ORIGINAL ARTICLE

Capsid Inhibition with Lenacapavir in Multidrug-Resistant HIV-1 Infection

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ABSTRACT

BACKGROUND

Patients with multidrug-resistant human immunodeficiency virus type 1 (HIV-1) infection have limited treatment options. Lenacapavir is a first-in-class capsid inhibitor that showed substantial antiviral activity in a phase 1b study.

METHODS

In this phase 3 trial, we enrolled patients with multidrug-resistant HIV-1 infection in two cohorts, according to the change in the plasma HIV-1 RNA level between the screening and cohort-selection visits. In cohort 1, patients were first randomly assigned in a 2:1 ratio to receive oral lenacapavir or placebo in addition to their failing therapy for 14 days; during the maintenance period, starting on day 15, patients in the lenacapavir group received subcutaneous lenacapavir once every 6 months, and those in the placebo group received oral lenacapavir, followed by subcutaneous lenacapavir; both groups also received optimized background therapy. In cohort 2, all the patients received open-label oral lenacapavir with optimized background therapy on days 1 through 14; subcutaneous lenacapavir was then administered once every 6 months starting on day 15. The primary end point was the percentage of patients in cohort 1 who had a decrease of at least 0.5 $\log_{10}$ copies per milliliter in the viral load by day 15; a key secondary end point was a viral load of less than 50 copies per milliliter at week 26.

RESULTS

A total of 72 patients were enrolled, with 36 in each cohort. In cohort 1, a decrease of at least 0.5 $\log_{10}$ copies per milliliter in the viral load by day 15 was observed in 21 of 24 patients (88%) in the lenacapavir group and in 2 of 12 patients (17%) in the placebo group (absolute difference, 71 percentage points; 95% confidence interval, 35 to 90). At week 26, a viral load of less than 50 copies per milliliter was reported in 81% of the patients in cohort 1 and in 83% in cohort 2, with a least-squares mean increase in the CD4+ count of 75 and 104 cells per cubic millimeter, respectively. No serious adverse events related to lenacapavir were identified. In both cohorts, lenacapavir-related capsid substitutions that were associated with decreased susceptibility developed in 8 patients during the maintenance period (6 with M66I substitutions).

CONCLUSIONS

In patients with multidrug-resistant HIV-1 infection, those who received lenacapavir had a greater reduction from baseline in viral load than those who received placebo. (Funded by Gilead Sciences; CAPELLA ClinicalTrials.gov number, NCT04150068.)

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N Engl J Med 2022;386:1793-803.
DOI: 10.1056/NEJMoa2115542

A Quick Take is available at NEJM.org

For most patients with human immunodeficiency virus type 1 (HIV-1) infection, an effective antiretroviral regimen can be devised.[1] However, some patients have multiple treatment failures due to viral resistance or unacceptable side effects to medication and no longer have durable viral suppression.[2,3] Patients with multidrug-resistant HIV-1 are at increased risk for hospitalization, progression to acquired immunodeficiency syndrome, and death.[4]

Lenacapavir is a first-in-class inhibitor of HIV-1 capsid function.[5] By interfering with capsid-mediated nuclear uptake of preintegration complexes and impairing virion production, lenacapavir inhibits viral replication at both early and late stages of the life cycle. In vitro, lenacapavir has antiviral activity against viral mutations that are resistant to major antiretroviral classes of drugs.[6,7] Lenacapavir can be administered in a long-acting fashion — up to every 6 months subcutaneously or weekly orally — because of its picomolar potency, low clearance, and slow release kinetics.[5,8,9] In a phase 1b study, lenacapavir showed substantial antiviral activity.[10] In the ongoing phase 3 CAPELLA trial, we assessed the efficacy and safety of lenacapavir in patients with multidrug-resistant HIV-1 infection.

Methods

Patients

From November 2019 through January 2021, we screened and enrolled patients at 42 investigational sites in 11 countries. Eligible patients were 12 years of age or older and had received a stable failing drug therapy (as indicated by an HIV-1 RNA level of ≥400 copies per milliliter) for at least 8 weeks, with documented resistance to at least two antiretroviral medications from at least three of the four main classes (nucleoside reverse-transcriptase inhibitors, non–nucleoside reverse-transcriptase inhibitors, protease inhibitors, and integrase strand-transfer inhibitors) and to no more than two fully active antiretroviral drugs from the four main classes that could be effectively combined. (For fixed-dose combination drugs, we evaluated the resistance to each of the individual components.) Full eligibility criteria are provided in the protocol, available with the full text of this article at NEJM.org.

Trial Design and Regimens

The trial design called for the enrollment of patients in one of two cohorts, according to the change in the plasma HIV-1 RNA level between the screening and cohort-selection visits occurring 14 to 30 days apart (Fig. 1A).

Cohort 1 was designed to include the first 36 patients who had a decrease of less than 0.5 $\log_{10}$ copies per milliliter (i.e., stable viremia confirming lack of response to the failing therapy) between the screening and cohort-selection visits and an HIV-1 RNA level of 400 copies or more per milliliter. These patients began a functional monotherapy period after having undergone randomization in a 2:1 ratio to receive either oral lenacapavir (600 mg on days 1 and 2 and 300 mg on day 8) or matching placebo in a directly observed fashion while continuing their failing therapy. The investigators, patients, and trial personnel were unaware of randomized assignments during the functional monotherapy period. In the maintenance period, starting on day 15, patients in the lenacapavir group received subcutaneous lenacapavir (927 mg as two 1.5-ml injections in the abdomen), which was subsequently administered by a health care professional once every 6 months, plus optimized background therapy. Those in the placebo group received oral lenacapavir (600 mg on days 15 and 16 and 300 mg on day 22), followed by subcutaneous lenacapavir plus optimized background therapy.

Cohort 2 was designed to include patients who had a decrease of at least 0.5 $\log_{10}$ copies per milliliter between the screening and cohort-selection visits, a viral load of less than 400 copies per milliliter, or both; patients who had been found to be eligible to participate in cohort 1 after closure of enrollment in that cohort could also be included. All the patients in cohort 2 received open-label oral lenacapavir (600 mg on days 15 and 16 and 300 mg on day 22), followed by subcutanneous lenacapavir, with optimized background therapy on day 1 and started to receive subcutaneous lenacapavir once every 6 months on day 15.

End Points and Assessments

Primary and secondary efficacy end points were evaluated in cohort 1. The primary efficacy end point was the percentage of patients who had a reduction from baseline of at least 0.5 $\log_{10}$ copies

per milliliter in the plasma HIV-1 RNA viral load (by TaqMan, version 2.0 [Roche]) by day 15 (end of the functional monotherapy period). The secondary end points were the percentage of patients with a viral load of less than 50 copies per milliliter and the percentage with a viral load of less than 200 copies per milliliter at week 26 after the initiation of subcutaneous lenacapavir. Other key efficacy end points included changes in the viral load and CD4+ count. Since cohort 2 was primarily designed to provide access to lenacapavir for patients who had met the same eligibility criteria as those in cohort 1 but were not eligible for randomization, the efficacy in this cohort was not included in the prespecified end points.

Virologic failure for the purpose of resistance analysis was defined as any of the following: a confirmed HIV-1 RNA load of at least 50 copies per milliliter and a decrease of less than 1 $\log_{10}$ copy per milliliter at week 4 after the initiation of oral lenacapavir, a confirmed rebound in the viral load to at least 50 copies per milliliter after a previous measure of less than 50 copies per milliliter, a confirmed increase from the nadir value of more than 1 $\log_{10}$ copy per milliliter, or a viral load of at least 50 copies per milliliter at week 26 or at the time of trial discontinuation.

We performed capsid genotypic and phenotypic resistance analysis (Monogram Biosciences) using a sample obtained at the initial visit for the evaluation of potential virologic failure; a sample that was obtained at the confirmation visit was tested for resistance to protease, reverse-transcriptase, and integrase inhibitors. We report the change in drug susceptibility as compared with wild-type control. Measurement of lenacapavir was performed with the use of a validated liquid chromatography–tandem mass spectrometry bioanalytical method with a range of 0.1 to 500 ng per milliliter.

OVERSIGHT

The trial was approved by the institutional review board or ethics committee at each site and was conducted in compliance with international laws and guidelines. All the patients provided written informed consent. The trial was designed and conducted by the sponsor (Gilead Sciences) in collaboration with the investigators. The sponsor collected the data, monitored trial conduct, and performed the statistical analyses.

STATISTICAL ANALYSIS

We calculated that a sample size of 36 patients (24 in the lenacapavir group and 12 in the placebo group) in cohort 1 would provide a power of more than 90% to detect an absolute difference between lenacapavir and placebo of 60 percentage points in the proportion of patients with a reduction of at least 0.5 $\log_{10}$ copies per milliliter on day 15 (the primary efficacy end point). We used Barnard's unconditional exact method to compare the between-group difference in proportions, with an alpha level set at 0.05 to evaluate superiority. The point estimate and the 95% confidence interval were calculated with the use of the Chan and Zhang method.[11] As a supportive analysis, we performed a rank analysis of covariance using the primary efficacy end point as a dependent variable, the trial group as a main effect, and the baseline HIV-1 RNA level as a covariate. We used the Food and Drug Administration Snapshots algorithm to assess the secondary end point of the percentage of patients in cohort 1 with a viral load below 50 copies per milliliter and below 200 copies per milliliter at week 26.[12] All the patients who had received at least one dose of lenacapavir were assessed for safety. Included in the analyses were all efficacy data through week 26 for both cohorts and all available cumulative safety data as of the data-cutoff date of August 5, 2021.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Of the 144 patients who underwent screening, 72 were enrolled in the trial (Fig. 1B). Of these patients, 36 were enrolled in cohort 1 (with 24 assigned to receive lenacapavir and 12 assigned to receive placebo during the functional monotherapy period), and 36 were enrolled in cohort 2 (Table 1). Three patients were enrolled in cohort 2 because they did not meet the inclusion criteria for cohort 1, and 33 patients were enrolled after cohort 1 had been closed. The randomized groups in cohort 1 were balanced with respect to demographic characteristics. However, the patients in the lenacapavir group had a lower median HIV-1 RNA value than those in the placebo group (4.2 $\log_{10}$ copies vs. 4.9 $\log_{10}$ copies per milliliter). Although most of the patients had severe immunodeficiency (75% with a CD4+ count of <200 cells per cubic millimeter), the

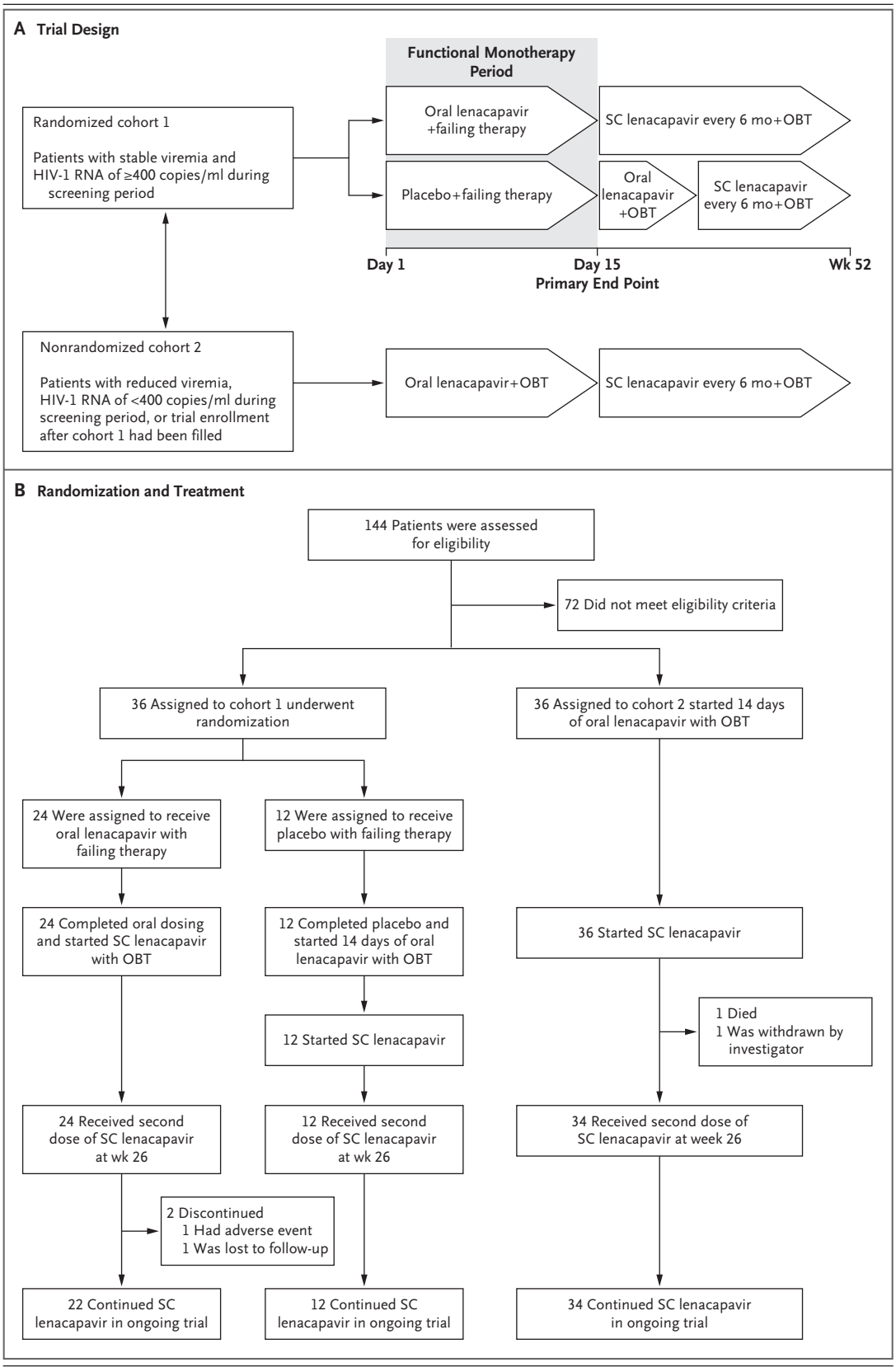

Figure 1 (facing page). Trial Design and Randomization.
Panel A shows the overall trial design in which patients with multidrug-resistant human immunodeficiency virus 1 (HIV-1) infection were assigned to one of two cohorts according to the change in their HIV-1 RNA viral load and $\log_{10}$ copies per milliliter between the screening and cohort-selection visits. In cohort 1, patients were randomly assigned to receive either oral lenacapavir or placebo plus their already failing drug therapy for the first 14 days and subsequently received subcutaneous (SC) lenacapavir or oral lenacapavir, respectively, along with optimized background therapy (OBT). In cohort 2, all the patients received oral lenacapavir, followed by SC lenacapavir once every 6 months, and started OBT at day 1. The primary end point was the percentage of patients in cohort 1 who had a decrease in viral load from baseline of at least 0.5 $\log_{10}$ copies per milliliter by day 15. Panel B shows the randomization and treatment schedules in the two cohorts as of the data cutoff at week 26. In cohort 2, among the 36 patients, 3 did not meet the criteria for reduced viremia during their cohort-selection visit, whereas 33 were enrolled in the trial after closure of cohort 1.

median CD4+ count was higher in the lenacapavir group than in the placebo group (172 cells vs. 85 cells per cubic millimeter). As compared with the overall global HIV-1 population, the trial patients had more advanced HIV-1 infection, which was consistent with a history of multidrug resistance, and a majority (58%) were from the United States (Table S1).

The patients in cohort 1 had undergone previous treatment with a median of nine antiretroviral medications and had a median overall susceptibility score for the failing regimens of 0.8. (The drug susceptibility score to an individual antiretroviral medication was determined according to a proprietary algorithm, with 1.0 indicating full susceptibility, 0.5 partial susceptibility, and 0 no susceptibility; the overall susceptibility score was a sum of individual susceptibility scores.) Resistance to all four major classes of antiretroviral medications was reported in 47% of the patients. Many of the patients had exhausted both the integrase (54%) and protease inhibitor (42%) classes owing to resistance, whereas others had resistance to agents that have recently been approved for heavily treatment-experienced adults (ibalizumab in 11 of 33 patients [33%] and fostemsavir in 10 of 33 [30%]). Of the 36 trial patients, 6 (17%) had no fully active agents in their optimized background therapy. The characteristics of the patients in cohort 2 were similar to those in cohort 1.

All the patients in cohorts 1 and 2 completed the functional monotherapy period or oral lenacapavir course, respectively, and all received their first dose of subcutaneous lenacapavir. One patient died (at week 10), and 3 patients discontinued lenacapavir: 1 because of an adverse event (a grade 1 injection-site nodule) at week 62, 1 because of loss to follow-up at week 26, and 1 at the investigator's discretion because of nonadherence to the regimen at week 16. For the safety analysis, the median duration of follow-up was 438 days (range, 292 to 583) in cohort 1 and 254 days (range, 90 to 513) in cohort 2.

EFFICACY

During the functional monotherapy period in cohort 1, the primary efficacy outcome of a reduction of at least 0.5 $\log_{10}$ copies per milliliter in HIV-1 RNA occurred in 21 of 24 patients (88%) in the lenacapavir group and in 2 of 12 patients (17%) in the placebo group (absolute difference, 71 percentage points; 95% confidence interval [CI], 35 to 90; P<0.001). The least-squares mean (±SE) change in the viral load was –2.10±0.15 $\log_{10}$ copies per milliliter in the lenacapavir group and 0.07±0.22 $\log_{10}$ copies per milliliter in the placebo group (least-squares mean difference, –2.17; 95% CI, –2.74 to –1.59) (Fig. 2A). In a post hoc analysis with adjustment for the baseline viral load, the between-group difference in percentages remained significant (88% vs. 17%; P<0.001).

During the maintenance period in cohort 1, in evaluations performed at 26 weeks, a viral load of less than 50 copies per milliliter was reported in 29 of 36 patients (81%; 95% CI, 64 to 92) and a viral load of less than 200 copies per milliliter in 32 of 36 patients (89%; 95% CI, 74 to 97) (Fig. 2B and Table S2). The mean change in viral load was –2.58±1.04 $\log_{10}$ copies per milliliter. In cohort 2, a viral load of less than 50 copies per milliliter was reported in 30 of 36 patients (83%) and a viral load of less than 200 copies per milliliter in 31 of 36 patients (86%). The mean change from baseline was –2.49±1.34 $\log_{10}$ copies per milliliter. While the patients were receiving lenacapavir, CD4+ counts increased at week 26 by a least-squares mean of 75 (95% CI, 40 to 110) in cohort 1 and 104 (95% CI, 69 to 139) in cohort 2 (Fig. 2C). Overall, the percentage of patients with a CD4+ count of less than 50 cells per cubic millimeter decreased from 24% (in 17 of 72 patients) to 0% (in 0 of 67 patients).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Cohort 1		Cohort 2	All Patients (N=72)
	Lenacapavir (N=24)	Placebo (N=12)	Lenacapavir (N=36)	
Median age (range) — yr	55 (24–71)	54 (27–59)	49 (23–78)	52 (23–78)
Female sex — no. (%)	7 (29)	3 (25)	8 (22)	18 (25)
Race — no. (%)†				
Black	10 (42)	6 (55)	11 (31)	27 (38)
White	12 (50)	4 (36)	13 (36)	29 (41)
Asian	2 (8)	1 (9)	12 (33)	15 (21)
Data could not be collected	0	1 (9)	0	1 (1)
Hispanic or Latinx ethnic group — no. (%)	6 (25)	4 (36)	5 (14)	15 (21)
Viral load‡				
Mean — $\log_{10}$ copies/ml	3.97±0.92	4.87±0.39	4.06±1.16	4.17±1.03
Median (range) — $\log_{10}$ copies/ml	4.2 (2.3–5.4)	4.9 (4.3–5.3)	4.5 (1.3–5.7)	4.5 (1.3–5.7)
Patients with >100,000 copies/ml — no. (%)	1 (4)	6 (50)	7 (19)	14 (19)
CD4+ count				
Mean — cells/mm^3	199±166	85±63	258±273	210±224
Median (range) — cells/mm^3	172 (16–827)	85 (6–237)	195 (3–1296)	150 (3–1296)
Distribution — no. (%)				
<50 cells/mm^3	3 (12)	4 (33)	9 (25)	16 (22)
50 to <200 cells/mm^3	13 (54)	7 (58)	10 (28)	30 (42)
200 to <500 cells/mm^3	7 (29)	1 (8)	12 (33)	20 (28)
≥500 cells/mm^3	1 (4)	0	5 (14)	6 (8)
Resistance to ≥2 drugs in major class — no. (%)				
NRTI	23 (96)	12 (100)	36 (100)	71 (99)
NNRTI	22 (92)	12 (100)	36 (100)	70 (97)
Protease inhibitor	20 (83)	8 (67)	30 (83)	58 (81)
INSTI	20 (83)	7 (58)	23 (64)	50 (69)
All 4 major classes	14 (58)	3 (25)	16 (44)	33 (46)
Resistance to entry inhibitor — no./total no. (%)				
Enfuvirtide	2/23 (9)	3/10 (30)	0/25 (0)	5/58 (9)
Fostemsavir	5/23 (22)	5/10 (50)	7/21 (33)	17/54 (31)
Ibalizumab	8/23 (35)	3/10 (30)	6/25 (24)	17/58 (29)
Maraviroc§	19/24 (79)	8/11 (73)	14/26 (54)	41/61 (67)
Composition of optimized background therapy — no. (%)				
NRTI	23 (96)	9 (75)	29 (81)	61 (85)
INSTI¶	16 (67)	9 (75)	22 (61)	47 (65)
Protease inhibitor¶	12 (50)	9 (75)	24 (67)	45 (62)
NNRTI	6 (25)	4 (33)	14 (39)	24 (33)
Ibalizumab	9 (38)	3 (25)	5 (14)	17 (24)
Maraviroc	2 (8)	4 (33)	4 (11)	10 (14)
Fostemsavir	3 (12)	0	5 (14)	8 (11)
Enfuvirtide	1 (4)	2 (17)	2 (6)	5 (7)

Table 1. (Continued.)

Characteristic	Cohort 1		Cohort 2	All Patients (N=72)
	Lenacapavir (N=24)	Placebo (N=12)	Lenacapavir (N=36)	
Median overall susceptibility score of optimized background therapy‖	2.0	1.3	2.0	2.0
Number of fully active agents in the optimized background therapy — no. (%)				
0	4 (17)	2 (17)	6 (17)	12 (17)
1	7 (29)	7 (58)	13 (36)	27 (38)
≥2	13 (54)	3 (25)	17 (47)	33 (46)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. INSTI denotes integrase strand-transfer inhibitor, NNRTI non–nucleoside reverse-transcriptase inhibitor, and NRTI nucleoside reverse-transcriptase inhibitor.
† Race was reported by the patients. In the placebo group, local regulators did not permit the collection of data regarding race or ethnicity in one patient. This patient was excluded from the denominator of the percentage calculation.
‡ Two participants in cohort 2 had a viral load of more than 400 copies per milliliter at screening but less than 50 copies per milliliter at enrollment.
§ Susceptibility to maraviroc was assessed by means of the Trofile coreceptor tropism assay (Monogram Biosciences), which indicates whether the activity of maraviroc is anticipated on the basis of coreceptor use (CCR5, CXCR4, or dual mix).
¶ Of the 72 patients in this category, 24 (33%) received dolutegravir twice a day and 22 (31%) received darunavir twice a day.
‖ The drug susceptibility score to an individual antiretroviral medication was determined according to a proprietary algorithm, with 1.0 indicating full susceptibility, 0.5 partial susceptibility, and 0 no susceptibility. The overall susceptibility score of the optimized background therapy was the sum of the individual scores. For historical resistance reports, the scores were derived from data provided by investigators.

The percentage of patients who had a viral load of less than 50 copies per milliliter at week 26 was higher among women, among those who were younger than 50 years of age, and among those who had a baseline viral load of less than 100,000 copies per milliliter (Table 2). The efficacy of lenacapavir was generally consistent regardless of the activity of the optimized background therapy, with similar results regardless of whether patients were receiving fully active agents or whether they had resistance to integrase inhibitors.

VIROLOGIC FAILURE AND RESISTANCE

Overall, 19 patients (11 in cohort 1 and 8 in cohort 2) met the criteria for resistance analysis and were evaluated for the emergence of capsid inhibitor resistance. Lenacapavir-associated capsid substitutions developed in 8 patients (4 in cohort 1 [1 in the lenacapavir group and 3 in the placebo group] and 4 in cohort 2) during the maintenance period. Among these patients, 6 had an M66I mutation (including one with M66I + N74D), 1 had a Q67H + K70R mutation, and 1 had a K70H mutation. The median change in lenacapavir susceptibility was an increase by a factor of 234 in the patients with M66I mutations, 15 in the patient with a Q67H + K70R mutation, and 265 in the patient with a K70H mutation. All the mutations occurred at amino acid residues that had previously been identified during selections for in vitro resistance.[5]

Despite emerging resistance to lenacapavir, 4 of 8 patients had resuppression of HIV-1 RNA levels (<50 copies per milliliter) during receipt of lenacapavir; among the 4 patients without resuppression, 2 continued to have viremia, 1 died at week 10, and 1 discontinued lenacapavir after week 4 (Table S3). Of the 8 patients, 4 had no fully active agents in their optimized background therapy and 4 had poor adherence to the background therapy. All 8 patients had therapeutic levels of lenacapavir (range, 17.7 to 107.0 ng per milliliter at the time of virologic failure). Of the remaining 11 patients (10 who had no emerging capsid mutations and 1 who had assay failure), 7 patients had resuppression of HIV-1 RNA levels while continuing to receive lenacapavir. No patients had emerging resistance to the components of the optimized background therapy.

SAFETY

During the functional monotherapy period in cohort 1, at least one adverse event was reported

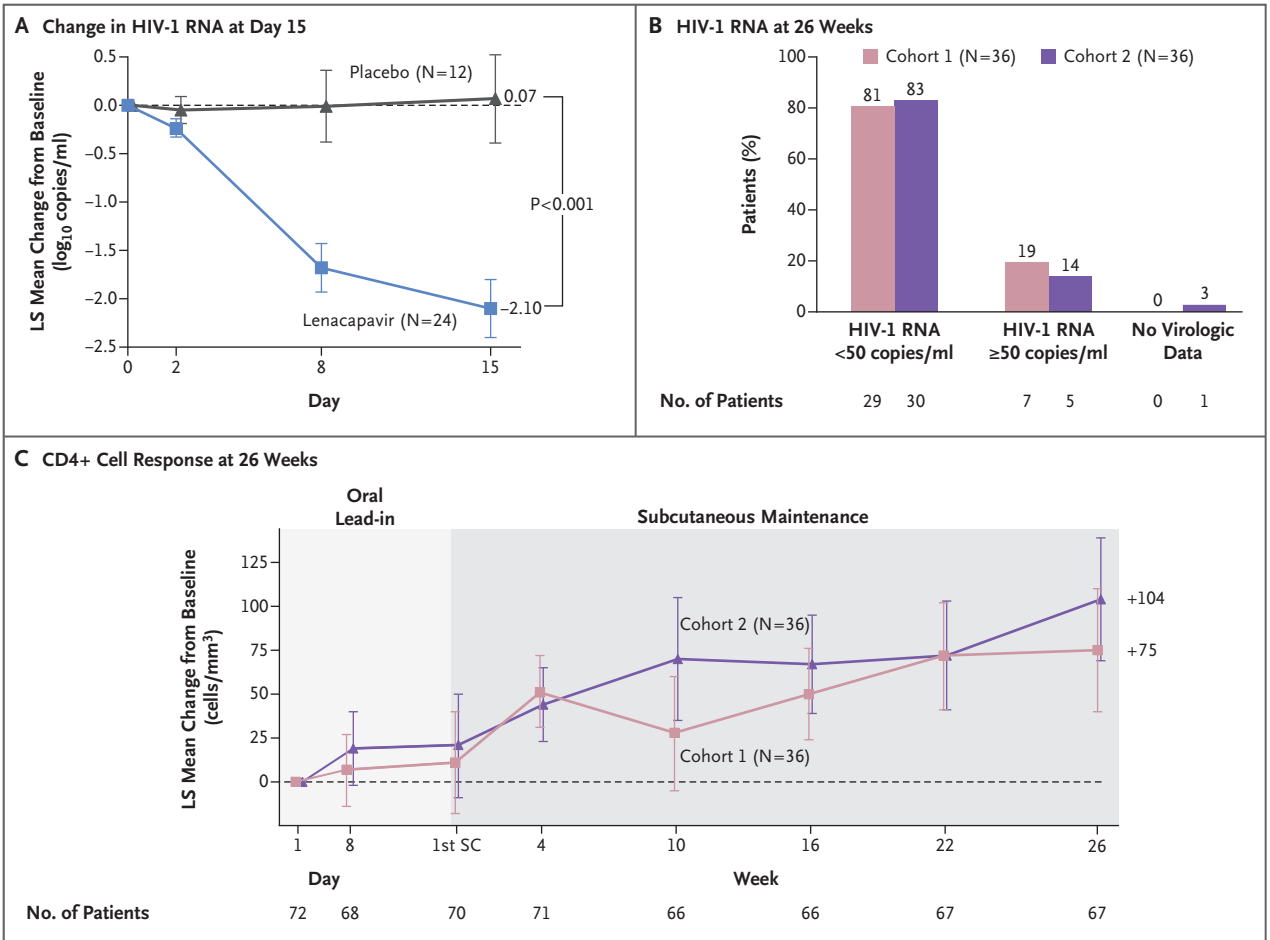

Figure 2. Antiviral Activity of Lenacapavir by Day 15 and Virologic and Immunologic Response at Week 26.

Panel A shows the least-squares (LS) mean change from baseline in the HIV-1 RNA level after adjustment for the baseline level in cohort 1 during the functional monotherapy (randomized) period. Panel B shows the percentage of patients who had less than 50 copies per milliliter of HIV-1 RNA in cohort 1 and cohort 2 at week 26. Panel C shows the LS mean change from baseline in the CD4+ count after adjustment for the baseline HIV-1 RNA and CD4+ values in each cohort through week 26 while the patients were receiving lenacapavir (i.e., excluding the period during which some patients in cohort 1 received placebo). In Panels A and C, I bars indicate 95% confidence intervals.

in 9 of 24 patients (38%) in the lenacapavir group and in 3 of 12 patients (25%) in the placebo group (Table S4). During this period, no serious adverse events or adverse events of grade 3 or higher were observed, and no patient discontinued either lenacapavir or placebo because of an adverse event. The only adverse event that was reported in more than 1 patient among those receiving oral lenacapavir during the functional monotherapy period was nausea (in 13% of the patients), as compared with no patients in the placebo group.

In a combined analysis of cohorts 1 and 2, all 72 patients received oral lenacapavir and at least one dose of subcutaneous lenacapavir, and 70 received the second dose of subcutaneous lenacapavir at week 26. Seven patients had serious adverse events, none of which were assessed by the investigator as being related to lenacapavir (Table S5). One participant in cohort 2 who had a history of non-Hodgkin's lymphoma and a baseline CD4+ count of 7 cells per cubic millimeter died from cancer at week 10. After the exclusion of injection-site reactions, the most common adverse events were nausea (in 13%), constipation (in 11%), and diarrhea (in 11%); these events were mostly grade 1 and were considered to be unrelated to lenacapavir (Table 3 and Tables S6 and S7).

At least one injection-site reaction related to

Table 2. Virologic Response at Week 26.*

Variable	Cohort 1 (N=36)	Cohort 2 (N=36)	All Patients (N=72)
		no. of patients/total no. (%)	
Age			
<50 yr	9/9 (100)	16/19 (84)	25/28 (89)
≥50 yr	20/27 (74)	14/17 (82)	34/44 (77)
Sex			
Male	20/26 (77)	22/28 (79)	42/54 (78)
Female	9/10 (90)	8/8 (100)	17/18 (94)
Black race			
Yes	13/16 (81)	9/11 (82)	22/27 (81)
No	16/19 (84)	21/25 (84)	37/44 (84)
CD4+ count at baseline			
<200 cells/mm^3	21/27 (78)	16/19 (84)	37/46 (80)
≥200 cells/mm^3	8/9 (89)	14/17 (82)	22/26 (85)
Viral load at baseline			
≤100,000 copies/ml	25/29 (86)	25/29 (86)	50/58 (86)
>100,000 copies/ml	4/7 (57)	5/7 (71)	9/14 (64)
Overall susceptibility score†			
0 to <1	4/6 (67)	4/5 (80)	8/11 (73)
1 to <2	11/12 (92)	10/11 (91)	21/23 (91)
≥2	14/18 (78)	16/20 (80)	30/38 (79)
Number of fully active antiretroviral agents†			
0	4/6 (67)	5/6 (83)	9/12 (75)
1	12/14 (86)	12/13 (92)	24/27 (89)
≥2	13/16 (81)	13/17 (76)	26/33 (79)
INSTI resistance			
Yes	23/27 (85)	20/23 (87)	43/50 (86)
No	5/8 (62)	9/12 (75)	14/20 (70)
Use of dolutegravir or darunavir			
Both dolutegravir and darunavir	10/12 (83)	8/12 (67)	18/24 (75)
Dolutegravir only	5/6 (83)	5/6 (83)	10/12 (83)
Darunavir only	7/9 (78)	11/11 (100)	18/20 (90)
No dolutegravir or darunavir	7/9 (78)	6/7 (86)	13/16 (81)
Use of ibalizumab			
Yes	9/12 (75)	3/5 (60)	12/17 (71)
No	20/24 (83)	27/31 (87)	47/55 (85)

* A virologic response was defined as an HIV-1 RNA level of less than 50 copies per milliliter.
† The overall susceptibility score in a given patient is the sum of individual scores according to the baseline optimized background therapy.

lenacapavir was reported in 45 patients (63%); these events included pain (in 31%), swelling (in 31%), erythema (in 25%), and nodule formation (in 24%) (Table S8 and Fig. S1). Most injection-site reactions, including pain, were grade 1 and resolved within days; nodules were all grade 1. No grade 4 injection-site reactions were reported. One patient discontinued lenacapavir because of a grade 1 formation of an injection-site nodule 10 weeks after receipt of the week 52 injection.

Laboratory abnormalities of grade 3 or higher occurred in 28% of the patients. Low levels of creatinine clearance or estimated glomerular filtration rate or high creatinine levels were transient or unconfirmed abnormalities. Episodes of hyperglycemia and glycosuria were transient, unconfirmed, or related to underlying diabetes (Table S9).

Table 3. Adverse Events.*

Adverse Event	Cohort 1 (N=36)	Cohort 2 (N=36)	All Patients (N=72)
		no. of patients (%)	
Injection-site reaction			
Related to lenacapavir†	23 (64)	22 (61)	45 (62)
Pain	10 (28)	12 (33)	22 (31)
Swelling	12 (33)	10 (28)	22 (31)
Erythema	8 (22)	10 (28)	18 (25)
Nodule formation	13 (36)	4 (11)	17 (24)
Induration	2 (6)	9 (25)	11 (15)
Any adverse event, excluding injection-site reaction			
Nausea	7 (19)	2 (6)	9 (12)
Constipation	7 (19)	1 (3)	8 (11)
Diarrhea	5 (14)	3 (8)	8 (11)
Abdominal distention	5 (14)	2 (6)	7 (10)
Arthralgia	4 (11)	2 (6)	6 (8)
Back pain	2 (6)	4 (11)	6 (8)
Cough	5 (14)	1 (3)	6 (8)
Headache	2 (6)	4 (11)	6 (8)
Pyrexia	3 (8)	3 (8)	6 (8)
Urinary tract infection	2 (6)	4 (11)	6 (8)
Covid-19	2 (6)	3 (8)	5 (7)
Fatigue	4 (11)	0	4 (6)
Oral candidiasis	3 (8)	1 (3)	4 (6)
Rash	2 (6)	2 (6)	4 (6)
Vomiting	1 (3)	3 (8)	4 (6)

* Listed are events that occurred in at least 5% of all the patients. Multiple adverse events were counted only once per patient for the highest severity grade for each preferred term. Covid-19 denotes coronavirus disease 2019.
† The relationship between the listed reaction and exposure to lenacapavir was determined by the investigator.

DISCUSSION

In this small randomized trial involving patients with multidrug-resistant HIV-1 infection with limited treatment options, lenacapavir led to a significant decrease in viral load as functional monotherapy. In combination with optimized background therapy, treatment with lenacapavir also led to a high rate of virologic suppression, along with a clinically meaningful increase in the CD4+ count. At week 26, the mean change in viral load in the two cohorts (70 patients) was –2.54 $\log_{10}$ copies per milliliter. Reductions in HIV-1 RNA levels that are maintained for 16 to 24 weeks have been associated with a reduced risk of disease progression and death.[13,14]

In this trial, the observed rate of virologic suppression was achieved even though 17% of the patients had no fully active agent in their optimized background therapy. Some patients had virus that was resistant to ibalizumab or fostemsavir at baseline, which illustrated their limited treatment options. In contrast, recent clinical trials involving patients with multidrug-resistant HIV-1 infection required that patients have at least one fully active agent in their optimized background therapy.[15,16]

Despite the small sample size, efficacy across subgroups that were defined according to the optimized background therapy suggests that lenacapavir contributed to treatment efficacy across a diverse and difficult-to-treat population. Included were patients who had resistance to integrase inhibitors or who had received background therapy that consisted of no more than one fully active agent or that did not contain either dolutegravir or darunavir. Most HIV-1 variants with mutations conferring resistance to lenacapavir have a reduction in replication capacity, which suggests that such variants may have a reduced ability to establish or maintain infection.[5] The clinical relevance of lenacapavir

resistance that we observed in this trial warrants further investigation, given that some patients had viral load suppression while continuing to receive lenacapavir despite emerging resistance and minimal or no change in the optimized background therapy.

One of the more encouraging findings was the restoration of CD4+ counts in both trial cohorts. Although we did not include clinical end points such as mortality in our trial, similar improvements in the CD4+ count have been associated with reductions in mortality and morbidity.[17,18]

Most adverse events were mild or moderate, including injection-site reactions. To some extent, injection-site reactions are expected after subcutaneous administration of lenacapavir owing to depot formation, and pain and swelling of short duration were reported in a minority of patients.

The administration of lenacapavir subcutaneously once every 6 months does not increase the pill burden for patients and maintains therapeutic levels between visits, which reduces the uncertainty and variability that often occur with incomplete adherence. Adherence to the components of background therapy with drugs other than lenacapavir will continue to be critical.

Limitations of this trial include its small sample size and limited follow-up. However, new treatment options for patients with multidrug-resistant HIV-1 infection are needed,[12,19] and longer-term data are being evaluated in this ongoing trial. Lenacapavir is also being evaluated in patients with HIV-1 who have received no previous treatment (ClinicalTrials.gov number, NCT04143594) and as preexposure prophylaxis for persons at high risk for HIV-1 infection (NCT04925752).

Supported by Gilead Sciences.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients who participated in this trial and their families; all participating investigators and support staff members; and David McNeel and Becky Norquist of Gilead Sciences for providing writing assistance with early drafts of the manuscript.

REFERENCES

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Washington, DC: Department of Health and Human Services (https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/guidelines-adult-adolescent-arv.pdf).
2. HIV drug resistance report 2019. Geneva: World Health Organization, 2019 (https://www.who.int/publications/i/item/WHO-CDS-HIV-19.21).
3. Surveillance of HIV drug resistance in adults receiving ART (acquired HIV drug resistance). Geneva: World Health Organization, 2014 (https://apps.who.int/iris/bitstream/handle/10665/112801/9789241507073_eng.pdf?sequence=1).
4. Grover D, Copas A, Green H, et al. What is the risk of mortality following diagnosis of multidrug-resistant HIV-1? J Antimicrob Chemother 2008;61:705-13.
5. Link JO, Rhee MS, Tse WC, et al. Clinical targeting of HIV capsid protein with a long-acting small molecule. Nature 2020;584:614-8.
6. Margot N, Ram R, Rhee M, Callebaut C. Absence of lenacapavir (GS-6207) phenotypic resistance in HIV gag cleavage site mutants and in isolates with resistance to existing drug classes. Antimicrob Agents Chemother 2021;65(3):e02057-e20.
7. Marcelin A-G, Charpentier C, Jary A, et al. Frequency of capsid substitutions associated with GS-6207 in vitro resistance in HIV-1 from antiretroviral-naive and -experienced patients. J Antimicrob Chemother 2020;75:1588-90.
8. Begley R, Lutz J, Rhee M, et al. GS-6207 sustained delivery formulation supports 6-month dosing interval. Presented at the 23rd International AIDS Conference, virtual, July 6–10, 2020 (https://programme.aids2020.org/Abstract/Abstract/8533). abstract.
9. Begley R, Rhee MS, West SK, Corpus J, Ling J, German P. PK, food effect, and safety of oral GS-6207, a novel HIV-1 capsid inhibitor. Presented at the Conference on Retroviruses and Opportunistic Infections, Boston, March 8–11, 2020 (https://www.croiconference.org/wp-content/uploads/sites/2/posters/2020/1430_5_Begley_00470.pdf).
10. Daar E, McDonald C, Crofoot G, et al. Dose-response relationship of subcutaneous long-acting HIV capsid inhibitor GS-6207. Presented at the Conference on Retroviruses and Opportunistic Infections, Boston, March 8–11, 2020 (https://www.croiconference.org/abstract/dose-response-relationship-of-subcutaneous-long-acting-hiv-capsid-inhibitor-gs-6207/).
11. Chan IS, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics 1999;55:1202-9.
12. Human immunodeficiency virus-1 infection: developing antiretroviral drugs for treatment. Guidance for industry. Food and Drug Administration, November 2015 (https://www.fda.gov/media/86284/download).
13. Marschner IC, Collier AC, Coombs RW, et al. Use of changes in plasma levels of human immunodeficiency virus type 1 RNA to assess the clinical benefit of antiretroviral therapy. J Infect Dis 1998;177:40-7.
14. Murray JS, Elashoff MR, Iacono-Connors LC, Cvetkovich TA, Struble KA. The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs. AIDS 1999;13:797-804.
15. Emu B, Fessel J, Schrader S, et al. Phase 3 study of ibalizumab for multidrug-resistant HIV-1. N Engl J Med 2018;379:645-54.
16. Kozal M, Aberg J, Pialoux G, et al. Fostemsavir in adults with multidrug-resistant HIV-1 infection. N Engl J Med 2020;382:1232-43.
17. Lawn SD, Little F, Bekker L-G, et al. Changing mortality risk associated with CD4 cell response to antiretroviral therapy in South Africa. AIDS 2009;23:335-42.
18. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. N Engl J Med 1997;337:725-33.
19. Guideline on the clinical development of medicinal products for the treatment of HIV infection. European Medicines Agency, January 2017 (https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-development-medicinal-products-treatment-hiv-infection_en.pdf).