efficacy of switching to a BIC/LEN STR in PWH who are VS on a CR[9]
  - BIC, a guideline-recommended INSTI, is primarily metabolized by CYP3A and UDP glucuronosyltransferase 1A1 (UGT1A1),[1,2,6] with similar contribution from these pathways
  - LEN, a first-in-class capsid inhibitor, is a substrate of CYP3A, UGT1A1, and P-gp, a moderate inhibitor of CYP3A, and a weak inhibitor of P-gp and breast cancer resistance protein[14-16]
- In the Phase 2 portion of ARTISTRY-1, a BIC + LEN fixed-dose combination was well tolerated and maintained virologic suppression through Week 48 in participants switching from a CR[9]
  - In Phase 3 of ARTISTRY-1, a BIC 75 mg/LEN 50 mg STR is being assessed

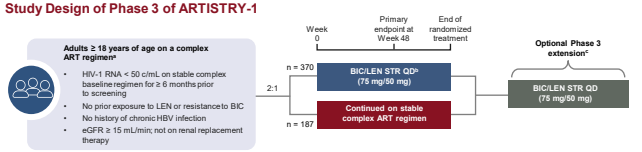
Objective

- To assess the DDI profile of BIC/LEN and representative CRs being used in the Phase 3 portion of ARTISTRY-1, in the context of frequently prescribed medications in the US

Methods

- ARTISTRY-1 (NCT05502341) is an ongoing randomized, open-label, multicenter, active-controlled Phase 2/3 study

Study Design of Phase 3 of ARTISTRY-1



A complex regimen was defined as:
- A regimen containing a boosted PI or NNRTI plus ≥ 1 other third agent from a class other than NRTI, or
- A regimen of ≥ 2 pills/day, or a regimen requiring dosing more than QD, or
- A regimen containing parenteral agent(s) (excluding a complete long-acting injectable regimen) as well as oral agents

Endpoints at Week 48:
- Primary endpoint: Proportion of participants with HIV-1 RNA ≥ 50 c/mL (by US FDA-defined Snapshot algorithm)
- Secondary endpoints:
  - Proportion of participants with HIV-1 RNA < 50 c/mL
  - Change from baseline in CD4 cell count
  - Proportion of participants with TEAEs through Week 48

[a]Due to viral resistance, intolerance, or contraindication to existing STRs.
[b]Participants received an oral loading dose of LEN 600 mg on Days 1 and 2 of treatment.
[c]Participants who switch from a CR in the extension phase will take the oral loading doses of LEN.
ART, antiretroviral therapy; BIC, bictegravir; c, copies; CD4, cluster of differentiation-4; CR, complex regimen; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; HBV, hepatitis B virus; LEN, lenacapavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; QD, once daily; STR, single tablet regimen; TEAE, treatment-emergent adverse event.

- The DDI profile of BIC/LEN and the top 6 most commonly used CRs from Phase 3 of ARTISTRY-1 was assessed with 18 frequently prescribed drugs in the US[a]
  - The top 10 most prescribed medications in the US were identified using the ClinCalc DrugStats Database 2022[17]: atorvastatin, metformin, lisinopril, levothyroxine, amlodipine, metoprolol, albuterol, losartan, omeprazole, gabapentin
  - A further 8 medications were identified from a literature search of commonly prescribed drugs in the elderly population: warfarin, apixaban, clopidogrel, fluticasone, prednisone, rosuvastatin, simvastatin, pravastatin
- DDI profiles were assessed using the Liverpool HIV Drug Interactions database[18] and/or US drug prescribing information
  - The DDI profiles for each of the individual drugs within the ART regimens of interest were combined

[a]Statins were to be used with caution during the ARTISTRY-1 study as concentrations may increase with LEN; the lowest dose was used, as appropriate, followed by titration to clinical response (maximum allowed dose: 10 mg simvastatin; 40 mg atorvastatin). Concomitant use of systemic corticosteroids with study drug may increase corticosteroid exposure; use of all systemic corticosteroids was limited to 7 days.

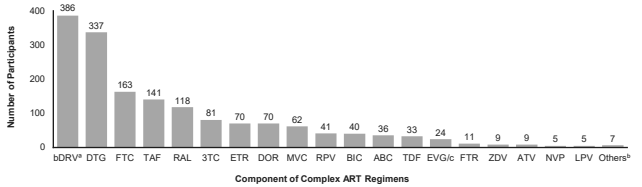
Results

Baseline Demographics

- The median (range) age of participants in Phase 3 of ARTISTRY-1 was 60 (22-84) years, with a median (range) of 7 (2-29) prior ART regimens
- In total, 96% of participants (n = 533) received ≥ 1 concomitant medication

For further details of baseline demographics and clinical characteristics, and the diversity of complex ART regimens in Phase 3 of ARTISTRY-1, please scan the QR code

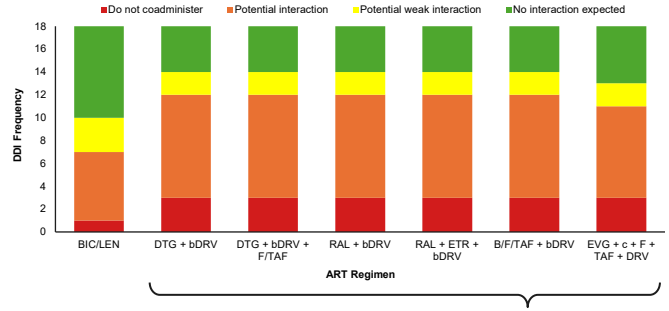
Number of Participants on Individual Antiretroviral Drugs as Part of Their Complex ART Regimen in the Phase 3 Portion of ARTISTRY-1



[a]DRV boosted with cobicistat or ritonavir.
[b]EFV (n = 2), CAB (n = 1), NFV (n = 1), ATV/c (n = 1), TPV (n = 1), IBAL (n = 1).
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; ATV, atazanavir; bDRV, boosted darunavir; BIC, bictegravir; c, cobicistat; CAB, cabotegravir; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ETR, etravirine; EVG, elvitegravir; FTC, emtricitabine; FTR, fostemsavir; IBAL, ibalizumab; LPV, lopinavir; MVC, maraviroc; NFV, nelfinavir; NVP, nevirapine; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TPV, tipranavir; ZDV, zidovudine.

- Of 557 participants enrolled and treated in Phase 3, the majority were on a CR containing a boosted PI and/or INSTI

DDI Profile of BIC/LEN and Representative[a] Complex ART Regimens



Concomitant Medication of Interest	BIC/LEN	Representative Complex ART Regimens
Albuterol		
Gabapentin		
Lisinopril		
Omeprazole		
Losartan		
Metoprolol		
Levothyroxine[b]		When coadministering with DRV/r or ETR, close monitoring of thyroid parameters is recommended, and adjustment of the levothyroxine dose may be necessary if clinically indicated
Pravastatin		When coadministering with bDRV or EVG + c + F + TAF, start with the lowest dose and titrate up to the desired clinical effect while monitoring for safety
Atorvastatin		When coadministering with bDRV or EVG + c + F + TAF, start with the lowest dose and titrate carefully while monitoring for safety
Prednisone		Monitoring is recommended when coadministering with bDRV, EVG/c, or ETR
Rosuvastatin		When coadministering with bDRV, start with the lowest dose and titrate up to the desired clinical effect while monitoring for safety
Amlodipine	LEN is expected to increase amlodipine concentrations by 60%; clinical monitoring is advised with dose adjustment if needed	Close monitoring is recommended when coadministering with bDRV or EVG/c. DRV/r and EVG/c are expected to increase amlodipine concentrations by ~100%; if coadministration is indicated, consider a dose reduction for amlodipine of 50%. With DRV/c, amlodipine should be started at low doses with careful titration to response
Apixaban	The product label for apixaban indicates that no dose adjustment is required for apixaban when coadministered with drugs that are not strong inhibitors of CYP3A4; monitoring for increased apixaban side effects is recommended	Use of bDRV or EVG/c and this anticoagulant is not recommended, although the US label gives the option to use apixaban at a reduced dose if needed
Metformin	Close monitoring should be considered when starting coadministration of BIC with metformin in those with moderate renal impairment, due to increased risk of lactic acidosis, and a dose adjustment of metformin should be considered if required	Reduction of the metformin dose should be highly considered in those who are taking DTG; careful monitoring and dose adjustment of metformin is recommended in those who are taking DRV/c or EVG + c + F + TAF; close monitoring should be considered when starting coadministration of BIC with metformin in those with moderate renal impairment, due to increased risk of lactic acidosis, and a dose adjustment of metformin should be considered if required
Warfarin	Monitor INR and adjust warfarin dose accordingly	Monitoring of INR is recommended
Fluticasone	Dose titration recommended in those who are taking LEN	
Simvastatin	Dose titration recommended in those who are taking LEN	
Clopidogrel		

[a]The top 6 most commonly used complex ART regimens in the Phase 3 portion of ARTISTRY-1 are shown.
[b]Potential interaction reported for DRV/r and ETR, but not for DRV/c or EVG + c + F + TAF + DRV (no interaction expected [green category]).
DDI categories are based on the Liverpool HIV Drug Interactions database (red: these drugs should not be coadministered; orange: potentially clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage, or timing of administration; yellow: potential interaction likely to be of weak intensity, additional action/monitoring or dosage adjustment is unlikely to be required; green: no clinically significant interaction expected).[18] Where more than one component of the ART regimen has a DDI identified with a drug of interest, the most severe category is shown. bDRV includes DDI profiles of both DRV/c and DRV/r.
ART, antiretroviral therapy; B/B/C, bictegravir/ bDRV; boosted darunavir; c, cobicistat; CYP3A4, cytochrome P450 3A4; DDI, drug-drug interaction; DRV, darunavir; DTG, dolutegravir; ETR, etravirine; EVG, elvitegravir; F, emtricitabine; INR, international normalized ratio; LEN, lenacapavir; r, ritonavir; RAL, raltegravir; TAF, tenofovir alafenamide.

- A larger number of potential DDIs were identified for ART regimens containing boosted PI than for BIC/LEN due to strong inhibition of the drug-metabolism pathway components CYP3A and P-gp by PK boosters cobicistat and ritonavir compared with moderate CYP3A inhibition and weak P-gp inhibition by LEN

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Disclosures: **PA**, **JMM-R**, **PS**, **BG-P**, and **DDM** are employees of, and hold stocks/shares in, Gilead Sciences, Inc.

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