Sunlenca®

(Lenacapavir)

Authorization Number: 68385, 68386
Authorization Date: 07-Jul-2023

Clinical Study Results

September 2023

Gilead Sciences Switzerland Sàrl
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Switzerland

TABLE OF CONTENTS

1. INTRODUCTION

As of 2020, Gilead discloses clinical study results of newly authorized products in Switzerland by Swissmedic according to the requirements laid out in Art. 71-73 TPO (Ordinance on Therapeutic Products).

Below you will find the information for clinical studies relevant for the marketing authorization for Sunlenca® (Lenacapavir) in Switzerland.

2. OVERVIEW ON CLINICAL STUDIES

Study number	Study title:	Indication:	EudraCT-Number:
GS-US-200-4625	A Phase 2/3 Study to Evaluate the Safety and Efficacy of Long Acting Capsid Inhibitor GS-6207 in Combination with an Optimized Background Regimen in Heavily Treatment Experienced People Living With HIV-1 Infection With Multidrug Resistance	HIV-1 Infection	2019-003814-16

3. STUDY SYNOPSIS GS-US-200-4625

INTERIM CLINICAL STUDY REPORT

Study Title:	A Phase 2/3 Study to Evaluate the Safety and Efficacy of Long Acting Capsid Inhibitor GS-6207 in Combination with an Optimized Background Regimen in Heavily Treatment Experienced People Living With HIV-1 Infection With Multidrug Resistance
Name of Test Drug:	Lenacapavir (LEN; GS-6207)
Dose and Formulation:	LEN 300 mg oral tablet LEN 309 mg/mL solution for subcutaneous injection
Indication:	HIV-1 Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
Study No.:	GS-US-200-4625
Phase of Development:	Phase 2/3
IND No.: **EudraCT No.:**	136260 2019-003814-16
ClinicalTrials.gov Identifier:	NCT04150068
Study Start Date:	21 November 2019 (First Participant Screened)
Study End Date:	05 October 2020 (Last Participant Last Observation for the Primary End Point) 01 April 2021 (Last Participant Last Observation for This Report)
Principal or Coordinating Investigator:	Name: Sorana Segal-Maurer, MD Affiliation: New York-Presbyterian Queens Hospital
Gilead Responsible Medical Monitor:	Name: Telephone: Fax:
Report Date:	08 June 2021

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

Study GS-US-200-4625
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 2/3 Study to Evaluate the Safety and Efficacy of Long Acting Capsid Inhibitor GS-6207 in Combination with an Optimized Background Regimen in Heavily Treatment Experienced People Living With HIV-1 Infection With Multidrug Resistance
Investigators: Multicenter study
Study Centers: 42 study centers in the United States (US) (23 centers), Thailand (4 centers), Italy (3 centers), France (3 centers), Canada (2 centers), Japan (2 centers), Dominican Republic, Spain, Germany, Taiwan, and South Africa (1 center each).
Publications: Segal-Maurer S, Castagna A, Berhe M, et al. Potent Antiviral Activity of Lenacapavir in Phase 2/3 in Heavily ART-Experienced PWH [Abstract 127]. Presented at: Conference on Retroviruses and Opportunistic Infections; 2021 March 6-10.
Study Period: 21 November 2019 (First Participant Screened) 05 October 2020 (Last Participant Last Visit for the Primary End Point) 01 April 2021 (Last Participant Last Visit for This Report)
Phase of Development: Phase 2/3

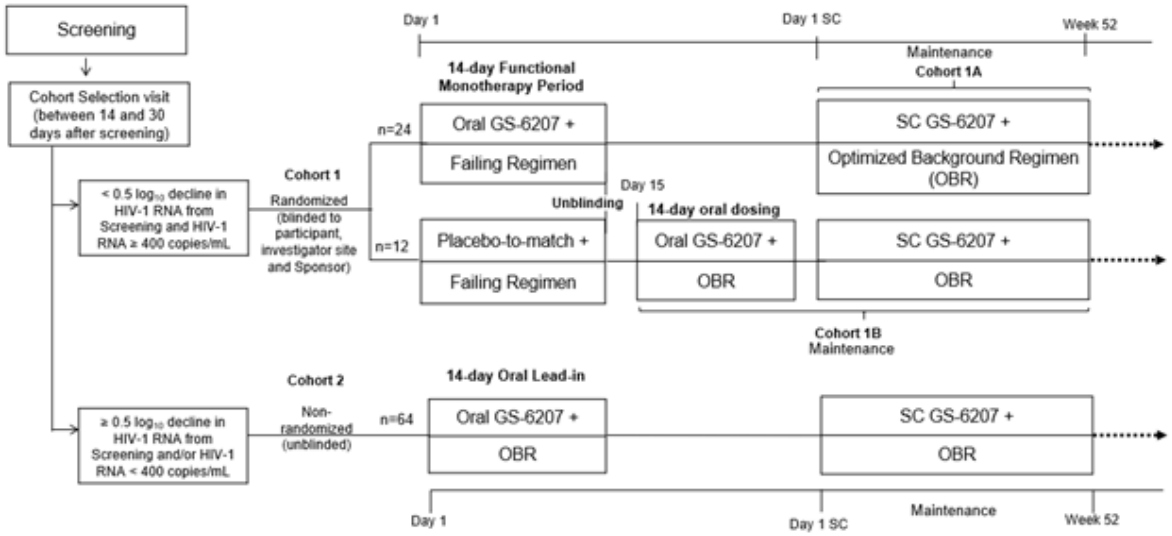
Study Objectives and End Points:

Primary Objective	Primary End Point
• To evaluate the antiviral activity of lenacapavir (LEN; GS-6207) administered as an add-on to a failing regimen (functional monotherapy) for people with HIV (PWH) with multidrug resistance (MDR)	• The proportion of participants in Cohort 1 achieving a reduction in HIV-1 RNA of ≥ 0.5 log10 copies/mL from baseline at the end of the Functional Monotherapy Period
Secondary Objective	
• To evaluate the safety and efficacy of LEN in combination with an optimized background regimen (OBR) at Weeks 26 and 52	**Secondary End Point** • The proportion of participants in Cohort 1 with plasma HIV-1 RNA < 50 copies/mL and < 200 copies/mL at Weeks 26 and 52 of treatment based on the US Food and Drug Administration (FDA)-defined snapshot algorithm **Other End Points** • Incidences of treatment-emergent adverse events (TEAEs) and graded laboratory abnormalities • The proportion of participants with HIV-1 RNA < 50 and < 200 copies/mL at Week 26 using the US FDA-defined snapshot algorithm • The change from baseline in HIV-1 RNA (log10 copies/mL) by visit • The change from baseline in CD4 cell count (cells/µL) by visit • The proportion of participants with HIV-1 RNA < 50 copies/mL by visit based on Missing = Failure (M = F) and Missing = Excluded (M = E) analyses

This clinical study report (CSR) describes the interim analysis at Week 26 and was conducted after all participants in Cohort 1 completed the Week 26 visit (ie, 26 weeks after the first dose of subcutaneous [SC] LEN) or had prematurely discontinued the study drug.

Methodology: This is a Phase 2/3, global, randomized, placebo-controlled multicenter study of LEN together with an OBR in PWH with MDR (to ≥ 2 antiretroviral [ARV] medications from each of ≥ 3 of the 4 main classes) who are failing their current regimen (defined as plasma HIV-1 RNA ≥ 400 copies/mL).

Participants who completed a screening visit returned to the clinic between 14 and 30 days later for a cohort-selection visit. HIV-1 RNA results from this cohort-selection visit were used to determine whether eligible participants participated in Cohort 1 or Cohort 2.



GS-6207 = lenacapavir (LEN); OBR = optimized background regimen; SC = subcutaneous

Number of Participants (Planned and Analyzed):

Planned: 36 (Cohort 1); 64 (Cohort 2)
Analyzed: 36 (Cohort 1); 36 (Cohort 2)

	Cohort 1				
Analysis Set	**LEN**	**Placebo**	**Total**	**Cohort 2**	**Total**
All Enrolled	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
FAS for Functional Monotherapy Period Analysis	24 (100.0%)	12 (100.0%)	36 (100.0%)	0	36 (50.0%)
PP Set for Functional Monotherapy Period Analysis	24 (100.0%)	11 (91.7%)	35 (97.2%)	0	35 (48.6%)
Added a new ARV during the Functional Monotherapy Period[a]	0	1 (8.3%)	1 (2.8%)	0	1 (1.4%)
FAS for All LEN Analysis	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
Safety Analysis Set for Functional Monotherapy Period Analysis	24 (100.0%)	12 (100.0%)	36 (100.0%)	0	36 (50.0%)
Safety Analysis Set for All LEN Analysis	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)
PK Analysis Set	24 (100.0%)	12 (100.0%)	36 (100.0%)	36 (100.0%)	72 (100.0%)

ARV = antiretroviral; FAS = Full Analysis Set; LEN = lenacapavir; PK = pharmacokinetic; PP = Per Protocol
a Initiated optimized background regimen on Day 1 in error

Diagnosis and Main Criteria for Inclusion: People with HIV who met the following criteria were included: heavily treatment-experienced (HTE) adults ≥ 18 years (at all sites) or adolescents aged ≥ 12 years and weighing ≥ 35 kg (at sites in North America and Dominican Republic); were receiving a stable failing regimen for > 8 weeks before screening and were willing to continue that regimen until Day 1.

Cohort 1 participants also had to be willing to continue their failing regimen from Day 1 until Day 14; had HIV-1 RNA ≥ 400 copies/mL at screening; had resistance to ≥ 2 ARV medications from each of ≥ 3 of the 4 main classes of ARV medications (nucleoside reverse transcriptase inhibitor [NRTI], nonnucleoside reverse transcriptase inhibitor [NNRTI], protease inhibitor [PI], or integrase strand-transfer inhibitor [INSTI]). Resistance to emtricitabine or lamivudine associated with the presence of the M184V/I reverse transcriptase mutation could not be used for the purpose of determining eligibility for this criterion; had ≤ 2 fully active ARV medications remaining from the 4 main classes that could be effectively combined to form a viable regimen in the opinion of the investigator based on resistance, tolerability, contraindication, safety, drug access, or acceptability to the participant; and were able and willing to receive an OBR together with LEN.

Duration of Treatment: Participants are treated for at least 54 weeks. Following successful completion of the Week 52 visit, participants will be given the option to attend visits at Week 62, 78, 88, 104, 114, 130 and continue to alternate between every 10 weeks and every 16 weeks. Participants willing to continue the study beyond Week 52 will receive SC LEN 927 mg every 6 months (26 weeks) starting at Week 52 visit, while continuing their OBR, until the product became accessible to participants through an access program or until Gilead elected to discontinue the study in the country.

Participants who decide not to receive SC LEN at Week 52 and not to continue the study will complete the study at the Week 52 visit.

Participants who decide to discontinue SC LEN early and do not wish to continue to attend study visits through the Week 52 visit or the next scheduled SC dosing visit, will complete 30-day, 90-day, and 180-day follow-up visits after the early termination visit.

Test Product, Dose, Mode of Administration, and Batch No.:

Oral Dosing of LEN or Placebo

Study Visits	Treatment
Days 1 or 15[a]	600 mg (2 × 300 mg)
Days 2 or 16 [a]	600 mg (2 × 300 mg)
Days 8 or 22 [a]	300 mg (1 × 300 mg)

a Days 15, 16, and 22 visits were applicable only to participants who received placebo in the Functional Monotherapy Period at Days 1, 2, and 8.

SC Dosing of LEN

Study Visits	Treatment
Day 1 SC	927 mg (309 mg/mL; 2 × 1.5 mL)
Week 26	927 mg (309 mg/mL; 2 × 1.5 mL)
Week 52	927 mg (309 mg/mL; 2 × 1.5 mL)
Every 6 months (26 weeks) thereafter	927 mg (309 mg/mL; 2 × 1.5 mL)

Batch numbers:

Lenacapavir 300 mg tablets: GJ1902H1, GJ1907D1

Lenacapavir 309 mg/mL for SC injection: GB1901A1, GB1905B1

Reference Therapy, Dose, Mode of Administration, and Batch No.:

Placebo tablets to match oral LEN.

Batch number: GJ1906B1

Criteria for Evaluation:

Efficacy: The primary end point was the proportion of participants in Cohort 1 achieving a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline at the end of the Functional Monotherapy Period. The secondary end points are the proportion of participants in Cohort 1 with plasma HIV-1 RNA < 50 copies/mL and < 200 copies/mL at Weeks 26 and 52 visits based on the US FDA-defined snapshot algorithm. This CSR describes the interim analysis at Week 26.

Resistance: Plasma samples for genotypic and phenotypic testing of HIV-1 were collected. Screening results and/or historical HIV-1 resistance reports were used to determine eligibility and to help construct the OBR. Participants who experienced either suboptimal virologic response or virologic rebound or were viremic at their last visit were considered to have virologic failure and underwent further testing. Virologic resistance data are detailed in a separate virology report.

Pharmacokinetics: Blood samples were collected from participants to determine LEN pharmacokinetics (PK) (and metabolites, as appropriate) in plasma.

Safety: Safety was evaluated through the incidence of TEAEs and treatment-emergent clinical laboratory abnormalities.

Statistical Methods:

Efficacy: The primary efficacy end point was the proportion of participants in Cohort 1 achieving a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline at the end of the Functional Monotherapy Period. The primary analysis of the efficacy end point was based on the Full Analysis Set (FAS) for the Functional Monotherapy Period analysis.

The null hypothesis was that there was no difference in the proportion of participants achieving a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline at the end of the Functional Monotherapy Period (between the LEN group and the placebo group in Cohort 1). The alternative hypothesis was that there was a difference (LEN − placebo) in the proportion of participants achieving a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline at the end of the Functional Monotherapy Period between the 2 treatment groups in Cohort 1. For participants with missing HIV-1 RNA values at the end of the Functional Monotherapy Period, the value was imputed using the last observation carried forward method. The difference in proportions between 2 treatment groups was compared using an unconditional exact method using 2 invert 1-sided tests with an alpha level at 0.05 to evaluate superiority.

A secondary analysis of the primary efficacy end point based on the Per-Protocol (PP) Analysis Set for the Functional Monotherapy Period analysis was also performed to evaluate the robustness of the primary end point based on the FAS.

The secondary efficacy end point was the proportion of participants in Cohort 1 with HIV-1 RNA < 50 and < 200 copies/mL at Weeks 26 and 52 using the US FDA-defined snapshot algorithm. Analysis was based on the FAS for the All LEN Analysis and included participants who receive at least 1 dose of SC injection. Only results at Week 26 are included in this CSR. Virologic outcome was defined as the following categories: HIV-1 RNA < 50 copies/mL (this included participants who had the last available on-treatment HIV-1 RNA < 50 copies/mL in the Week 26 analysis window); HIV-1 RNA ≥ 50 copies/mL; no virologic data in the Week 26 analysis window.

The proportion of participants in Cohort 1 with HIV-1 RNA < 200 copies/mL at Week 26 was also summarized in the same manner using the US FDA-defined snapshot algorithm.

The proportion of participants in Cohort 2 with HIV-1 RNA < 50 and < 200 copies/mL at Week 26 using the US FDA-defined snapshot algorithm was summarized in the same manner as defined for the secondary efficacy end point. Analysis was based on FAS for the All LEN Analysis that included participants who received at least 1 dose of SC injection and who had reached Week 26 at the time for the Week 26 analysis.

Baseline and the change from baseline in HIV-1 RNA (log_{10} copies/mL) and CD4 cell count (cells/μL) by visit was summarized by visit using descriptive statistics.

Mean and median change from baseline in HIV-1 RNA (log_{10} copies/mL) was plotted by visit.

Number and percentage of participants with HIV-1 RNA < 50 copies/mL by visit was analyzed using M = F and M = E analyses. The number and percentage of participants with HIV-1 RNA in the following categories was summarized: < 20 copies/mL (20 copies/mL not detectable; < 20 copies/mL detectable); 20 to < 50 copies/mL; 50 to < 200 copies/mL; 200 to < 400 copies/mL; 400 to < 1000 copies/mL; ≥ 1000 copies/mL; missing (only applicable to M = F analysis).

Analysis of the other efficacy end points was based on the FAS.

Pharmacokinetics: All PK analyses were summarized based on the PK Analysis Set. Individual participant concentration data for LEN was listed and summarized using descriptive statistics. The results of PK analyses are not discussed in this interim report.

Safety: Safety analyses were based on the Safety Analysis Set. Adverse event and clinical laboratory data were summarized by treatment group using descriptive statistics. Adverse events were coded using the MedDRA, Version 23.1. Summaries (number and percentage of participants) of TEAEs (by system organ class and preferred term) were provided by treatment group. Additional summaries included summaries for AEs by grade and investigator's assessment of relationship to study drug.

Additional analysis of AEs was performed for injection site reactions (ISR) related to study drug, which was defined as an AE related to study drug reported as any event within the MedDRA high-level term of "injection site reactions."

Graded laboratory abnormalities were defined using the grading scheme in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (corrected Version 2.1, dated July 2017). Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time after baseline, were summarized by treatment group.

SUMMARY OF RESULTS:

Participant Disposition and Demographics:

Disposition:

Overall, in Cohorts 1 and 2, 72 participants were enrolled in the study and were included in the Safety Analysis Set (Cohort 1: LEN, 24 participants; placebo, 12 participants; Cohort 2: LEN + OBR, 36 participants). All 72 participants completed the Functional Monotherapy (Cohort 1, 36 participants) or Oral Lead-in Period (Cohort 2, 36 participants), and all received Day 1 SC LEN. One participant in Cohort 2 discontinued study drug in the Maintenance Period due to death on Study Day 90.

Demographics:

Cohort 1

In Cohort 1, demographic and baseline characteristics were generally similar between the LEN and placebo groups. The majority of participants were male (72.2%; 26 of 36 participants), White (45.7%, 16 participants) or Black (45.7%, 16 participants), and not Hispanic or Latino (71.4%, 25 participants). Median age was 54 years (range: 24 to 71 years).

Baseline disease characteristics were consistent with the profile of the HTE population, with a median (range) number of prior ARV medications of 9 (2, 24), and 75% of participants with CD4 cell count < 200 cells/μL (a hallmark of severe immune suppression and the criterion to diagnose AIDS). Differences were seen between the LEN and placebo groups in HIV-1 RNA (log_{10} copies/mL), HIV-1 RNA categories, and CD4 cell counts and CD4 percentage.

The most common prior ARV medications were as follows: INSTI (97.2%), NRTI (94.4%), NNRTI (88.9%), and PI (83.3%). Known resistance to ≥ 2 drugs in class was as follows: NRTI (97.2%), NNRTI (94.4%), PI (77.8%), and INSTI (75.0%).

The median number of ARVs in the failing regimen for Cohort 1 was 3 (range: 1 to 7). The composition of participants' failing regimens were characteristic of those of PWH with MDR, for example, PI (boosted darunavir twice daily), INSTI (dolutegravir twice daily), chemokine receptor 5 entry inhibitor (maraviroc), CD4-directed post attachment (ibalizumab), attachment inhibitor (fostemsavir, which was investigational at the time of enrollment), and fusion inhibitor (enfuvirtide).

The median number of ARVs in the OBR was 4 (range: 2 to 7). The composition of participants' failing regimens and OBRs were similar, suggesting that they had few remaining treatment options prior to enrolling. Specifically, 6 out of 36 (16.7%) of participants continued their failing regimens as OBRs, suggesting there were no viable agents that could have further optimized the regimen.

The percentage of participants by number of fully active ARV agents in the OBR were as follows: 16.7% (0 fully active ARV agents), 38.9% (1 fully active ARV agent), 25.0% (2 fully active ARV agents), and 19.4% (≥ 3 fully active ARV agents).

Cohort 2

In Cohort 2, the majority of participants were male (77.8%; 28 of 36 participants), White (36.1%, 13 participants) or Asian (33.3%, 12 participants), and not Hispanic or Latino (86.1%, 31 participants). Median age was 49 years (range: 23 to 78 years).

The baseline disease characteristics, prior ARVs, failing regimens, OBR regimen, and resistance characteristics for Cohort 2 were consistent with the profile of the HTE population.

Efficacy Results:

Reduction in HIV 1 RNA of ≥ 0.5 log_{10} copies/mL

A significantly greater percentage of participants receiving LEN had a reduction in HIV-1 RNA of ≥ 0.5 log_{10} copies/mL from baseline at the end of the Functional Monotherapy Period compared than those receiving placebo (87.5% vs 16.7%; $P < 0.0001$). To address the imbalance in baseline HIV-1 RNA between the LEN and placebo groups, a post hoc analysis of the primary efficacy end point with adjustment for baseline HIV-1 RNA using rank analysis of covariance was conducted. Results from this post hoc analysis confirmed that the difference between the groups remained statistically significant: 87.5% versus 16.7%; $P = 0.0003$. To address the imbalance in baseline CD4 cell count between the LEN and placebo groups, post hoc analyses of the primary efficacy end point were conducted in participants with comparable or clinically relevant CD4 cell counts. These analyses showed that the difference between groups remained statistically significant for the comparison between participants in the LEN group with a low baseline CD4 cell count (median: 98.5 cells/µL; n = 12) and participants in the placebo group (median: 84.5 cells/µL; n = 12) ($P = 0.0008$) and between participants in the LEN and placebo groups with a baseline CD4 cell count < 200 cells/µL ($P < 0.0001$).

The results of the PP Analysis Set were consistent with those for the FAS and confirmed the primary end point (reduction in HIV-1 RNA of ≥ 0.5 log_{10} copies/mL from baseline: LEN 87.5% vs 9.1%; $P < 0.0001$).

HIV-1 RNA < 50 Copies/mL and < 200 Copies/mL

The percentages of participants in Cohort 1 with HIV-1 RNA < 50 and < 200 copies/mL at Week 26 using the US FDA-defined snapshot algorithm were 80.6% (29 of 36 participants) and 88.9% (32 of 36 participants), respectively. The percentages of participants in Cohort 2 with HIV-1 RNA < 50 and < 200 copies/mL at Week 26 using the US FDA-defined snapshot algorithm were 66.7% (4 of 6 participants) and 66.7% (4 of 6 participants), respectively.

Change From Baseline in HIV-1 RNA

For the Functional Monotherapy Period, mean (SD) baseline HIV-1 RNA values were lower for participants who received LEN than those who received placebo, as follows: LEN 3.97 (0.922) log_{10} copies/mL; placebo 4.87 (0.393) log_{10} copies/mL (difference in LSM: −0.90; 95% CI: −1.47, −0.33; $P = 0.0028$). At the end of the Functional Monotherapy Period, mean (SD) changes from baseline in HIV-1 RNA were greater for participants who received LEN than those who received placebo, as follows: LEN −1.93 (0.893) log_{10} copies/mL; placebo −0.29 (0.614) log_{10} copies/mL (adjusted difference in LSM by baseline log_{10} HIV-1 RNA: −2.17; 95% CI: −2.74, −1.59; $P < 0.0001$).

For the All LEN Analysis, mean (SD) baseline HIV-1 RNA values were 4.11 (1.031) $\log_{10}$ copies/mL. The mean (SD) change from baseline in HIV-1 RNA at Week 26 was −2.45 (1.162) $\log_{10}$ copies/mL.

Change From Baseline in CD4 Cell Count

For the All LEN Analysis, mean (SD) change from baseline at Week 26 was 90 (102.1) cells/µL.

HIV-1 RNA < 50 copies/mL Using Imputation Methods (M = F, M = E)

For the M = F analysis, the percentage of participants with HIV-1 RNA < 50 copies/mL at Week 26 was 78.6% (33 of 42 participants), respectively. Similar results were seen for the M = E approach.

Subgroup Analysis

Despite the limitations of the small sample size in some subgroups, the efficacy of LEN by baseline CD4 cell count and HIV-1 RNA level was generally as expected, since low CD4 cell counts and high HIV-1 RNA levels are factors known to limit virologic response. However, the general trend of the efficacy analyses by various subgroups of OBR suggests that the contribution of LEN toward efficacy was clinically meaningful. Specifically, the efficacy of LEN in subgroups of participants who were considered more difficult to treat did not appear to be clinically meaningfully lower than those who were considered not as difficult to treat (ie, those with no fully active agents versus those with fully active agents, those with INSTI resistance versus those without, those without either dolutegravir or darunavir in the OBR versus those with either).

Pharmacokinetics Results: The results of the PK analyses are not discussed in this interim report.

Safety Results: LEN was well tolerated through a median (Q1, Q3) study duration of 346 (254, 405) days and 156 (106, 191) days for Cohorts 1 and 2, respectively.

Adverse Events

Functional Monotherapy Period

During the Functional Monotherapy Period, the percentages of participants who experienced AEs were: LEN 37.5% (9 of 24 participants); placebo 25.0% (3 of 12 participants). Nausea was the only AE reported in > 1 participant (LEN 12.5%, 3 participants).

Adverse event considered related to study drugs that was reported in > 1 participant was as follows: nausea (8.3%, 2 participants; LEN group).

No deaths, serious adverse events (SAEs), AEs leading to discontinuation of study drug, or Grade 3 or higher AEs, were reported in either the LEN or placebo group.

All LEN Analysis

In the All LEN Analysis, the percentage of participants who received LEN in Cohort 1 and 2 who experienced AEs was 91.7% (66 of 72 participants). The most commonly reported AEs were injection site swelling (29.2%, 21 of 72 participants), injection site erythema (26.4%, 19 participants), and injection site pain (25.0%, 18 participants). Some ISRs were attributed to enfuvirtide.

The majority of AEs were Grade 1 or 2 in severity. Grade 3 or higher AEs were reported for 13 participants (18.1%). Grade 3 or higher AEs that were reported for ≥ 2 participants were injection site erythema (5.6%, 4 participants), injection site edema, injection site pain, and injection site swelling (2.8%, 2 participants each). Four participants experienced Grade 3 or higher AEs that were considered related to study drug: rash and abdominal abscess, injection site swelling and injection site erythema, injection site pain, and immune reconstitution inflammatory syndrome (1 participant each).

Overall, 62.5% (45 of 72 participants) experienced treatment-related AEs. The most commonly reported treatment-related AEs were injection site swelling (26.4%, 19 participants), injection site erythema (23.6%, 17 participants), and injection site pain (19.4%, 14 participants).

Serious AEs were reported for 4 participants (5.6%); no SAEs were reported in > 1 participant. No SAEs were considered related to study drug. One SAE of cancer resulted in death which was also reported as an AE leading to premature discontinuation from the study. This participant in Cohort 2 died on Study Day 90, and the cause of death was reported as cancer.

No participant discontinued study drug due to an AE.

For the All LEN Analysis, 40 participants (55.6%) experienced a study drug–related ISR. All were Grade 1 or 2 with the exception of 2 participants (2.8%) who experienced a Grade 3 ISR which resolved after a few days. Three participants experienced Grade 3 ISRs that were attributed to enfuvirtide. The median (Q1, Q3) total duration of any study drug–related ISR was 8 (3, 57) days. The most frequently reported ISRs (reported in ≥ 10% of participants overall) and their duration in median (Q1, Q3) days were as follows:

- Injection site swelling (26.4%, 19 participants), 11 (5, 20) days
- Injection site erythema (23.6%, 17 participants), 6 (3, 8) days
- Injection site pain (19.4%, 14 participants), 3 (2, 6) days
- Injection site nodule (18.1%, 13 participants, 153 (72, 232) days
- Injection site induration (12.5%, 9 participants, 71 (29, 171) days

Laboratory Evaluations

There were no clinically relevant changes from baseline in clinical chemistry or hematology parameters either in the Functional Monotherapy Period or Maintenance Period. The median values were generally within reference ranges.

Functional Monotherapy Period

The majority of participants had at least 1 graded laboratory abnormality (LEN 75.0% [18 of 24 participants]; placebo 75.0% [9 of 12 participants]). The majority of abnormalities were Grade 1 or 2. Grade 3 laboratory abnormalities were reported for 3 participants (12.5%) in the LEN group (increased creatinine, hyperglycemia [nonfasting], and increased lipase) and no participants in the placebo group. No participants experienced Grade 4 laboratory abnormalities. None of the graded laboratory abnormalities were considered clinically relevant.

All LEN Analysis

For the All LEN Analysis, the majority of the participants had at least 1 graded laboratory abnormality (91.7%, 66 of 72 participants). The majority of abnormalities were Grade 1 or 2.

Grade 3 laboratory abnormalities were reported for 15 participants (20.8%) and Grade 4 laboratory abnormalities were reported for 4 participants (5.6%).

For the All LEN Analysis, there were no clinically relevant changes from baseline in ALT, AST, total bilirubin, or alkaline phosphatase. One participant (2.8%) experienced a Grade 3 increase in ALT and a Grade 4 increase in AST which were reported as an AE of immune reconstitution inflammatory syndrome associated with an ongoing medical history of chronic hepatitis B.

Grade 3 or 4 renal laboratory abnormalities for the All LEN Analysis were reported as follows:

- Grade 3 increased creatinine: 5 participants (6.9%)
- Grade 3 low creatinine clearance or eGFR: 7 participants (9.7%)
- Grade 4 increased creatinine: 1 participant (1.4%)

For both the Functional Monotherapy Period and All LEN Analysis, none of these laboratory abnormalities were clinically relevant, as they were transient, improved on subsequent visits despite continued exposure to the study drug, or participants had previous underlying conditions such as diabetes.

There were no clinically significant changes in vital signs. The median increase in body weight by Week 26 was 2.0 kg.

CONCLUSIONS:

The conclusions from this Week 26 interim analysis of Study GS-US-200-4625 are as follows:

- Lenacapavir met the primary end point of superiority to placebo. A significantly greater proportion of participants receiving LEN (87.5%) had a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline than those receiving placebo (16.7%).
- Lenacapavir led to a rapid and clinically relevant decline in viral load when added to a failing regimen in HTE PWH.
- Lenacapavir in combination with an OBR led to high rates of virologic suppression at Week 26. These results were consistent even in participants who had suboptimal OBR (eg, low OSS, no or 1 fully active agent, INSTI resistance, no dolutegravir or darunavir), demonstrating a clinically meaningful contribution of LEN towards virologic suppression.
- There were clinically meaningful increases in CD4 cell count from baseline to Week 26.
- LEN administered orally or subcutaneously was generally safe and well tolerated. There were no discontinuations from study drug due to AEs.

3.1. Protocol Amendments and Description

Protocol Amendment 1 (18 December 2019)

Addition of ClinicalTrials.gov identifier.

Addition of nonclinical pharmacology and toxicology studies information to the introduction of the protocol.

Clarification that patient reported outcomes (PROs) are to be completed if available.

Change in the name of the HIV Symptom Index to the Symptoms Distress Module.

Specified that the PROs were to be completed prior to other study procedures.

Removal of language associated with the use of illegal or illicit drugs.

Specified the disallowed medications and contraceptive methods that are not approved in Japan.

Revision of the study procedures table and the associated footnote in reference to PRO changes.

Update to nonclinical reproductive toxicity and in vitro induction data.

Protocol Amendment 2 (01 September 2020)

Correction of the concentration of LEN injection from 300 mg/mL to 309 mg/mL to accurately reflect the label claim of the finished product based on improved accuracy on measurement of the product density since Protocol Amendment 1. No changes to the actual product concentration have been made.

Correction of SC dose from 300 mg to 309 mg and 900 mg to 927 mg.

Change in SC product name from LEN sodium injection, 300 mg/mL to LEN injection, 309 mg/mL.

Addition of GS-6207 drug product's International Nonproprietary Name (lenacapavir, LEN).

Addition of Phase 1 study (GS-US-200-4333) data.

Clarification of language in the biomarker testing section.

Addition of the requirement for the collection of participant's meal time in the dosage and drug administration section.

Update to prior and concomitant medication section.

Revision of inclusion criterion 9.

Addition of guidance for rescreening of participants.

Correction of suboptimal virologic response criteria.

Update to follow-up visits requirement.

Revision of Grade 3/Grade 4 retest requirements.

Renamed Gilead's Pharmacovigilance and Epidemiology group to Gilead GLPS. Name change was made throughout the protocol.

Broadened the second FAS definition to include all participants who receive at least 1 dose of LEN.

Updated the secondary analyses windows at Week 26 and Week 52 to begin from the start of LEN therapy (oral) instead of the start of LEN SC therapy.

Update to the contraceptive requirements and revised the duration for pregnancy/pregnancy outcome reporting requirements.

Addition of the risks and mitigation strategies associated with an ongoing pandemic (COVID-19).

Contingency measures implemented to manage study conduct during disruption of the study as a result of COVID-19 pandemic that were not included in a protocol amendment or administrative letter are described in the study's Coronavirus Outbreak Crisis Management Plan.

3.2. GS-US-200-4625: List of Principal Investigators

GS-US-200-4625: List of Principal Investigators

Geographic Region/ Country Principal Investigator	Investigator No.	Study Site	No. of Subjects Enrolled	No. of Additional Subjects Transferred From Another Study Site[a]
		National Hospital Organization Osaka National Hospital 2-1-14, Hoenzaka, Chuo-ku, Osaka-City, Osaka, 540-0006, Japan		
		National Hospital Organization Nagoya Medical Center 4-1-1 Sannomaru, Naka-ku, Nagoya, Aichi, 460-0001, Japan		
		Taoyuan General Hospital, Ministry of Health and Welfare No 1492, Zhongshan Rd, Taoyuan Dist, Taoyuan, 330, Taiwan		
		National Taiwan University Hospital 7 Chung-Shan South Road, Taipei,100, Taiwan		
		Kaohsiung Medical University Chung-Ho Memorial Hospital No.100, Tzyou 1st Road, Kaohsiung, 807, Taiwan		
		The HIV Netherlands Australia Thailand Research Collaboration, HIV-NAT Thai Red Cross AIDS Research Center, 104 Ratchadumri Road, Puthumwan, Bangkok, 10330, Thailand		

Geographic Region/ Country Principal Investigator	Investigator No.	Study Site	No. of Subjects Enrolled	No. of Additional Subjects Transferred From Another Study Site[a]
		Faculty of Medicine, Khon Kaen University 123 Mitrapatp Road, Amphur Muang, Khon Kaen, 40002, Thailand		
		Siriraj Hospital Department of Preventive and Social Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok, 10700, Thailand		
		Bamrasnaradura Infectious Diseases Institute 38 Tiwanon Road, Muang, Nonthaburi, 11000, Thailand		
		Hôpital Saint-Antoine 184 rue du Faubourg Saint-Antoine, Paris, 75012, France		
		Hôpital Saint-Louis 1, avenue Claude Vellefaux, Paris, 75010, France		
		Hôpital Sainte-Marguerite 270, Boulevard Sainte Marguerite, Marseille, 13009, France		
		Hôpital Bichat-Claude Bemard 46, Rue Henri Huchard, Paris Cedex 18, 75877, France		
		ICH Study Center GmbH & Co. KG Grindelalle 35, Hamburg, 20146, Germany		

Geographic Region/ Country Principal Investigator	Investigator No.	Study Site	No. of Subjects Enrolled	No. of Additional Subjects Transferred From Another Study Site[a]
		U.O.C Immunodeficienze Virali - Istituto Nazionale Malattie Infettive Lazzaro Spallanzani IRCCS Via Portuense, 292, Roma, 00149, Italy		
		Divisione di Malattie Infettive, IRCCS Ospedale San Raffaele Via Stamira D´Ancona 20, Milano, 20127, Italy		
		U.O.C Malattie Infettive - ASST Spedali Civili Di Brescia Piazzale Spedali Civili, 1, Brescia, 25123, Italy		
		U.O.C Malattie Infettive - Fondazione Policlinico Universitario A. Gemelli IRCCS Largo Agostino Gemelli, 8, Roma, 00168, Italy		
		The Aurum Institute: Pretoria Clinical Trial Centre Unit U3-U7, The Enterprise Building, The Innovation Hub, 6 Mark Shuttleworth Street, Petroria, Gauteng, 0087, South Africa		
		Helen Joseph Hospital Perth Road, Westdene, Johannesburg, Gauteng, 2092, South Africa		

Geographic Region/ Country Principal Investigator	Investigator No.	Study Site	No. of Subjects Enrolled	No. of Additional Subjects Transferred From Another Study Site[a]
		Hospital Clinic de Barcelona Calle Villarroel, 170, Barcelona, 08036, Spain Hospital Clinic de Barcelona Calle Villarroel, 170, Barcelona, 08036, Spain		
		Instituto Dominicano de Estudios Virologicos (IDEV) Dr. Piñeyro 211, Zona Universitaria Santo Domingo, 10103, Dominican Republic		
		Hospital Dr. Salvador Bienvenido Gautier Calle Alexander Fleming 1, Ensanche La Fe, Santo Domingo, 10514, Dominican Republic		
		Maple Leaf Research 14 College Street, Suite 403, Toronto, ON M5G 1K2, Canada		
		Vancouver ID Research and Care Centre Society 201-1200 Burrard Street. Vancouver, BC, V6Z2C7, Canada		
		Clinique de Medecine Urbaine du Quartier Latin 1733 rue Berri, 2nd floor, Montreal, Quebec, Canada, H2L 4E9, Canada		
		Northstar Medical Center 2835 North Sheffield Avenue, Suite 500, Chicago, IL, 60657, United States		

Geographic Region/ Country Principal Investigator	Investigator No.	Study Site	No. of Subjects Enrolled	No. of Additional Subjects Transferred From Another Study Site[a]
		North Texas Infectious Diseases Consultants, P.A. 3409 Worth Street, Dallas, TX, 75246, United States		
		Central Texas Clinical Research 900 East 30th Street, Suite 302, Austin, TX, 78705, United States		
		Howard Brown Health Center 4025 North Sheridan Road, Chicago, IL, 60613, United States		
		The Crofoot Research Center, INC. 3701 Kirby Drive, Suite 1230, Houston, TX, 77098, United States		
		Orlando Immunology Center 1707 North Mills Ave, Orlando, FL, 32803, United States		
		Chatham County Health Department 107B Fahm Street, Savannah, GA, 31401, United States		
		Washington Health Institute 1140 Varnum Street NE, Suite 203, Washington, DC, 20017, United States		
		Eisenhower Medical Center at Rimrock 4791 E. Palm Canyon Drive, Palm Springs, CA, USA, 92264, United States		

Geographic Region/ Country Principal Investigator	Investigator No.	Study Site	No. of Subjects Enrolled	No. of Additional Subjects Transferred From Another Study Site[a]
		North Shore University Hospital/ Division of Infectious Diseases 400 Community Drive, Manhasset, New York, USA, 11030, United States		
		Mills Clinical Research 9201 Sunset Blvd. Suite 812, Los Angeles, CA, 90069, United States		
		Yale University; School of Medicine 135 College Street, Suite 323, New Haven, CT,06510, United States		
		Triple O Research Institute, P.A. 2580 Metrocentre Blvd, Suite 4, West Palm Beach, FL, 33407, United States		
		Atrium Health-Infectious Disease Consultants 4539 Hedgemore Drive, Suite 100, Charlotte, NC, USA, 28209, United States		
		Midway Immunology and Research Center 360 East Midway Road, Fort Pierce, FL, 34982, United States		
		315 se 14th Street, Fort Lauderdale, FL, 33316, United States		

Geographic Region/ Country Principal Investigator	Investigator No.	Study Site	No. of Subjects Enrolled	No. of Additional Subjects Transferred From Another Study Site[a]
		5901 W Olympic Blvd., Suite 420, Los Angeles, CA, 90036, United States		
		Floridian Clinical Research 14791 Oak Lane, Miami Lakes, FL, 33016, United States		
		Diagnostic Clinic of Longview Center for Clinical Research (DCOL) 707 Hollybrook Drive, Suite 501, Longview, Texas, 75605, United States		
North America/ United States Segal-Maurer, Sorana, MD		New York-Presbyterian/Queens 56-45 Main Street, suite #S212, Flushing, New York, 11355, United States		
		St Hope Foundation 6800 W Loop South, Ste 500, 560, 580, Bellaire, TX, 77401, United States		
		AIDS Arms Inc. DBA Prism Health North Texas 219 Sunset Avenue Suite 116-A, Dallas, TX, 75208, United States		
		Methodist University Hospital/University of Tennessee Health Science Center, Clinical Research Center 1265 Union Avenue, 8 East, Room E-804, Memphis, TN, 38104, United States		

Geographic Region/ Country Principal Investigator	Investigator No.	Study Site	No. of Subjects Enrolled	No. of Additional Subjects Transferred From Another Study Site[a]
		The Miriam Hospital 180 Corliss Street, Third Floor, Providence, RI, 02904, United States		
		Clinical Alliance for Research and Education - Infectious Diseases, LLC (CARE-ID) 3289 Woodburn Road Suite 250, Annandale, VA, 22003, United States		
		Jacobi Medical Center 1400 Pelham Parkway South, Bronx, NY, 10461, United States		
		Emory Hospital Midtown Infectious Disease Clinic 550 Peachtree Street, NE, 7th Floor MOT, Atlanta, GA, 30308, United States		
		Atlanta Infectious Disease Group PC 275 Collier Road, Suite 450, Atlanta, GA, USA, 30309, United States		

a Blank cells in this column indicate no subjects transferred from another study site