



# Lenacapavir: a first-in-class HIV-1 capsid inhibitor

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## Purpose of review

This review summarizes available data for lenacapavir, an investigational first-in-class agent that disrupts functioning of HIV capsid protein across multiple steps in the viral life cycle.

## Recent findings

Lenacapavir demonstrated picomolar potency *in vitro* with no cross resistance to existing antiretroviral classes and potent antiviral activity in persons with HIV-1. In persons with HIV-1, there was no preexisting resistance to lenacapavir regardless of treatment history. Lenacapavir can be administered orally either daily or weekly and subcutaneously up to every 6 months. In heavily treatment-experienced persons with multidrug-resistant HIV-1 and in treatment-naïve persons with HIV-1, lenacapavir in combination with other antiretroviral agents led to high rates of virologic suppression and was well tolerated.

## Summary

Ongoing studies are evaluating long-acting dosing of lenacapavir for treating HIV-1 in combination with other antiretrovirals and preventing HIV-1 as a single agent.

## Keywords

capsid, every 6 months, HIV-1, lenacapavir, long-acting, subcutaneous

## INTRODUCTION

Combination antiretroviral therapy (cART) suppresses HIV-1 replication and increases CD4<sup>+</sup> cell counts. Persons on cART are projected to have life-spans equivalent to those without HIV-1 and do not transmit the virus to sexual partners if viral load is below detectable levels [1,2]. In addition, preexposure prophylaxis (PrEP) is highly effective in preventing new infections among individuals at risk. However, oral cART and PrEP regimens need to be taken every day and require near-perfect adherence to minimize the emergence of drug resistant variants and prevent new infection, respectively.

Suboptimal adherence is a major cause of incomplete viral suppression, and there are multiple barriers to adherence, such as inconvenience, side effects, stigma and discrimination [3]. Some persons with HIV-1 (PWH) eventually lose virologic, immunologic or clinical benefit from individual regimens, and PWH with multiple prior regimen failures and significant drug resistance have limited treatment options. Therefore, developing well tolerated and effective therapies for heavily treatment-experienced (HTE) individuals with multidrug-resistant HIV-1 is a priority.

Lenacapavir is a novel, first-in-class, multistage, selective inhibitor of HIV capsid protein. In clinical studies, lenacapavir has demonstrated successful antiviral activity and adequate pharmacokinetic exposure for up to 6 months after a single

subcutaneous injection. As described in the following section, existing Phase 1, 2 and 2/3 data support lenacapavir use in both HTE and treatment-naïve PWH in combination with antiretroviral agents.

## MECHANISM OF ACTION

Lenacapavir interferes with multiple stages of the HIV life cycle (Fig. 1). By binding to two neighbouring subunits of the HIV capsid protein, lenacapavir interferes with their interactions essential for multiple phases of the viral replication cycle [4,5]. These include capsid-mediated nuclear uptake of preintegration complexes, virion production and proper capsid core formation. Virus produced in the presence of lenacapavir displays improperly shaped capsids that can enter new target cells but cannot replicate.

## IN-VITRO POTENCY AND RESISTANCE PROFILE

In HIV-1 infected MT-4 cells, lenacapavir showed a mean half-maximum effective concentration (EC<sub>50</sub>)

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## KEY POINTS

- Lenacapavir is a highly potent first-in-class capsid inhibitor in clinical development as a long-acting subcutaneous or oral agent with a half-life of 8–12 weeks and 10–12 days, respectively.
- Lenacapavir has no overlapping resistance with any approved agents, and there are no preexisting resistance or polymorphisms that reduce viral susceptibility to lenacapavir.
- Lenacapavir in combination with other antiretroviral agents led to high rates of virologic suppression in heavily treatment-experienced and treatment-naïve PWH.
- Emergent resistance to lenacapavir was seen in clinical studies, but it was often associated with high fitness cost.
- Lenacapavir has a potential to meet the diverse needs of PWH and individuals at risk with a flexible dosing interval (daily, weekly or up to every 6 months) and route of administration (injectable or oral).

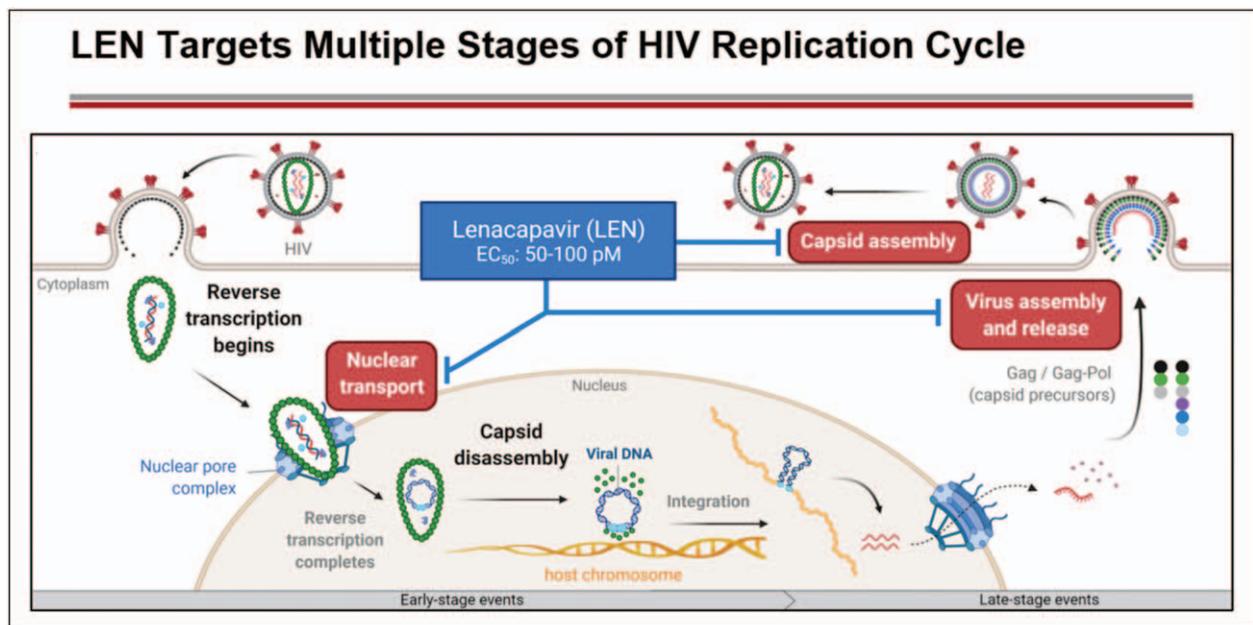
of 105 pmol/l, making it significantly more potent than many existing antiretroviral drugs [4<sup>11</sup>]. Lenacapavir showed picomolar mean EC<sub>50</sub> values in primary human CD4<sup>+</sup> T cells (32 pmol/l) and macrophages (56 pmol/l) infected with HIV-1 and was broadly active against two HIV-2 isolates (885 pmol/l). In addition, lenacapavir displays similar antiviral activity against HIV-1 clinical isolates (A, A1, AE, AG, B, BF, C, D, G and H), with a mean

EC<sub>50</sub> value of 0.24 nmol/l and range from 0.15 to 0.36 nmol/l, in HEK293T cells [4<sup>11</sup>,6].

In-vitro resistance selection assays in MT-2 cells and human peripheral blood mononuclear cells identified Q67H and N74D as the major resistance-associated mutations. Additional variants included L56I, M66I, K70N, Q67H/N74S and Q67H/T107N. These resistance-associated mutations, alone or in combination, confer reduced susceptibility to lenacapavir (six to >3200-fold resistance relative to wild-type). All but the low-level resistant variant Q67H (six-fold resistance to lenacapavir relative to wild-type virus) display reduced replication capacity *in vitro*. For example, M66I variant had only 1.5% replication capacity relative to wild type [6]. However, the clinical relevance of these findings is yet to be established.

Lenacapavir maintains potent antiviral activity against HIV-1 site-directed mutants and clinical isolates resistant to currently approved antiretrovirals in the following classes: nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs) and protease inhibitors [7].

Lenacapavir is expected to be fully active regardless of prior treatment history because of its first-in-class nature. Among 1500 PWH, including treatment-naïve ( $n=500$ ) or treatment-experienced ( $n=1000$ ;  $n=500$  with protease inhibitor experience and  $n=500$  without), none of the lenacapavir resistance mutations identified during in-vitro selection experiments was detected [8]. These data were



**FIGURE 1.** Lenacapavir targets multiple stages of the HIV replication cycle. Adapted from [4<sup>11</sup>,5].

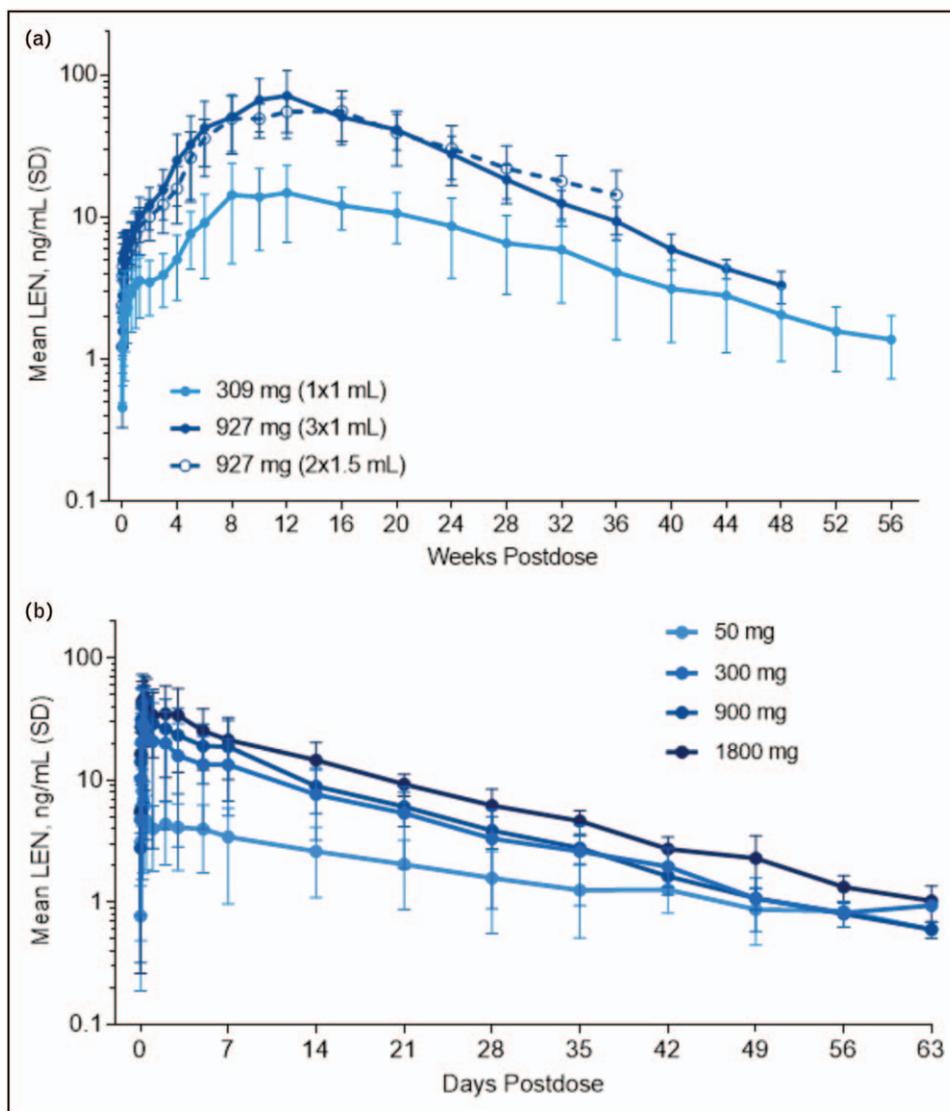
confirmed in 182 treatment-naïve individuals participating in CALIBRATE (see below), whose viruses had mean  $EC_{50}$  fold-change of 1.0 (range: 0.5–2.5) comparable to that of wild-type [6,9]. In addition, the antiviral activity of lenacapavir in clinical isolates is unaffected by the presence of naturally occurring Gag polymorphisms or Gag cleavage site mutations associated with protease inhibitor treatment and resistance to maturation inhibitors [7]. In contrast, those polymorphisms and mutations lead to reduced susceptibility to maturation inhibitors. These data suggest that lenacapavir is expected to have full activity regardless of prior treatment history.

### PHARMACOKINETIC PROFILE

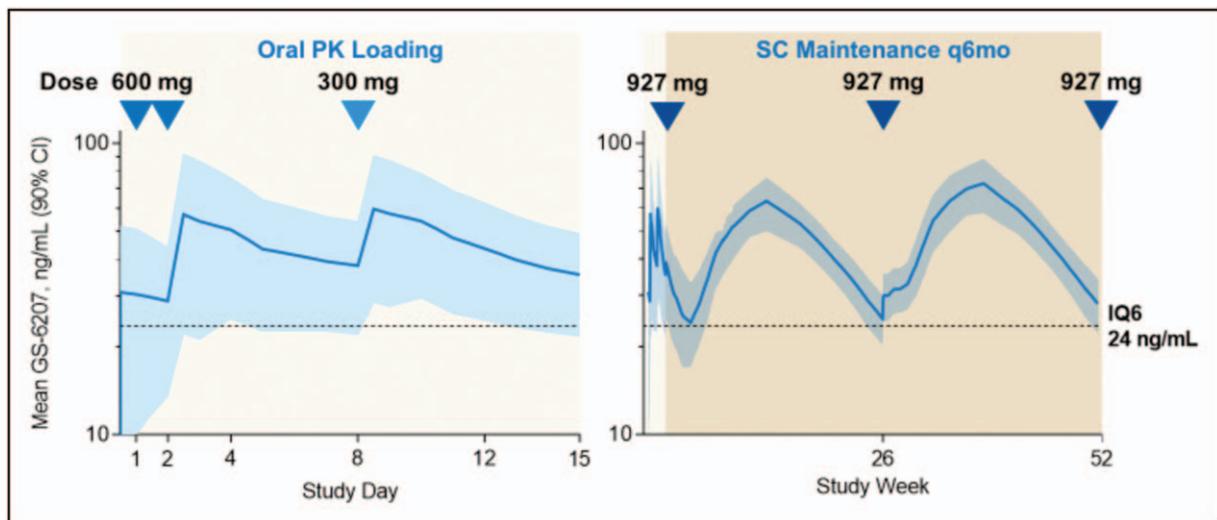
In a single-ascending clinical study in healthy participants, subcutaneous administration of lenacapavir

had a slow, sustained release and dose-proportional increases in exposures up to 927 mg (Fig. 2). The slow release of lenacapavir from the administration site creates a complex absorption profile, with delayed and first-order absorption kinetics resulting in a  $T_{max}$  of 77–84 days postdose and apparent  $t_{1/2}$  from 8 to 12 weeks [10<sup>¶</sup>]. After a single, 927 mg subcutaneous dose of lenacapavir, target plasma concentrations are sustained for at least 6 months, corresponding to a mean inhibitory quotient of at least 6 (i.e. six-fold higher than the protein-adjusted  $EC_{95}$ ). However, a slow initial rise after administration of subcutaneous lenacapavir in the first few weeks was noted, leading to consideration of initial pharmacokinetic loading with oral lenacapavir.

For oral tablets, single-dose administration in the range from 50 to 1800 mg showed increased



**FIGURE 2.** Observed lenacapavir plasma concentrations following oral (a) and subcutaneous (b) administration. Adapted from [10<sup>¶</sup>,11<sup>¶</sup>].



**FIGURE 3.** Predicted lenacapavir pharmacokinetics for phase 2/3 oral and subcutaneous combination regimens in healthy volunteers. Adapted from [10<sup>\*</sup>].

exposure with higher doses, but this increase is not dose proportional (Fig. 2) [11<sup>\*</sup>]. Oral lenacapavir has a  $t_{1/2}$  of nearly 10–12 days, and absorption is not affected by the presence of food. In ongoing clinical studies, oral lenacapavir is being used for initial pharmacokinetic loading prior to initiating subcutaneous administration every 6 months (Fig. 3). In addition, oral lenacapavir can be administered daily or weekly in combination with other antiretroviral agents, which can facilitate development of multiple lenacapavir-containing regimens with dosing intervals ranging from daily to weekly or even up to every 6 months.

### DRUG–DRUG INTERACTIONS

The potential for drug–drug interactions with lenacapavir were evaluated in a clinical study [12<sup>\*</sup>]. Inhibitors of CYP3A and CYP3A/P-gp increased lenacapavir exposures, but not to a clinically relevant extent, supporting their coadministration with lenacapavir (e.g. cobicistat). Strong inducers of CYP3A/P-gp/UGT1A1 (e.g. rifampin) reduced lenacapavir exposures significantly, and their coadministration is contraindicated. Lenacapavir is a moderate inhibitor of CYP3A and caution is required for coadministration with sensitive CYP3A substrates with a narrow therapeutic window. There is no restriction on co-administration of lenacapavir with BCRP, P-gp and OATP substrates or with acid-reducing agents. Most of the commonly used antiretroviral agents have no clinically relevant drug–drug interaction potential with lenacapavir. However, some are not recommended due to strong inhibition potential (e.g. boosted atazanavir, which

inhibits all three of CYP3A/P-gp/UGT1A1) or moderate induction potential (e.g. efavirenz, nevirapine or boosted tipranavir). Sex-affirming hormones and oral contraceptives are not expected to have clinically relevant drug–drug interactions with lenacapavir.

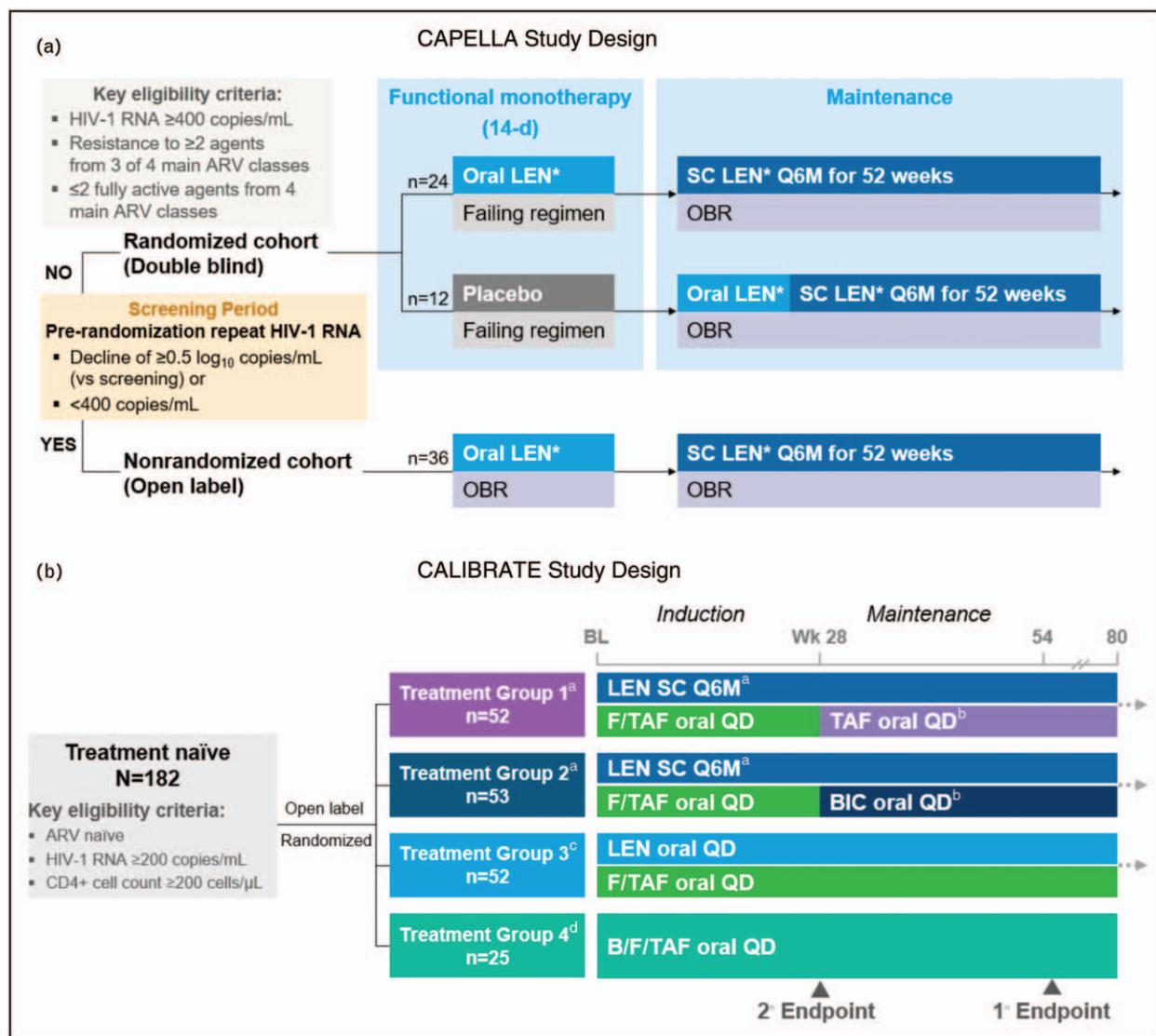
### LENACAPAVIR FOR TREATMENT OF PERSONS WITH HIV-1: CLINICAL STUDIES

#### Proof of concept

In PWH not taking antiretroviral therapy, lenacapavir demonstrated potent antiviral activity, with declines of up to 2.3  $\log_{10}$  copies/ml in 10 days in a proof-of-concept, dose-ranging study of single subcutaneous doses (20, 50, 150, 450 or 750 mg;  $n = 6/\text{cohort}$ ) [13<sup>\*</sup>]. The  $E_{\text{max}}$  on Day 10 postdose was predicted to be a 2.1  $\log_{10}$  decline in HIV-1 RNA, and the mean lenacapavir concentration of at least 4.4 ng/ml (inhibitory quotient  $\geq 1.1$ ) was predicted to provide near maximal antiviral activity.

#### CAPELLA study (clinicaltrials.gov identifier: NCT04150068)

Thirty-six HTE PWH who were failing their existing regimen were randomly assigned (2 : 1) to lenacapavir or placebo in a double-blind manner (Fig. 4) [14<sup>\*</sup>,15<sup>\*</sup>]. Participants had HIV-1 RNA at least 400 c/ml and were resistant to at least two agents from at least three of the four major antiretroviral classes. For the first 2 weeks, in addition to receiving their existing antiretroviral regimen, 24 participants received oral lenacapavir (600 mg on Days 1 and 2



**FIGURE 4.** Study designs of CAPELLA (a) and CALIBRATE (b). Adapted from [15<sup>\*</sup>,16<sup>\*</sup>]. (a) Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 ml) in the abdomen on Day 15. OBR, optimized background regimen (investigational agents, such as fostemsavir, were allowed; atazanavir (ATV), ATV/cobicistat, ATV/ritonavir, efavirenz, entecavir, nevirapine, tipranavir were not allowed). (b) <sup>a</sup>LEN oral lead-in (600 mg on Days 1 and 2, 300 mg on Day 8) followed by LEN SC 927 mg on Day 15; F/TAF 200/25 mg; <sup>b</sup>Participants in TG 1 and 2 will need HIV-1 RNA results  $< 50$  copies/ml at Wks 16 and 22 to initiate either TAF 25 mg or BIC 75 mg at Wk 28; those with HIV-1 RNA  $\geq 50$  copies/ml will discontinue study at Wk 28; <sup>c</sup>LEN 600 mg on Days 1 and 2, followed by LEN 50 mg from Day 3; F/TAF 200/25 mg; <sup>d</sup>B/F/TAF 50/200/25 mg. ARV, antiretroviral; BIC, B, bictegravir; BL, baseline; DMC, data monitoring committee; QD, once daily; Q6M, every 6 months; TG, treatment group; Wk, Week.

and 300 mg on Day 8), and 12 received placebo. Thus, these first 14 days were considered a period of functional monotherapy. At Day 15, all participants initiated an investigator-selected optimized background regimen. Those initially assigned to oral lenacapavir started subcutaneous lenacapavir (927 mg) every 6 months, while those on placebo started a lenacapavir 2-week oral lead-in, followed by subcutaneous, 6-month dosing. Subsequently, an additional nonrandomized cohort of 36 participants

received 14 weeks of oral lenacapavir followed by subcutaneous lenacapavir every 6 months.

Following initiation of lenacapavir, rapid reductions in HIV-1 RNA were observed among the 36 randomized patients; at the end of the first 14 days (functional monotherapy), 88% (21/24) receiving lenacapavir had a reduction in HIV-1 RNA of at least 0.5  $\log_{10}$  copies/ml compared with 17% (2/12) receiving placebo. At Week 26, 81% of randomized participants (29/36) had HIV-1 RNA less than

50 copies/ml. Four randomized participants had emergent lenacapavir resistance. Lenacapavir was well tolerated. No serious adverse events related to study drug occurred, and there were no discontinuations due to adverse events.

### **CALIBRATE study (clinicaltrials.gov identifier: NCT04143594)**

Lenacapavir is also being evaluated in an open-label, Phase 2, active-controlled, induction-maintenance study of treatment-naïve PWH with CD4<sup>+</sup> cell counts at least 200 cells/ $\mu$ l (Fig. 4). Participants were randomized (2:2:2:1) to one of four treatment groups [16<sup>\*</sup>]. The first and second groups received lenacapavir (given initially orally for loading/lead-in, then subcutaneously) with oral daily emtricitabine/tenofovir alafenamide, prior to switching from emtricitabine/tenofovir alafenamide to oral daily tenofovir alafenamide (Group 1) or bicitegravir (Group 2). The third group received oral daily lenacapavir with emtricitabine/tenofovir alafenamide throughout the study. The fourth group, a control arm, received oral daily bicitegravir/emtricitabine/tenofovir alafenamide.

Lenacapavir, administered subcutaneously or orally, in combination with emtricitabine/tenofovir alafenamide led to high rates of viral suppression by Week 28 (94%;  $n = 147/157$ ). One participant receiving subcutaneous lenacapavir and emtricitabine/tenofovir alafenamide had emergent resistance to lenacapavir. Lenacapavir was well tolerated. No serious adverse events or Grade 4 adverse events were reported as related to study drug. Two participants discontinued due to adverse events (both due to Grade 1 injection site induration).

### **Lenacapavir for prevention of HIV-1 in persons at risk: preclinical studies**

GS-CA1, a close lenacapavir analogue active against both HIV-1 and SIV, has been evaluated as a long-acting PrEP agent in a macaque rectal SHIV challenge model [17]. Uninfected Indian rhesus macaques received a single subcutaneous injection of vehicle control (placebo), 150 mg/kg (low dose) or 300 mg/kg (high dose) GS-CA1, followed by weekly escalating titre SHIV challenges starting 1 week post-dosing. After a total of 15 challenges, eight out of eight placebo-exposed animals became infected, whereas two out of eight animals receiving low-dose GS-CA1 and five out of eight receiving high-dose GS-CA1 remained protected. The median time to infection was 7.5 weeks in the placebo group, 16 weeks in the low-dose GS-CA1 group and not reached due to insufficient number of infections in the high-dose

group. Relative to the placebo group, the low-dose and high-dose treatment groups demonstrated an 86% ( $P = 0.0061$ ) and 96% ( $P = 0.0002$ ) reduction in risk of infection, respectively, as determined by Cox regression analysis. Notably, on the basis of a 2-week infection-to-detection window, treatment group infections occurred only after plasma GS-CA1 concentrations fell below 2X paEC95.

### **Future directions**

As a first in class capsid inhibitor, lenacapavir demonstrated potent antiviral activity in individuals with HIV-1, prophylactic activity in macaques and high efficacy in combination with other antiretrovirals for individuals at two ends of the treatment spectrum: those initiating therapy for the first time and those who are heavily treatment experienced with multidrug resistance. Future studies will investigate ways to translate the unique properties of lenacapavir, such as its novel mechanism of action with no preexisting resistance, flexible route of administration (oral or injectable) and dosing interval (daily, weekly or up to every 6 months), into clinical benefit. Lenacapavir has the potential to address the diverse needs of individuals with HIV-1, who have varied treatment histories, prior resistance, status of viremia and preferences for daily or long-acting therapy, as well as those at risk for HIV-1.

Long-acting regimens with infrequent dosing, for example injectable up to every 6 months or oral weekly, have a potential role in addressing challenges with adherence to oral daily therapy and treatment fatigue associated with it. Subcutaneous lenacapavir administered by healthcare providers every 6 months coincides with the minimum clinical visit schedule and does not pose additional treatment burden for many PWH. An oral weekly regimen could benefit individuals who prefer an oral regimen but one that can be taken less frequently than daily. There are ongoing efforts to develop a long-acting partner agent to be combined with lenacapavir for a complete long-acting injectable or oral weekly regimen. Currently, lenacapavir is being evaluated in combination with islatravir, a nucleoside reverse transcriptase translocation inhibitor (NRTTI) as an oral weekly regimen in virologically suppressed PWH (ClinicalTrials.gov Identifier: NCT05052996). An injectable regimen of islatravir and lenacapavir with a longer dosing interval is also being developed.

Subcutaneous lenacapavir administered every 6 months is being evaluated as PrEP in two Phase 3 studies: PURPOSE-1 (ClinicalTrials.gov Identifier: NCT04994509) in adolescent girls and young

women at risk of HIV-1 infection and PURPOSE-2 (ClinicalTrials.gov Identifier: NCT04925752) in cis-gender men, transgender women, transgender men and sex nonbinary people at least 16 years of age at risk for HIV-1 infection.

Lenacapavir is a first-in-class capsid inhibitor with long-acting properties. It has the potential to be developed as part of an injectable regimen with an up to 6-month dosing interval or an oral regimen with an up to weekly dosing interval, providing additional treatment options to address the diverse needs of persons with HIV-1 and for those who would benefit from PrEP.

## Acknowledgements

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None.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- ■ of outstanding interest

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This conference presentation describes lenacapavir subcutaneous pharmacokinetics supporting a dosing interval of 6 months.

11. Begley R, Rhee M, West SK, *et al.* PK, food effect, and safety of oral GS-6207, a novel HIV-1 capsid inhibitor. 2020 Conference on Retroviruses and Opportunistic Infections; Boston, Massachusetts, USA; March 8–11, 2020. Abstract 470.

This conference presentation describes lenacapavir oral pharmacokinetics supporting loading and weekly dosing.

12. Begley R, Lutz J, Dvory-Sobol H, *et al.* Clinical evaluation of drug interactions ■ with oral lenacapavir and probe drugs. 2021 Conference on Retroviruses and Opportunistic Infections; Virtual; March 6–10, 2021. Abstract 89.

This conference presentation describes oral lenacapavir as a victim and perpetrator of drug interactions.

13. Daar E, McDonald C, Crofoot G, *et al.* Dose-response relationship of subcutaneous long-acting HIV capsid inhibitor GS-6207. 2020 Conference on Retroviruses and Opportunistic Infections; Boston, Massachusetts, USA; March 8–11, 2020. Poster 3691.

This conference presentation describes a proof-of-concept study demonstrating that single subcutaneous doses of lenacapavir resulted in a decline of up to 2.3-log<sub>10</sub> copies/mL at Day 10 in persons with HIV not taking antiretroviral therapy.

14. Segal-Maurer S, Castagna A, Berhe M, *et al.* Potent antiviral activity of ■ lenacapavir in Phase 2/3 in heavily ART-experienced PWH. 2021 Conference on Retroviruses and Opportunistic Infections; Virtual; March 6–10, 2021. Abstract 127.

This conference presentation describes the primary endpoint of a study in heavily treatment-experienced persons with HIV, in which lenacapavir demonstrated potent antiviral activity (1.9 log<sub>10</sub> decline) at Day 15 when added to a failing regimen.

15. Molina J-M, Segal-Maurer S, Stellbrink HJ, *et al.* Efficacy and safety of long-acting subcutaneous lenacapavir in Phase 2/3 in heavily treatment-experienced people with HIV: Week 26 results (Capella Study). 2021 International AIDS Society Conference; Virtual; July 18–21, 2021. Abstract OALX01B02.

This conference presentation describes the safety and efficacy of lenacapavir in combination with an optimized background regimen in heavily treatment-experienced persons with HIV at Week 26 (secondary endpoint) and demonstrated high rates of virologic suppression (81%).

16. Gupta SK, Berhe M, Crofoot G, *et al.* Long-acting subcutaneous lenacapavir ■ dosed every 6 months as part of a combination regimen in treatment-naïve people with HIV: Interim 16-week results of a randomized, open-label, Phase 2 induction-maintenance study (CALIBRATE). 2021 International AIDS Society Conference; Virtual; July 18–21, 2021. Abstract OALB0302.

This conference presentation describes the safety and efficacy of lenacapavir in combination with emtricitabine/tenofovir alafenamide in treatment-naïve persons with HIV at Week 28 and demonstrated high rates of virologic suppression (94%).

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