LAPaL
THE LONG-ACTING THERAPEUTICS PATENTS AND LICENCES DATABASE

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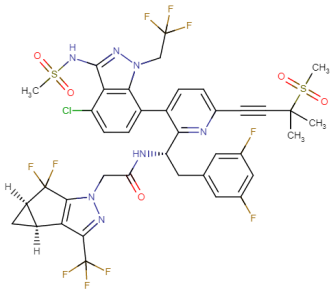


# Lenacapavir (LEN)

## Developer(s)

Gilead Sciences Inc.

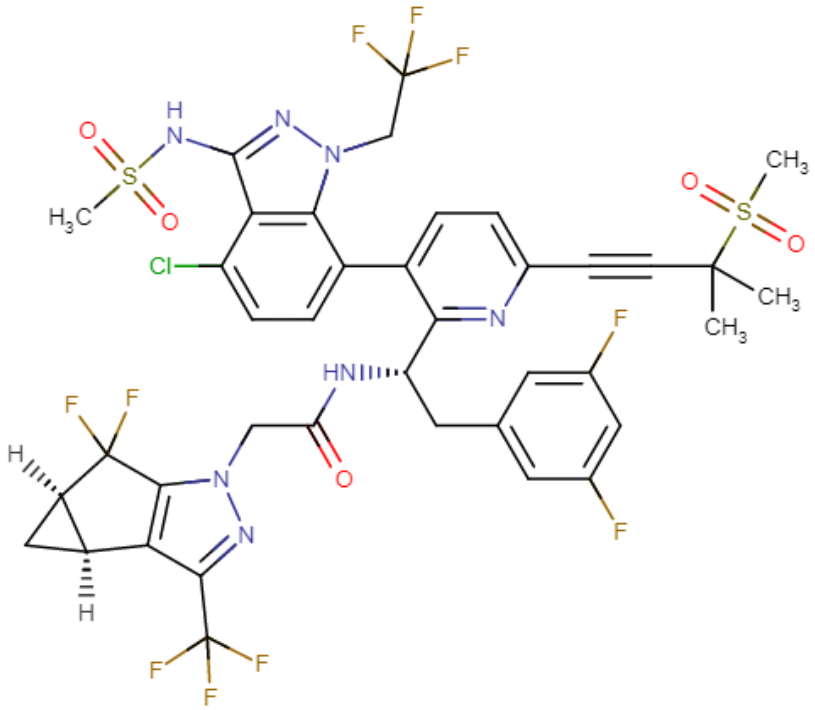
Originator

https://www.gilead.com/

United States

Gilead Sciences, Inc. is a multinational biopharmaceutical company that develops and manufactures innovative medicines for life-threatening diseases, including anti-viral therapeutics for HIV/AIDS, Hepatitis B, Hepatitis C and Covid-19. Headquartered in Foster City, California, Gilead was originally founded in 1987 and is currently listed on both the S&P 500 and the NASDAQ Biotechnology Index.

# Drug structure




Lenacapavir Chemical Structure

Sourced from DrugBank

# Drug information

## Associated long-acting platforms

Aqueous Solution

## Administration route

Subcutaneous, Oral

## Therapeutic area(s)

HIV

### Use case(s)

Pre-Exposure Prophylaxis (PrEP)
Treatment

## Use of drug

### Ease of administration

Administered by a community health worker
Administered by a nurse
Administered by a specialty health worker
Self-administered
To be determined

### User acceptance

Not provided

## Drug information

### Drug's link(s)

https://go.drugbank.com/drugs/DB15673

### Generic name

Lenacapavir

### Brand name

Sunlenca

### Compound type

Small molecule

### Summary

Lenacapavir (LEN), also known as GS-6207, is a first in-class HIV-1 capsid inhibitor used in combination with other antiretrovirals for the treatment of multi-drug resistant HIV-1 infection, and has potential application as HIV pre-exposure prophylaxis. LEN is utilised combinatorially for HIV-1 treatment, as it displays excellent synergy and no known cross-resistance with any other currently approved class of antiretroviral, in addition to possessing antiviral activity at picomolar levels. Long-acting versions of LEN are administered every 26 weeks (six months) as a subcutaneous injection following an initial oral-loading period. LEN was approved in the EU for the treatment of HIV-positive adults with multidrug resistance in Aug 2022, and received approval from the U.S. FDA in Dec 2022.

### Approval status

Lenacapavir (SUNLENCA) 463.5mg/3ml subcutaneous injection is approved for use in the United States, United Kingdom, Canada, UAE, South Korea, Hong Kong, Japan, Australia, Israel, and the European Union (27-member states of the European Union, as

well as Norway, Iceland and Liechtenstein) for HIV-1 treatment under certain conditions.

### Regulatory authorities

US FDA granted Breakthrough Therapy Designation for SUNLECA in combination with other antiretroviral drugs for heavily treatment-experienced patients (HTE) adults with multi-drug resistant (MDR) HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations. A European Marketing Authorization was issued for the use of SUNLECA and it has also been classified as ‘Fast-Track Reimbursement’ by the Ministry of Health, Labour and Welfare, Japan, and ‘Part 1- Schedule 1 & Schedule 3 Poison’ by the Department of Health, Hong Kong.

## Delivery device(s)

No delivery device

# Scale-up and manufacturing prospects

## Scale-up prospects

Compound is commercially manufactured.

## Tentative equipment list for manufacturing

Equipment: Stainless steel pharmaceutical reactors, glass-lined reactors, rotary evaporator (rotovap), flash chromatography columns, stainless steel autoclave, cooling bath, silica gel chromatography columns, vacuum distillation apparatus, simulated moving bed chromatography system, Chiralpak columns.

## Manufacturing

Storage of injectable lenacapavir in borosilicate vials is contraindicated due to issues with chemical compatibility. Instead, it is recommended that vials are made from aluminosilicate glass.

## Specific analytical instrument required for characterization of formulation

Proton nuclear magnetic resonance (1H NMR), High-performance liquid chromatography (HPLC), Ultra-Performance Liquid Chromatography (UPLC).

# Clinical trials

## CAPELLA

### Identifier

NCT04150068

### Link

https://clinicaltrials.gov/ct2/show/NCT04150068

### Phase

Phase II/III

### Status

Active, not recruiting

### Sponsor

Gilead Sciences

### More details

Not provided

### Purpose

Evaluate the antiviral activity of Lenacapavir (formerly GS-6207) administered as an add-on to a failing regimen (functional monotherapy) in people living with HIV with multi-drug resistance.

### Interventions

**Intervention 1**

Drug: Oral Lenacapavir

Dosage: 300 mg

**Intervention 2**

Drug: Oral Lenacapavir Placebo

Dosage: 0 mg

**Intervention 3**

Drug: Subcutaneous Lenacapavir

Dosage: 927 mg

**Intervention 4**

Drug: Failing ARV Regimen

**Intervention 5**

Drug: Optimized Background Regimen (OBR)

## Countries

United States of America

Canada

France

Germany

Italy

Japan

South Africa

Spain

Taiwan, Province of China

Thailand

Dominican Republic

## Sites / Institutions

Not provided

## Trials dates

### Anticipated Start Date

Not provided

### Actual Start Date

2019-11-21

### Anticipated Date of Last Follow-up

2024-06-26

### Estimated Primary Completion Date

Not provided

### Estimated Completion Date

2027-01-01

### Actual Primary Completion Date

2020-10-05

### Actual Completion Date

Not provided

## Studied populations

### Age Cohort

- Children
- Adolescents
- Adults
- Older Adults

### Genders

- All

### Accepts pregnant individuals

Unspecified

**Accepts lactating individuals**

Unspecified

**Accepts healthy individuals**

No

## Comments about the studied populations

Adult aged ≥ 18 years (at all sites) or adolescent aged ≥ 12 and weighing ≥ 35 kg (at sites in North America and Dominican Republic). Currently receiving a stable failing ARV regimen for > 8 weeks. Have HIV-1 RNA ≥ 400 copies/mL at screening. Have multidrug resistance (resistance to ≥2 agents from ≥3 of the 4 main classes of ARV). Have no more than 2 fully active ARV remaining from the 4 main classes that can be effectively combined to form a viable regimen. Able and willing to receive an Optimized Background Regimen (OBR) together with Lenacapavir.

## Health status

Positive to : HIV

Negative to : HCV

## Study type

Interventional (clinical trial)

## Enrollment

72

## Allocation

Randomized

## Intervention model

Sequential assignment

## Intervention model description

Not provided

## Masking

Quadruple-blind masking

## Masking description

Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

## Frequency of administration

Bi-yearly

## Studied LA-formulation(s)

Injectable

## Studied route(s) of administration

Oral
Subcutaneous

## Use case

Treatment

## Key results

| Type of key results | Title | Website link |
|---|---|---|
| Article | Capsid Inhibition with Lenacapavir in Multidrug-Resistant HIV-1 Infection | https://www.nejm.org/doi/10.1056/NEJM |

# CALIBRATE

## Identifier

NCT04143594

## Link

https://clinicaltrials.gov/ct2/show/NCT04143594

## Phase

Phase II

## Status

Completed

## Sponsor

Gilead Sciences

## More details

Not provided

## Purpose

Evaluate the efficacy of Lenacapavir containing regimens in people living with HIV

## Interventions

### Intervention 1

Drug: Oral Lenacapavir

Dosage: 600 mg and 300 mg

### Intervention 2

Drug: F/TAF

Dosage: 200/25 mg

**Intervention 3**

Drug: Subcutaneous Lenacapavir

Dosage: 927 mg

**Intervention 4**

Drug: TAF

Dosage: 25 mg

**Intervention 5**

Drug: BIC

Dosage: 75 mg

## Countries

United States of America

Puerto Rico

Dominican Republic

## Sites / Institutions

Not provided

## Trials dates

**Anticipated Start Date**

Not provided

**Actual Start Date**

2019-11-22

**Anticipated Date of Last Follow-up**

2023-10-03

**Estimated Primary Completion Date**

Not provided

**Estimated Completion Date**

Not provided

**Actual Primary Completion Date**

2021-09-30

**Actual Completion Date**

2023-09-13

## Studied populations

**Age Cohort**

- Adults
- Older Adults

**Genders**

- All

**Accepts pregnant individuals**

Unspecified

**Accepts lactating individuals**

Unspecified

**Accepts healthy individuals**

No

## Comments about the studied populations

Antiretroviral (ARV) naïve with no use of any ARV within one month of screening. Use of pre-exposure prophylaxis (PrEP) (any duration), post-exposure prophylaxis (PEP) (any duration), or HIV-1 treatment (< 10 days therapy total) > 1 month prior to screening is permitted. HIV-1 RNA ≥ 200 copies/mL at screening. CD4+ cell count ≥ 200 cells/microliter at screening.

## Health status

Positive to : HIV

Negative to : HCV, HBV

## Study type

Interventional (clinical trial)

## Enrollment

183

## Allocation

Randomized

## Intervention model

Parallel Assignment

## Intervention model description

Not provided

## Masking

Open label

## Masking description

None (Open Label)

## Frequency of administration

Bi-yearly

## Studied LA-formulation(s)

Injectable

## Studied route(s) of administration

Oral

Subcutaneous

## Use case

Treatment

## Key results

| Type of key results | Title | Website link |
|---|---|---|
| Abstract | CROI 2022: Lenacapavir: 54 week results in treatment-naive participants of CALIBRATE study | https://i-base.info/htb/42313 |
| Article | Lenacapavir administered every 26 weeks or daily in combination with oral daily antiretroviral therapy for initial treatment of HIV: a randomised, open-label, active-controlled, phase 2 trial | https://doi.org/10.1016/S2352-3018(22)00291-0 |
| Article | Interim Resistance Analysis of Long-Acting Lenacapavir in Treatment-Naïve People with HIV at 28 Weeks | https://doi.org/10.1093%2Fofid%2Fofab |

## PURPOSE 1

### Identifier

NCT04994509

### Link

https://clinicaltrials.gov/study/NCT04994509

### Phase

Phase III

### Status

Active, not recruiting

### Sponsor

Gilead Sciences

### More details

The goal of this study is to evaluate the efficacy in preventing HIV infection of the study drugs, lenacapavir (LEN) and emtricitabine/tenofovir alafenamide (F/TAF), in adolescent girls and young women.

### Purpose

Pre-Exposure Prophylaxis Study of Lenacapavir and Emtricitabine/Tenofovir Alafenamide in Adolescent Girls and Young Women at Risk of HIV Infection

### Interventions

**Intervention 1**

Oral Lenacapavir (LEN)

Dosage: 600 mg

**Intervention 2**

Subcutaneous (SC) Lenacapavir (LEN)

Dosage: 927 mg

**Intervention 3**

Oral F/TAF

Dosage: 200/25 mg

**Intervention 4**

Oral F/TDF

Dosage: 200/300 mg

**Intervention 5**

Placebo SC LEN

Dosage: 0 mg

## Countries

South Africa

Uganda

## Sites / Institutions

Not provided

## Trials dates

**Anticipated Start Date**

Not provided

**Actual Start Date**

2021-08-30

**Anticipated Date of Last Follow-up**

2024-02-26

**Estimated Primary Completion Date**

2024-09-01

**Estimated Completion Date**

2027-07-01

**Actual Primary Completion Date**

Not provided

**Actual Completion Date**

Not provided

## Studied populations

**Age Cohort**

- Children
- Adults

**Genders**

- Female

**Accepts pregnant individuals**

Yes

**Accepts lactating individuals**

Yes

**Accepts healthy individuals**

Yes

## Comments about the studied populations

Key Inclusion Criteria: * Incidence Phase * HIV-1 status unknown at initial screening and no prior human immunodeficiency virus (HIV)-1 testing within the last 3 months. * Sexually active (has had \> 1 vaginal intercourse within the last 3 months) with cisgender male individuals (CGM). * Randomized Phase * Negative fourth generation

HIV-1 antibody (Ab)/antigen (Ag) test confirmed with central HIV-1 testing. * Estimated glomerular filtration rate (GFR) ≥ 60 mL/min at screening. * Body weight ≥ 35 kg. Key Exclusion Criteria: * Prior receipt of an HIV vaccine. * Prior use of long-acting systemic HIV pre-exposure prophylaxis (PrEP) or or HIV PEP (postexposure prophylaxis). Note: Other protocol defined Inclusion/Exclusion criteria may apply.

### Health status

Negative to : HIV

### Study type

Interventional (clinical trial)

### Enrollment

5368

### Allocation

Randomized

### Intervention model

Parallel Assignment

### Intervention model description

Not provided

### Masking

Double-blind masking

### Masking description

Double (Participant, Investigator)

### Frequency of administration

Bi-yearly

## Studied LA-formulation(s)

Injectable

## Studied route(s) of administration

Oral

Subcutaneous

## Use case

PrEP

## Key results

| Type of key results | Title | Website link |
|---|---|---|
| Article | Various Resources related to PURPOSE trials | https://www.purposestudies.com/study-investigators/ |
| Abstract | Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women | https://www.nejm.org/doi/full/10.1056/N |

## PURPOSE 2

### Identifier

NCT04925752

### Link

https://clinicaltrials.gov/study/NCT04925752

### Phase

Phase III

### Status

Active, not recruiting

### Sponsor

Gilead Sciences

### More details

The goal of this clinical study is to test how well the study drug, lenacapavir (LEN), works in preventing the risk of HIV.

### Purpose

Study of Lenacapavir for HIV Pre-Exposure Prophylaxis in People Who Are at Risk for HIV Infection

### Interventions

**Intervention 1**
Oral Lenacapavir (LEN)
Dosage: 600 mg

**Intervention 2**

Oral F/TDF

Dosage: 200/300 mg

**Intervention 3**

Subcutaneous (SC) Lenacapavir (LEN)

Dosage: 927 mg

**Intervention 4**

Placebo SC LEN

Dosage: 0 mg

**Intervention 5**

Placebo to match F/TDF

Dosage: 0 mg

## Countries

United States of America

Brazil

Puerto Rico

South Africa

Thailand

Argentina

Peru

## Sites / Institutions

Not provided

## Trials dates

### Anticipated Start Date

Not provided

### Actual Start Date

2021-06-28

**Anticipated Date of Last Follow-up**

2024-07-11

**Estimated Primary Completion Date**

2024-12-01

**Estimated Completion Date**

2028-05-01

**Actual Primary Completion Date**

Not provided

**Actual Completion Date**

Not provided

## Studied populations

**Age Cohort**

- Children
- Adults
- Older Adults

**Genders**

- All

**Accepts pregnant individuals**

Unspecified

**Accepts lactating individuals**

Unspecified

**Accepts healthy individuals**

Yes

## Comments about the studied populations

Key Inclusion Criteria: Incidence Phase * CGM, TGW, TGM, and GNB who have

condomless receptive anal sex with partners assigned male at birth and are at risk for HIV infection. * HIV-1 status unknown at screening and no prior HIV-1 testing within the last 3 months. * Sexually active with ≥ 1 partner assigned male at birth (condomless receptive anal sex) in the last 12 months and 1 of the following: * Condomless receptive anal sex with ≥ 2 partners in the last 12 weeks. * History of syphilis, rectal gonorrhea, or rectal chlamydia in the last 24 weeks. * Self-reported use of stimulants with sex in the last 12 weeks. Randomized Phase * Negative local rapid fourth generation HIV-1/2 Ab/Ag, central fourth generation HIV-1/2 Ab/Ag, and HIV-1 RNA quantitative nucleic acid amplification

### Health status

Considered high risk to : HIV
Negative to : HIV, HCV, HBV

### Study type

Interventional (clinical trial)

### Enrollment

3295

### Allocation

Randomized

### Intervention model

Parallel Assignment

### Intervention model description

Not provided

### Masking

Double-blind masking

## Masking description

Double (Participant, Investigator)

## Frequency of administration

Bi-yearly

## Studied LA-formulation(s)

Injectable

## Studied route(s) of administration

Oral
Subcutaneous

## Use case

PrEP

## Key results

| Type of key results | Title | Website link |
|---|---|---|
| Article | Proactive strategies to optimize engagement of Black, Hispanic/Latinx, transgender, and nonbinary individuals in a trial of a novel agent for HIV pre-exposure prophylaxis (PrEP) | https://pubmed.ncbi.nlm.nih.gov/35657 |

| Type of key results | Title | Website link |
| --- | --- | --- |
| Article | Gilead’s Twice-Yearly Lenacapavir for HIV Prevention Reduced HIV Infections by 96% and Demonstrated Superiority to Daily Truvada® in Second Pivotal Phase 3 Trial | https://www.gilead.com/news/news-details/2024/gileads-twiceyearly-lenacapavir-for-hiv-prevention-reduced-hiv-infections-by-96-and-demonstrated-superiority-to-daily-truvada |

# GS-US-536-5816

## Identifier

NCT04811040

## Link

https://clinicaltrials.gov/ct2/show/NCT04811040

## Phase

Phase I

## Status

Completed

## Sponsor

Gilead Sciences

## More details

Not provided

## Purpose

Evaluate the safety and tolerability of a combination of the broadly neutralizing antibodies (bNAbs) teropavimab (formerly GS-5423) and GS-2872 in combination with the HIV capsid inhibitor lenacapavir

## Interventions

### Intervention 1

Drug: Oral Lenacapavir

### Intervention 2

Drug: Subcutaneous Lenacapavir

**Intervention 3**

Biological: Teropavimab

**Intervention 4**

Biological: Zinlirvimab

## Countries

United States of America

## Sites / Institutions

Not provided

## Trials dates

**Anticipated Start Date**

Not provided

**Actual Start Date**

2021-04-08

**Anticipated Date of Last Follow-up**

2023-10-26

**Estimated Primary Completion Date**

Not provided

**Estimated Completion Date**

Not provided

**Actual Primary Completion Date**

2023-04-18

**Actual Completion Date**

2023-10-17

## Studied populations

### Age Cohort

- Adults
- Older Adults

### Genders

- All

### Accepts pregnant individuals

Unspecified

### Accepts lactating individuals

Unspecified

### Accepts healthy individuals

No

## Comments about the studied populations

On first-line antiretroviral therapy (ART) for ≥ 2 years prior to screening. A change in ART regimen ≥ 28 days prior to screening for reasons other than virologic failure (VF) (eg, tolerability, simplification, drug-drug interaction profile) is allowed.

## Health status

Positive to : HIV
Negative to : HCV, HBV
Other health status: No history of opportunistic infection or illness indicative of Stage 3 HIV disease; No comorbid condition(s) requiring ongoing immunosuppression.

## Study type

Interventional (clinical trial)

## Enrollment

32

## Allocation

Randomized

## Intervention model

Parallel Assignment

## Intervention model description

Not provided

## Masking

Double-blind masking

## Masking description

Double (Participant, Investigator). Clinical pharmacologist and sponsor are not masked to treatment assignment.

## Frequency of administration

Not provided

## Studied LA-formulation(s)

Injectable

## Studied route(s) of administration

Oral
Subcutaneous

## Use case

Treatment

## Key results

Not provided

# GS-US-200-4072

## Identifier

NCT03739866

## Link

https://clinicaltrials.gov/ct2/show/NCT03739866

## Phase

Phase I

## Status

Completed

## Sponsor

Gilead Sciences

## More details

Not provided

## Purpose

Separately evaluate the short-term antiviral activity of both lenacapavir and tenofovir alafenamide with respect to plasma HIV-1 RNA reduction in antiretroviral or capsid inhibitor naïve patients

## Interventions

### Intervention 1

Drug: Lenacapavir Subcutaneous Injection
Dosage: 20 mg, 50 mg, 150 mg, 450 mg and 750 mg

**Intervention 2**

Drug: Placebo

Dosage: 0 mg

**Intervention 3**

Drug: B/F/TAF

Dosage: 50/200/25 mg

**Intervention 4**

Drug: TAF

Dosage: 200 mg and 600 mg

## Countries

United States of America

## Sites / Institutions

Not provided

## Trials dates

**Anticipated Start Date**

Not provided

**Actual Start Date**

2018-11-26

**Anticipated Date of Last Follow-up**

2021-03-16

**Estimated Primary Completion Date**

Not provided

**Estimated Completion Date**

Not provided

**Actual Primary Completion Date**

2019-11-14

**Actual Completion Date**

2020-06-15

## Studied populations

**Age Cohort**

- Adults
- Older Adults

**Genders**

- All

**Accepts pregnant individuals**

No

**Accepts lactating individuals**

No

**Accepts healthy individuals**

No

## Comments about the studied populations

Treatment naïve or experienced but CAI and integrase strand transfer inhibitor (INSTI) naïve, and have not received any antiretroviral therapy (ART) within 12 weeks of screening.

## Health status

Positive to : HIV

## Study type

Interventional (clinical trial)

## Enrollment

53

## Allocation

Randomized

## Intervention model

Parallel Assignment

## Intervention model description

Not provided

## Masking

Double-blind masking

## Masking description

Double (Participant, Investigator)

## Frequency of administration

Other(s) : "Single dose "

## Studied LA-formulation(s)

Injectable

## Studied route(s) of administration

Subcutaneous

## Use case

Treatment

## Key results

| Type of key results | Title | Website link |
| --- | --- | --- |
| Article | Clinical targeting of HIV capsid protein with a long-acting small molecule | https://doi.org/10.1038/s41586-020-2443-1 |

## PURPOSE 3

### Identifier

NCT06101329

### Link

https://clinicaltrials.gov/study/NCT06101329

### Phase

Phase II

### Status

Recruiting

### Sponsor

Gilead Sciences

### More details

Not provided

### Purpose

Evaluate the Pharmacokinetics, Safety, and Acceptability of Twice Yearly Long-acting Subcutaneous Lenacapavir for Pre-Exposure Prophylaxis in Cisgender Women in the United States.

### Interventions

**Intervention 1**

Drug: Lenacapavir Tablet

Dosage: 600 mg

**Intervention 2**

Drug: Long-acting Subcutaneous Lenacapavir Injection

Dosage: 927 mg

**Intervention 3**

Drug: Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF)

Dosage: 200/300 mg

## Countries

United States of America

## Sites / Institutions

Not provided

## Trials dates

**Anticipated Start Date**

Not provided

**Actual Start Date**

2023-11-17

**Anticipated Date of Last Follow-up**

2024-08-12

**Estimated Primary Completion Date**

2028-01-01

**Estimated Completion Date**

2028-01-01

**Actual Primary Completion Date**

Not provided

**Actual Completion Date**

Not provided

## Studied populations

### Age Cohort

- Adults
- Older Adults

### Genders

- Cisgender female

### Accepts pregnant individuals

Unspecified

### Accepts lactating individuals

Unspecified

### Accepts healthy individuals

Unspecified

## Comments about the studied populations

Cisgender women aged 18 and older who report at least one episode of condomless vaginal or anal sex with a cisgender man in the twelve months prior to enrollment.

## Health status

Negative to : HIV, HBV
Considered at low risk of : HIV

## Study type

Interventional (clinical trial)

## Enrollment

250

## Allocation

Randomized

## Intervention model

Parallel Assignment

## Intervention model description

Not provided

## Masking

Open label

## Masking description

None (Open Label)

## Frequency of administration

Bi-yearly

## Studied LA-formulation(s)

Injectable

## Studied route(s) of administration

Oral
Subcutaneous

## Use case

PrEP

## Key results

Not provided

## PURPOSE 4

### Identifier

NCT06101342

### Link

https://clinicaltrials.gov/study/NCT06101342

### Phase

Phase II

### Status

Recruiting

### Sponsor

Gilead Sciences

### More details

PWUD (People Who Use Drugs).

### Purpose

Evaluate the Pharmacokinetics and Safety of Twice Yearly Long-Acting Subcutaneous Lenacapavir for Pre-Exposure Prophylaxis in People Who Inject Drugs.

### Interventions

**Intervention 1**

Drug: Long-acting Subcutaneous Lenacapavir Injection

Dosage: 927 mg

**Intervention 2**

Drug: Lenacapavir Tablet

Dosage: 600 mg

**Intervention 3**

Drug: Emtricitabine/tenofovir disoproxil fumarate (F/TDF)

Dosage: 200/300 mg

## Countries

United States of America

## Sites / Institutions

Not provided

## Trials dates

**Anticipated Start Date**

Not provided

**Actual Start Date**

2023-12-13

**Anticipated Date of Last Follow-up**

2024-08-08

**Estimated Primary Completion Date**

2027-07-01

**Estimated Completion Date**

2027-07-01

**Actual Primary Completion Date**

Not provided

**Actual Completion Date**

Not provided

## Studied populations

**Age Cohort**

- Adults
- Older Adults

**Genders**

- All

**Accepts pregnant individuals**

Unspecified

**Accepts lactating individuals**

Unspecified

**Accepts healthy individuals**

Yes

## Comments about the studied populations

Participant inclusion criteria requires a positive urine drug screen for any drug of misuse including (but not limited to) opioids (eg, fentanyl, heroin), stimulants (eg, cocaine, amphetamines), psychoactive drugs (eg, benzodiazepines), or a combination of these drugs. Participants must also display evidence of recent injection(s) (eg, track marks) and self-report of injection paraphernalia sharing within the last 30 days.

## Health status

Negative to : HIV, HBV, TB
Considered high risk to : HIV

## Study type

Interventional (clinical trial)

## Enrollment

250

## Allocation

Randomized

## Intervention model

Parallel Assignment

## Intervention model description

Not provided

## Masking

Open label

## Masking description

None (Open Label)

## Frequency of administration

Bi-yearly

## Studied LA-formulation(s)

Injectable

## Studied route(s) of administration

Oral
Subcutaneous

## Use case

PrEP

## Key results

Not provided

# GS-US-536-5939

## Identifier

NCT05729568

## Link

https://clinicaltrials.gov/study/NCT05729568

## Phase

Phase II

## Status

Active, not recruiting

## Sponsor

Gilead Sciences

## More details

Not provided

## Purpose

Evaluate the Safety and Efficacy of bNAbs GS-5423 and GS-2872 in Combination With Lenacapavir as Long-Acting Treatment Dosed Every 6 Months in Virologically Suppressed Adults With HIV-1 Infection.

## Interventions

### Intervention 1

Drug: Teropavimab (Formerly GS-5423)

### Intervention 2

Drug: Zinlirvimab (Formerly GS-2872)

**Intervention 3**

Drug: Lenacapavir Tablet

Dosage: 600 mg

**Intervention 4**

Drug: Lenacapavir Injection

Dosage: 927 mg

**Intervention 5**

Drug: Antiretroviral Therapy

## Countries

United States of America

Australia

Canada

Puerto Rico

## Sites / Institutions

Not provided

## Trials dates

**Anticipated Start Date**

Not provided

**Actual Start Date**

2023-05-15

**Anticipated Date of Last Follow-up**

2024-07-12

**Estimated Primary Completion Date**

2025-03-01

**Estimated Completion Date**

2029-12-01

**Actual Primary Completion Date**

2024-07-02

**Actual Completion Date**

Not provided

## Studied populations

**Age Cohort**

- Adults
- Older Adults

**Genders**

- All

**Accepts pregnant individuals**

Unspecified

**Accepts lactating individuals**

Unspecified

**Accepts healthy individuals**

No

## Comments about the studied populations

Participants are required to be receiving a stable ART regimen with no clinically significant documented resistance (except isolated NRTI mutations). Plasma HIV-1 RNA < 50 copies/mL at screening visit 2 and documented plasma HIV-1 RNA < 50 copies/mL for ≥ 12 months preceding screening visit 2.

## Health status

Positive to : HIV

Negative to : HCV, HBV

## Study type

Interventional (clinical trial)

## Enrollment

83

## Allocation

Randomized

## Intervention model

Parallel Assignment

## Intervention model description

Not provided

## Masking

Open label

## Masking description

None (Open Label)

## Frequency of administration

Bi-yearly

## Studied LA-formulation(s)

Injectable

## Studied route(s) of administration

Subcutaneous

## Use case

Treatment

## Key results

Not provided

# IMEA 070

## Identifier

NCT06289361

## Link

https://clinicaltrials.gov/study/NCT06289361

## Phase

Marketed

## Status

Not yet recruiting

## Sponsor

Institut de Médecine et d'Epidémiologie Appliquée - Fondation Internationale Léon M'Ba

## More details

Immunovirological follow-up and safety of HIV-infected patients receiving lenacapavir under compassionate access in France between 01/01/2021 and 12/31/2023

## Purpose

Cohort IMEA 070 -Lenacapavir Compassional

## Interventions

Not provided

## Countries

France

## Sites / Institutions

Not provided

## Trials dates

### Anticipated Start Date

2024-04-01

### Actual Start Date

Not provided

### Anticipated Date of Last Follow-up

2024-03-20

### Estimated Primary Completion Date

2024-04-15

### Estimated Completion Date

2024-07-30

### Actual Primary Completion Date

Not provided

### Actual Completion Date

Not provided

## Studied populations

### Age Cohort

- Adults
- Older Adults

### Genders

- All

### Accepts pregnant individuals

Unspecified

**Accepts lactating individuals**

Unspecified

**Accepts healthy individuals**

No

## Comments about the studied populations

Not provided

## Health status

Positive to : HIV

## Study type

Observational studies (incl. patient registries)

## Enrollment

58

## Allocation

Not provided

## Intervention model

Not provided

## Intervention model description

Not provided

## Masking

Not provided

## Masking description

Not provided

## Frequency of administration

Bi-yearly

## Studied LA-formulation(s)

Injectable

## Studied route(s) of administration

Subcutaneous

## Use case

Treatment

## Key results

Not provided

## PURPOSE 5

### Identifier

NCT06513312

### Link

https://clinicaltrials.gov/study/NCT06513312

### Phase

Phase II

### Status

Not yet recruiting

### Sponsor

Gilead Sciences

### More details

The goals of this clinical study are to learn more about the study drug lenacapavir (LEN), by comparing the consistent and continuous use of LEN and emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®) (F/TDF), then by observing the safety of LEN and F/TDF, evaluating the acceptability of LEN injections and oral F/TDF, and observe how LEN moves throughout the body in people who would benefit from pre-exposure prophylaxis (PrEP). The primary objective of this study is to compare LEN and F/TDF consistent and continuous use among people who would benefit from PrEP.

### Purpose

Study of Lenacapavir Taken Twice a Year for HIV Pre-Exposure Prophylaxis (PrEP)

### Interventions

**Intervention 1**

Drug: Lenacapavir Injection

Dosage: 927 mg

**Intervention 2**

Drug: Lenacapavir Tablet

Dosage: 600 mg

**Intervention 3**

Drug: Emtricitabine/tenofovir disoproxil fumarate (F/TDF)

Dosage: 200/300 mg

## Countries

France

United Kingdom

## Sites / Institutions

Not provided

## Trials dates

**Anticipated Start Date**

2024-09-01

**Actual Start Date**

Not provided

**Anticipated Date of Last Follow-up**

2024-08-22

**Estimated Primary Completion Date**

2027-01-01

**Estimated Completion Date**

2029-07-01

### Actual Primary Completion Date

Not provided

### Actual Completion Date

Not provided

## Studied populations

### Age Cohort

- Adults
- Older Adults

### Genders

- Cisgender female
- Cisgender male
- Transgender female
- Transgender male
- Gender non-binary
- All

### Accepts pregnant individuals

Unspecified

### Accepts lactating individuals

Unspecified

### Accepts healthy individuals

Yes

## Comments about the studied populations

Key Inclusion Criteria: - Able to comprehend and provide a signed written informed consent, which must be obtained prior to initiation of study procedures. - Cisgender men who have sex with men, transgender women, transgender men, cisgender women, and nonbinary people - Increased likelihood of HIV acquisition as indicated by at least one of the following: - Condomless sex with ≥ 2 partners in the past 6 months

- Diagnosis of a bacterial sexually transmitted infection (STI) in the past 12 months - Engagement in sex work or transactional sex in the past 12 months - Use of ≥ 2 courses of nonoccupational HIV post-exposure prophylaxis (nPEP) in the past 12 months - Condomless sex with a partner living with HIV who has unknown or unsuppressed viral load (≥ 200 copies/mL) in the past 12 months

### Health status

Negative to : HIV

### Study type

Interventional (clinical trial)

### Enrollment

262

### Allocation

Randomized

### Intervention model

Parallel Assignment

### Intervention model description

Not provided

### Masking

Open label

### Masking description

None (Open Label)

### Frequency of administration

Bi-yearly

## Studied LA-formulation(s)

Injectable

## Studied route(s) of administration

Subcutaneous

## Use case

PrEP

## Key results

Not provided

# Excipients

## Proprietary excipients used

No proprietary excipient used

## Novel excipients or existing excipients at a concentration above Inactive Ingredients Database (IID) for the specified route of administration

No novel excipient or existing excipient used

## Residual solvents used

No residual solvent used

# Patent info

# Compound patent families

## Patent informations

| Patent description | Representative patent | Categories | Patent holder | Licence with MPP | Patent source |
|---|---|---|---|---|---|
| Lenacapavir use in HIV pre-exposure prophylaxis (PrEP)<br>Expiry date: 2040-11-25 | WO2021108544 | Use | | Yes | |

## Patent status

| Patent status/countries | Low, Low- middle and upper-middle | High income |
|---|---|---|
| Granted | | Australia, United States of America |
| Filed | China, Albania, Serbia, Türkiye, North Macedonia, India | Australia, Canada, Liechtenstein, Italy, Norway, Malta, Denmark, Belgium, United Kingdom, Greece, Netherlands, Hungary, Croatia, Switzerland, Spain, San Marino, Slovenia, Austria, Romania, Iceland, Cyprus, Finland, France, Bulgaria, Slovakia, Poland, Latvia, Ireland, Estonia, Germany, Luxembourg, Portugal, Czechia, Lithuania, Monaco, Sweden, Japan, Taiwan, Province of China, Hong Kong |
| Not in force | World Intellectual Property Organization (WIPO), Morocco, Tunisia, Bosnia and Herzegovina, Cambodia, Montenegro, Moldova, Republic of | World Intellectual Property Organization (WIPO), Japan, Korea, Republic of, United States of America |

## MPP Licence(s)

**Bilateral licence on lenacapavir (LEN)**

https://www.gilead.com/-/media/gileadcorpredesign/pdf/Other/LEN-VL.pdf

## Patent informations

| Patent description | Representative patent | Categories | Patent holder | Licence with MPP | Patent source |
|---|---|---|---|---|---|
| Lenacapavir use to treat multidrug resistant HIV infection in heavily treatment-experienced<br>Expiry date: 2039-07-15 | WO2020018459 | | | Yes | |

## Patent status

| Patent status/countries | Low, Low- middle and upper-middle | High income |
|---|---|---|
| Granted | | Australia, United States of America |
| Filed | China, Albania, Serbia, Türkiye, North Macedonia | Australia, Canada, Liechtenstein, Italy, Norway, Malta, Denmark, Belgium, United Kingdom, Greece, Netherlands, Hungary, Croatia, Switzerland, Spain, San Marino, Slovenia, Austria, Romania, Iceland, Cyprus, Finland, France, Bulgaria, Slovakia, Poland, Latvia, Ireland, Estonia, Germany, Luxembourg, Portugal, Czechia, Lithuania, Monaco, Sweden, Japan, Korea, Republic of, Taiwan, Province of China, United States of America |
| Not in force | World Intellectual Property Organization (WIPO), Morocco, Tunisia, Bosnia and Herzegovina, Cambodia, Montenegro, Moldova, Republic of | World Intellectual Property Organization (WIPO), Canada, Japan, Korea, Republic of |

## MPP Licence(s)

**Bilateral licence on lenacapavir (LEN)**

https://www.gilead.com/-/media/gileadcorpredesign/pdf/Other/LEN-VL.pdf

## Patent informations

| Patent description | Representative patent | Categories | Patent holder | Licence with MPP | Patent source |
|---|---|---|---|---|---|
| Lenacapavir manufacturing processess and intermediates<br>Expiry date: 2039-02-15 | WO2019161280 | Intermediate(s), Process | | Yes | |

## Patent status

| Patent status/countries | Low, Low- middle and upper-middle | High income |
|---|---|---|
| Granted | China, Albania, Türkiye, North Macedonia, India | Australia, Liechtenstein, Italy, Norway, Malta, Denmark, Belgium, United Kingdom, Greece, Netherlands, Switzerland, Spain, Slovenia, Austria, Cyprus, Finland, France, Bulgaria, Slovakia, Poland, Latvia, Ireland, Estonia, Germany, Luxembourg, Portugal, Czechia, Sweden, Japan, Korea, Republic of, Taiwan, Province of China, United States of America, Hong Kong |
| Filed | China, Albania, Serbia, Türkiye, North Macedonia, India | Australia, Canada, Liechtenstein, Italy, Norway, Malta, Denmark, Belgium, United Kingdom, Greece, Netherlands, Hungary, Croatia, Switzerland, Spain, San Marino, Slovenia, Austria, Romania, Iceland, Cyprus, Finland, France, Bulgaria, Slovakia, Poland, Latvia, Ireland, Estonia, Germany, Luxembourg, Portugal, Czechia, Lithuania, Monaco, Sweden |
| Not in force | World Intellectual Property Organization (WIPO), Argentina, Morocco, Tunisia, Serbia, Bosnia and Herzegovina, Cambodia, Montenegro, Moldova, Republic of | World Intellectual Property Organization (WIPO), Hungary, Croatia, San Marino, Romania, Iceland, Lithuania, Monaco, Japan, Korea, Republic of, Bahamas |

## MPP Licence(s)

**Bilateral licence on lenacapavir (LEN)**

https://www.gilead.com/-/media/gileadcorpredesign/pdf/Other/LEN-VL.pdf

## Patent informations

| Patent description | Representative patent | Categories | Patent holder | Licence with MPP | Patent source |
|---|---|---|---|---|---|
| Crystalline forms of Lenacapavir sodium salt<br>Expiry date: 2038-08-16<br>Lenacapavir solid forms, including pharmaceutically acceptable salts and cocrystals of the inhibitor, as well as crystalline forms of the salts and cocrystals, for use in the treatment of a Retroviridae viral infection including an infection caused by the HIV virus. The present disclosure also relates to pharmaceutical compositions containing the novel salts, cocrystals, and crystalline forms thereof, and methods of treating or preventing a Retroviridae viral infection. | WO2019035904 | Polymorphs | Gilead Sciences, Inc | Yes | |

## Patent status

| Patent status/countries | Low, Low- middle and upper-middle | High income |
|---|---|---|
| Granted | Türkiye, North Macedonia, Albania, Serbia | Belgium, Germany, France, Luxembourg, Netherlands, Switzerland, United Kingdom, Sweden, Italy, Austria, Liechtenstein, Greece, Spain, Denmark, Monaco, Portugal, Ireland, Finland, Cyprus, Bulgaria, Czechia, Estonia, Slovakia, Hungary, Poland, Iceland, Malta, Norway, San Marino, Croatia, Romania, Latvia, Lithuania, Slovenia, Australia, Canada, Japan, Korea, Republic of, Taiwan, Province of China, United States of America, Hong Kong |

| Patent status/countries | Low, Low- middle and upper-middle | High income |
|---|---|---|
| Filed | Türkiye, North Macedonia, Albania, Serbia, China, India | Belgium, Germany, France, Luxembourg, Netherlands, Switzerland, United Kingdom, Sweden, Italy, Austria, Liechtenstein, Greece, Spain, Denmark, Monaco, Portugal, Ireland, Finland, Cyprus, Bulgaria, Czechia, Estonia, Slovakia, Hungary, Poland, Iceland, Malta, Norway, San Marino, Croatia, Romania, Latvia, Lithuania, Slovenia, Canada, United States of America, Hong Kong |
| Not in force | World Intellectual Property Organization (WIPO), North Macedonia, Albania, Bosnia and Herzegovina, Montenegro, Serbia, Moldova, Republic of, Morocco, Tunisia, Cambodia, Argentina, Bangladesh | World Intellectual Property Organization (WIPO), Luxembourg, Denmark, Monaco, Finland, Cyprus, Bulgaria, Estonia, Hungary, Iceland, Malta, San Marino, Croatia, Romania, Latvia, Lithuania, Japan, Taiwan, Province of China |

## MPP Licence(s)

**Bilateral licence on lenacapavir (LEN)**

https://www.gilead.com/-/media/gileadcorpredesign/pdf/Other/LEN-VL.pdf

## Patent informations

| Patent description | Representative patent | Categories | Patent holder | Licence with MPP | Patent source |
|---|---|---|---|---|---|
| Lenacapavir compound and its use in HIV (oral and parenteral)<br>Expiry date: 2037-08-17<br>The present disclosure relates to novel compounds for use in the treatment of a Retroviridae viral infection including an infection caused by the HIV virus. The present disclosure also relates to intermediates for its preparation and to pharmaceutical compositions containing said novel compound. | WO2018035359 | Compound | Gilead Sciences, Inc | Yes | |

## Patent status

| Patent status/countries | Low, Low- middle and upper-middle | High income |
|---|---|---|
| Granted | Türkiye, North Macedonia, Morocco, Brazil, China, Colombia, Dominican Republic, Turkmenistan, Belarus, Tajikistan, Kazakhstan, Azerbaijan, Kyrgyzstan, Armenia, Mexico, Peru, Botswana, Gambia (the), Ghana, Kenya, Lesotho, Malawi, Mozambique, Namibia, Sierra Leone, Liberia, Sao Tome and Principe, Sudan, Eswatini, Tanzania, United Republic of, Zambia, Zimbabwe, Indonesia, Malaysia, Ukraine, South Africa, Uzbekistan | Belgium, Germany, France, Luxembourg, Netherlands, Switzerland, United Kingdom, Sweden, Italy, Austria, Liechtenstein, Greece, Spain, Denmark, Portugal, Ireland, Finland, Cyprus, Bulgaria, Czechia, Estonia, Slovakia, Hungary, Poland, Iceland, Malta, Norway, Croatia, Romania, Latvia, Lithuania, Slovenia, Australia, Canada, Russian Federation, Hong Kong, Israel, Japan, Korea, Republic of, New Zealand, Singapore, Taiwan, Province of China, United States of America, Bahamas, Bahrain, Kuwait, Qatar, Saudi Arabia, Oman, United Arab Emirates, Macao, Panama |

| Patent status/countries | Low, Low- middle and upper-middle | High income |
|---|---|---|
| Filed | Türkiye, North Macedonia, Albania, Serbia, Morocco, Argentina, China, Costa Rica, Jordan, Philippines, India, Uganda, Egypt, Guatemala, Indonesia, Nigeria, Thailand, Ukraine, Viet Nam | Belgium, Germany, France, Luxembourg, Netherlands, Switzerland, United Kingdom, Sweden, Italy, Austria, Liechtenstein, Greece, Spain, Denmark, Monaco, Portugal, Ireland, Finland, Cyprus, Bulgaria, Czechia, Estonia, Slovakia, Hungary, Poland, Iceland, Malta, Norway, San Marino, Croatia, Romania, Latvia, Lithuania, Slovenia, Australia, Chile, Hong Kong, Korea, Republic of, Singapore, Taiwan, Province of China, United States of America, Saudi Arabia, Panama |
| Not in force | World Intellectual Property Organization (WIPO), North Macedonia, Albania, Bosnia and Herzegovina, Montenegro, Serbia, Moldova, Republic of, Colombia, Dominican Republic, Ecuador, Peru, Rwanda, Uganda, Bangladesh, Bolivia (Plurinational State of), Cuba, Benin, Cameroon, Burkina Faso, Chad, Guinea-Bissau, Comoros, Mali, Senegal, Congo, Guinea, Gabon, Niger, Equatorial Guinea, Mauritania, Togo, Côte d'Ivoire, Central African Republic, Pakistan, Paraguay, El Salvador, Venezuela (Bolivarian Republic of) | World Intellectual Property Organization (WIPO), Monaco, Malta, San Marino, Japan, Korea, Republic of, Uruguay, Trinidad and Tobago |

## MPP Licence(s)

**Bilateral licence on lenacapavir (LEN)**

https://www.gilead.com/-/media/gileadcorpredesign/pdf/Other/LEN-VL.pdf

## Patent informations

| Patent description | Representative patent | Categories | Patent holder | Licence with MPP | Patent source |
|---|---|---|---|---|---|
| Lenacapavir and analogues (Markush formula) and their use in HIV<br>Expiry date: 2034-02-28<br>Compounds of formula (I) or salts thereof are disclosed. Also disclosed are pharmaceutical compositions comprising a compound of formula I, processes for preparing compounds of formula I, intermediates useful for preparing compounds of formula I and therapeutic methods for treating a Retroviridae viral infection including an infection caused by the HIV virus. | WO2014134566 | Compound | Gilead Sciences, Inc | Yes | |

## Patent status

| Patent status/countries | Low, Low- middle and upper-middle | High income |
|---|---|---|
| Granted | Türkiye, North Macedonia, Albania, Bosnia and Herzegovina, Montenegro, Serbia, Brazil, China, Costa Rica, Cuba, Turkmenistan, Belarus, Tajikistan, Kazakhstan, Azerbaijan, Kyrgyzstan, Armenia, Mexico, Peru, Philippines, Ukraine, Botswana, Gambia (the), Ghana, Kenya, Lesotho, Malawi, Mozambique, Namibia, Sierra Leone, Liberia, Rwanda, Sudan, Eswatini, Tanzania, United Republic of, Zambia, Zimbabwe, Benin, Cameroon, Burkina Faso, Chad, Guinea-Bissau, Comoros, Mali, Senegal, Congo, Guinea, Gabon, Niger, Equatorial Guinea, Mauritania, Togo, Côte d'Ivoire, Central African Republic, Colombia, Indonesia, Malaysia, Viet Nam, South Africa | Belgium, Germany, France, Luxembourg, Netherlands, Switzerland, United Kingdom, Sweden, Italy, Austria, Liechtenstein, Greece, Spain, Denmark, Monaco, Portugal, Ireland, Finland, Cyprus, Bulgaria, Czechia, Estonia, Slovakia, Hungary, Poland, Iceland, Malta, Norway, San Marino, Croatia, Romania, Latvia, Lithuania, Slovenia, Australia, Canada, Chile, Russian Federation, Hong Kong, Israel, Japan, Korea, Republic of, New Zealand, Singapore, Taiwan, Province of China, United States of America, Bahrain, Kuwait, Qatar, Saudi Arabia, Oman, United Arab Emirates, Macao, Panama |

| Patent status/countries | Low, Low- middle and upper-middle | High income |
|---|---|---|
| Filed | Türkiye, North Macedonia, Albania, Serbia, Argentina, Costa Rica, Ukraine, India, Egypt, Thailand | Belgium, Germany, France, Luxembourg, Netherlands, Switzerland, United Kingdom, Sweden, Italy, Austria, Liechtenstein, Greece, Spain, Denmark, Monaco, Portugal, Ireland, Finland, Cyprus, Bulgaria, Czechia, Estonia, Slovakia, Hungary, Poland, Iceland, Malta, Norway, San Marino, Croatia, Romania, Latvia, Lithuania, Slovenia, United States of America |
| Not in force | World Intellectual Property Organization (WIPO), North Macedonia, Albania, Bosnia and Herzegovina, Montenegro, Serbia, Argentina, Brazil, China, Moldova, Republic of, Peru, Uganda, Bolivia (Plurinational State of), Colombia, Ecuador, Malaysia, Paraguay, Pakistan, El Salvador, Venezuela (Bolivarian Republic of), Viet Nam, South Africa | World Intellectual Property Organization (WIPO), Luxembourg, Denmark, Monaco, Finland, Cyprus, Bulgaria, Estonia, Malta, San Marino, Croatia, Romania, Latvia, Lithuania, Australia, Canada, Hong Kong, Japan, New Zealand, Singapore, United States of America, Uruguay, Bahamas |

## MPP Licence(s)

**Bilateral licence on lenacapavir (LEN)**

https://www.gilead.com/-/media/gileadcorpredesign/pdf/Other/LEN-VL.pdf

# Supporting material

## Publications

Link JO, Rhee MS, Tse WC, Zheng J, Somoza JR, Rowe W, Begley R, Chiu A, Mulato A, Hansen D, Singer E, Tsai LK, Bam RA, Chou CH, Canales E, Brizgys G, Zhang JR, Li J, Graupe M, Morganelli P, Liu Q, Wu Q, Halcomb RL, Saito RD, Schroeder SD, Lazerwith SE, Bondy S, Jin D, Hung M, Novikov N, Liu X, Villasenor AG, Cannizzaro CE, Hu EY, Anderson RL, Appleby TC, Lu B, Mwangi J, Liclican A, Niedziela-Majka A, Papalia GA, Wong MH, Leavitt SA, Xu Y, Koditek D, Stepan GJ, Yu H, Pagratis N, Clancy S, Ahmadyar S, Cai TZ, Sellers S, Wolckenhauer SA, Ling J, Callebaut C, Margot N, Ram RR, Liu YP, Hyland R, Sinclair GI, Ruane PJ, Crofoot GE, McDonald CK, Brainard DM, Lad L, Swaminathan S, Sundquist WI, Sakowicz R, Chester AE, Lee WE, Daar ES, Yant SR, Cihlar T: Clinical targeting of HIV capsid protein with a long-acting small molecule. Nature. 2020 Aug;584(7822):614-618. doi: https://doi.org/10.1038/s41586-020-2443-1. Epub 2020 Jul 1.

Oral antiretroviral agents provide life-saving treatments for millions of people living with HIV, and can prevent new infections via pre-exposure prophylaxis1-5. However, some people living with HIV who are heavily treatment-experienced have limited or no treatment options, owing to multidrug resistance6. In addition, suboptimal adherence to oral daily regimens can negatively affect the outcome of treatment-which contributes to virologic failure, resistance generation and viral transmission-as well as of pre-exposure prophylaxis, leading to new infections1,2,4,7-9. Long-acting agents from new antiretroviral classes can provide much-needed treatment options for people living with HIV who are heavily treatment-experienced, and additionally can improve adherence10. Here we describe GS-6207, a small molecule that disrupts the functions of HIV capsid protein and is amenable to long-acting therapy owing to its high potency, low in vivo systemic clearance and slow release kinetics from the subcutaneous injection site. Drawing on X-ray crystallographic information, we designed GS-6207 to bind tightly at a conserved interface between capsid protein monomers, where it interferes with capsid-protein-mediated interactions between proteins that are essential for multiple phases of the viral replication cycle. GS-6207 exhibits antiviral

activity at picomolar concentrations against all subtypes of HIV-1 that we tested, and shows high synergy and no cross-resistance with approved antiretroviral drugs. In phase-1 clinical studies, monotherapy with a single subcutaneous dose of GS-6207 (450 mg) resulted in a mean log10-transformed reduction of plasma viral load of 2.2 after 9 days, and showed sustained plasma exposure at antivirally active concentrations for more than 6 months. These results provide clinical validation for therapies that target the functions of HIV capsid protein, and demonstrate the potential of GS-6207 as a long-acting agent to treat or prevent infection with HIV.

Zhuang S, Torbett BE: Interactions of HIV-1 Capsid with Host Factors and Their Implications for Developing Novel Therapeutics. Viruses. 2021 Mar 5;13(3). pii: v13030417. doi: https://doi.org/10.3390/v13030417

The Human Immunodeficiency Virus type 1 (HIV-1) virion contains a conical shell, termed capsid, encasing the viral RNA genome. After cellular entry of the virion, the capsid is released and ensures the protection and delivery of the HIV-1 genome to the host nucleus for integration. The capsid relies on many virus-host factor interactions which are regulated spatiotemporally throughout the course of infection. In this paper, we will review the current understanding of the highly dynamic HIV-1 capsid-host interplay during the early stages of viral replication, namely intracellular capsid trafficking after viral fusion, nuclear import, uncoating, and integration of the viral genome into host chromatin. Conventional anti-retroviral therapies primarily target HIV-1 enzymes. Insights of capsid structure have resulted in a first-in-class, long-acting capsid-targeting inhibitor, GS-6207 (Lenacapavir). This inhibitor binds at the interface between capsid protein subunits, a site known to bind host factors, interferes with capsid nuclear import, HIV particle assembly, and ordered assembly. Our review will highlight capsid structure, the host factors that interact with capsid, and high-throughput screening techniques, specifically genomic and proteomic approaches, that have been and can be used to identify host factors that interact with capsid. Better structural and mechanistic insights into the capsid-host factor interactions will significantly inform the understanding of HIV-1 pathogenesis and the development of capsid-centric antiretroviral therapeutics.

Bester SM, Wei G, Zhao H, Adu-Ampratwum D, Iqbal N, Courouble VV, Francis AC, Annamalai AS, Singh PK, Shkriabai N, Van Blerkom P, Morrison J, Poeschla EM, Engelman AN, Melikyan GB, Griffin PR, Fuchs JR, Asturias FJ, Kvaratskhelia M: Structural and mechanistic bases for a potent HIV-1 capsid inhibitor. Science. 2020 Oct 16;370(6514):360-364. doi: https://doi.org/10.1126/science.abb4808

The potent HIV-1 capsid inhibitor GS-6207 is an investigational principal component of long-acting antiretroviral therapy. We found that GS-6207 inhibits HIV-1 by stabilizing and thereby preventing functional disassembly of the capsid shell in infected cells. X-ray crystallography, cryo-electron microscopy, and hydrogen-deuterium exchange experiments revealed that GS-6207 tightly binds two adjoining capsid subunits and promotes distal intra- and inter-hexamer interactions that stabilize the curved capsid lattice. In addition, GS-6207 interferes with capsid binding to the cellular HIV-1 cofactors Nup153 and CPSF6 that mediate viral nuclear import and direct integration into gene-rich regions of chromatin. These findings elucidate structural insights into the multimodal, potent antiviral activity of GS-6207 and provide a means for rationally developing second-generation therapies.

Singh K, Gallazzi F, Hill KJ, Burke DH, Lange MJ, Quinn TP, Neogi U, Sonnerborg A: GS-CA Compounds: First-In-Class HIV-1 Capsid Inhibitors Covering Multiple Grounds. Front Microbiol. 2019 Jun 20;10:1227. doi: https://doi.org/10.3389/fmicb.2019.01227

Recently reported HIV-1 capsid (CA) inhibitors GS-CA1 and GS-6207 (an analog of GS-CA1) are first-in-class compounds with long-acting potential. Reportedly, both compounds have greater potency than currently approved anti-HIV drugs. Due to the limited access to experimental data and the compounds themselves, a detailed mechanism of their inhibition is yet to be delineated. Using crystal structures of capsid-hexamers bound to well-studied capsid inhibitor PF74 and molecular modeling, we predict that GS-CA compounds bind in the pocket that is shared by previously reported CA inhibitors and host factors. Additionally, comparative modeling suggests that GS-CA compounds have unique structural features contributing to interactions

with capsid. To test their proposed binding mode, we also report the design of a cyclic peptide combining structural units from GS-CA compounds, host factors, and previously reported capsid inhibitors. This peptide (Pep-1) binds CA-hexamer with a docking score comparable to GS-CA compounds. Affinity determination by MicroScale thermophoresis (MST) assays showed that CA binds Pep-1 with a ~7-fold better affinity than well-studied capsid inhibitor PF74, suggesting that it can be developed as a possible CA inhibitor.

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 Feb 17;65(3). pii: AAC.02057-20. doi: https://doi.org/10.1128/aac.02057-20. Print 2021 Feb 17

Lenacapavir (LEN; GS-6207) is a potent first-in-class inhibitor of HIV-1 capsid with long-acting properties and the potential for subcutaneous dosing every 3 months or longer. In the clinic, a single subcutaneous LEN injection (20 mg to 750 mg) in people with HIV (PWH) induced a strong antiviral response, with a >2.3 mean log10 decrease in HIV-1 RNA at day 10. HIV-1 Gag mutations near protease (PR) cleavage sites have emerged with the use of protease inhibitors (PIs). Here, we have characterized the activity of LEN in mutants with Gag cleavage site mutations (GCSMs) and mutants resistant to other drug classes. HIV mutations were inserted into the pXXLAI clone, and the resulting mutants (n = 70) were evaluated using a 5-day antiviral assay. LEN EC50 fold change versus the wild type ranged from 0.4 to 1.9 in these mutants, similar to that for the control drug. In contrast, reduced susceptibility to PIs and maturation inhibitors (MIs) was observed. Testing of isolates with resistance against the 4 main classes of drugs (n = 40) indicated wild-type susceptibility to LEN (fold change ranging from 0.3 to 1.1), while reduced susceptibility was observed for control drugs. HIV GCSMs did not impact the activity of LEN, while some conferred resistance to MIs and PIs. Similarly, LEN activity was not affected by naturally occurring variations in HIV Gag, in contrast to the reduced susceptibility observed for MIs. Finally, the activity of LEN was not affected by the presence of resistance mutations to the 4 main antiretroviral (ARV) drug classes. These data support the evaluation of LEN in PWH with multiclass

resistance.

Swanstrom, A.E. *et al.* (2023). Long-acting lenacapavir protects macaques against intravenous challenge with simian-tropic HIV. *eBioMedicine*, 95, p. 104764. DOI: 10.1016/j.ebiom.2023.104764.

## Background

Long-acting subcutaneous lenacapavir (LEN), a first-in-class HIV capsid inhibitor approved by the US FDA for the treatment of multidrug-resistant HIV-1 with twice yearly dosing, is under investigation for HIV-1 pre-exposure prophylaxis (PrEP). We previously derived a simian-tropic HIV-1 clone (stHIV-A19) that encodes an HIV-1 capsid and replicates to high titres in pigtail macaques (PTM), resulting in a nonhuman primate model well-suited for evaluating LEN PrEP in vivo.

## Methods

Lenacapavir potency against stHIV-A19 in PTM peripheral blood mononuclear cells in vitro was determined and subcutaneous LEN pharmacokinetics were evaluated in naïve PTMs in vivo. To evaluate the protective efficacy of LEN PrEP, naïve PTMs received either a single subcutaneous injection of LEN (25 mg/kg, N = 3) or vehicle (N = 4) 30 days before a high-dose intravenous challenge with stHIV-A19, or 7 daily subcutaneous injections of a 3-drug control PrEP regimen starting 3 days before stHIV-A19 challenge (N = 3).

## Findings

In vitro, LEN showed potent antiviral activity against stHIV-A19, comparable to its potency against HIV-1. In vivo, subcutaneous LEN displayed sustained plasma drug exposures in PTMs. Following stHIV-A19 challenge, while all vehicle control animals became productively infected, all LEN and 3-drug control PrEP animals were protected from infection.

## Interpretation

These findings highlight the utility of the stHIV-A19/PTM model and support the clinical development of long-acting LEN for PrEP in humans.

## Additional documents

No documents were uploaded

## Useful links

- Gilead Announces First Global Regulatory Approval of Sunlenca® (Lenacapavir)
- PURPOSE PrEP Studies Overview: Prevention With a Purpose
- An Overview of Lenacapavir for PrEP Trials (AVAC)

# Access principles

## Collaborate for development

Consider on a case by case basis, collaborating on developing long acting products with potential significant public health impact, especially for low- and middle-income countries (LMICs), utilising the referred to long-acting technology

Not provided

## Share technical information for match-making assessment

Provide necessary technical information to a potential partner, under confidentiality agreement, to enable preliminary assessment of whether specific medicines of public health importance in LMICs might be compatible with the referred to long-acting technology to achieve a public health benefit

Not provided

## Work with MPP to expand access in LMICs

In the event that a product using the referred to long-acting technology is successfully developed, the technology IP holder(s) will work with the Medicines Patent Pool towards putting in place the most appropriate strategy for timely and affordable access in low and middle-income countries, including through licensing

Not provided

# Comment & Information

Not provided