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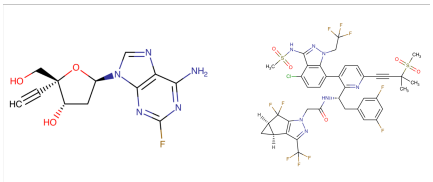


MK-8591D (Islatravir and Lenacapavir)

Developer(s)

Merck

Originator

https://www.merck.com/

United States

Merck & Co., Inc. is an American multinational pharmaceutical company known as Merck Sharp & Drone (MSD) in territories outside of the USA and Canada. Merck was originally established in 1891, and is headquartered in Rahway, New Jersey. The company is particularly well known for developing and manufacturing biologic therapies, vaccines, medicines and animal health products.

Gilead Sciences

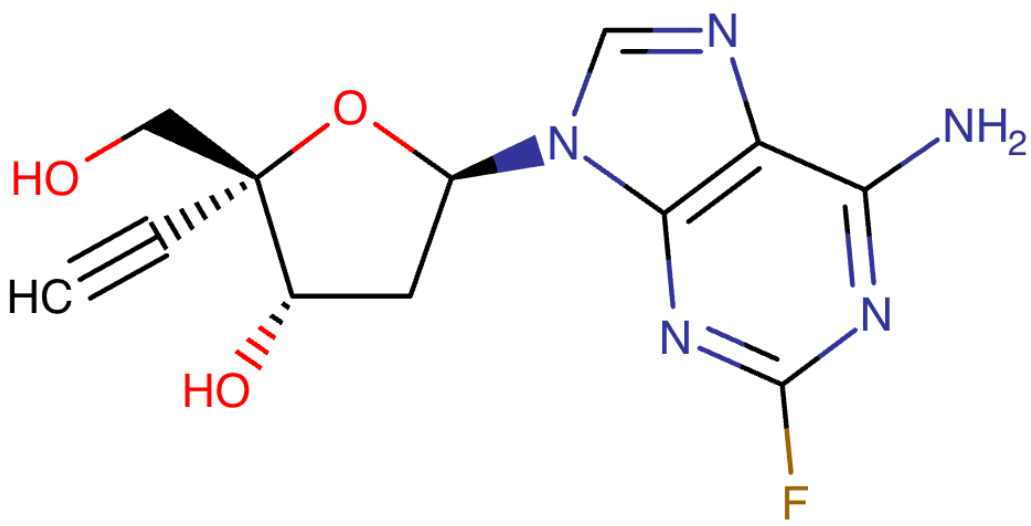
Originator

https://www.gilead.com/

United States

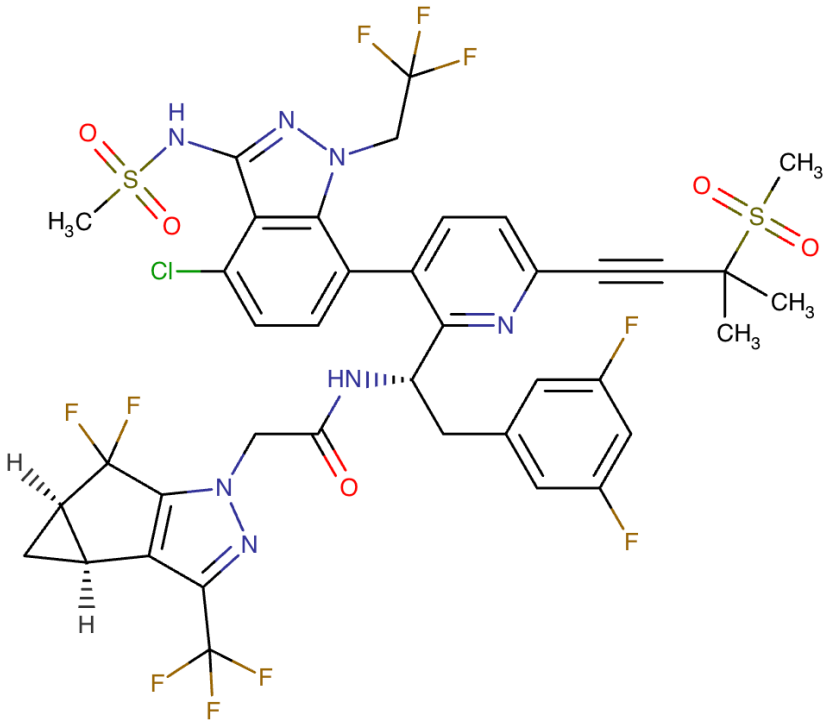
Gilead Sciences, Inc. is a multinational biopharmaceutical company that develops and manufactures innovative medicines for life-threatening diseases, including anti-viral therapeutics for HIV/AIDS, Hepatitis B, Hepatitis C and Covid-19. Headquartered in Foster City, California, Gilead was originally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

Drug structure



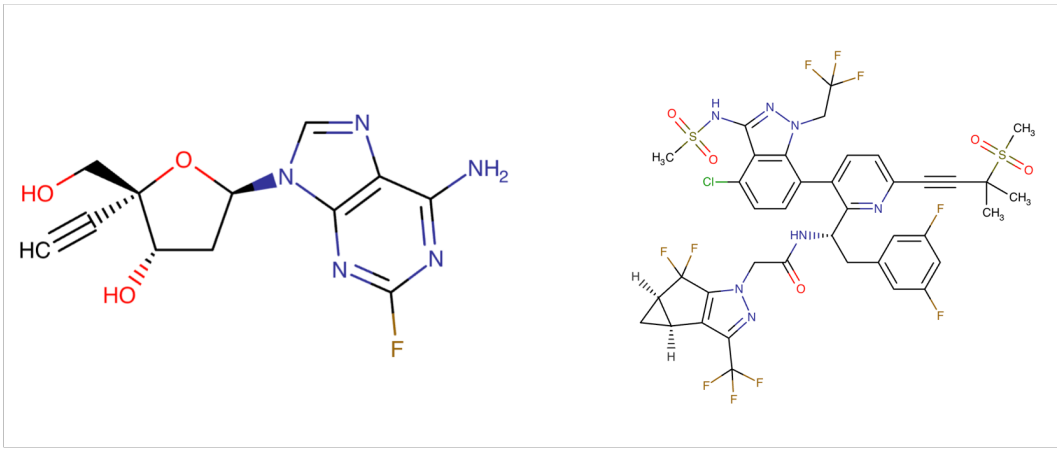
Islatravir Chemical Structure

Sourced from DrugBank



Lenacapavir Chemical Structure

Sourced from DrugBank



Islatravir and Lenacapavir Chemical Structure

Composite Adapated from DrugBank

Drug information

Associated long-acting platforms

Oral solid form

Administration route

Oral

Therapeutic area(s)

HIV

Use case(s)

Treatment

Use of drug

Ease of administration

Self-administered

User acceptance

Not provided

Dosage

Available dose and strength

fixed dose combination of 300 mg lenacapavir + 2 mg islatravir

Frequency of administration

Not provided

Maximum dose

Not provided

Recommended dosing regimen

investigational doses used: https://clinicaltrials.gov/study/NCT06630286

Additional comments

Not provided

Dosage link(s)

Not provided

Drug information

Drug's link(s)

https://go.drugbank.com/drugs/DB15653
https://go.drugbank.com/drugs/DB15673

Generic name

MK-8591D (islatravir and lenacapavir fixed dose combination)

Brand name

Not provided

Compound type

Small molecule

Summary

Islatravir and Lenacapavir (ISL+LEN) is an investigational drug combination currently in clinical development for the treatment of HIV-1. Islatravir (MK-8591) is a nucleoside reverse transcriptase translocation inhibitor under evaluation in several ongoing clinical trials. Lenacapavir is a first in-class HIV-1 capsid inhibitor also being studied as a potential long-acting option in multiple ongoing studies for HIV treatment. The ISL+LEN combination is a proposed once-weekly oral fixed-dose combination regimen consisting of ISL 2mg and LEN 300mg. Once-weekly dosing has the potential to address adherence challenges versus daily oral ART. The pharmacokinetic profiles and potent antiviral activities of both ISL and LEN support their continued development as an investigational drug combination.

Approval status

Islatravir and lenacapavir (ISL+LEN) is an investigational drug combination and is not currently approved in any jurisdiction globally. The safety and efficacy of the ISL+LEN

combination has not yet been established. Pivotal studies are ongoing (Phase III ISLEND-1 and ISLEND-2 studies of lenacapavir/islatravir for the treatment of virally suppressed HIV)

Regulatory authorities

In March 2021, Gilead Sciences and Merck announced that they have entered into an agreement to co-develop and co-commercialize long-acting treatments in HIV that combine Gilead’s investigational capsid inhibitor, lenacapavir, and Merck’s investigational nucleoside reverse transcriptase translocation inhibitor, islatravir, into a two-drug regimen with the potential to provide new treatment options for people living with HIV. Gilead Sciences anticipates a commercial launch of lenacapavir + islatravir for the treatment of HIV in 2027.

Delivery device(s)

No delivery device

Scale-up and manufacturing prospects

Scale-up prospects

Lenacapavir is commercially manufactured by Gilead Sciences. Several synthetic chemical processes describing the manufacture of islatravir (ISL) have been published. However, these approaches have proved to be complex and highly inefficient, with marked difficulty in controlling 2’-deoxyribonucleoside anomer stereochemistry and the requirement for several protecting-group manipulations. To counter these issues, Merck developed a highly innovative and extraordinarily efficient approach utilising directed evolution to create a novel three-step biocatalytic cascade for ISL synthesis.

Tentative equipment list for manufacturing

Islatravir: EasyMax 102 and 402 equipped with FireStringO2 sensors and the EasySampler 1210 system. A thermal gas flow controller (Aalborg, USA) to monitor and control oxidation air-gas flow to the reactor, with a suitable compressed air-source. Lenacapavir: 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

For Islatravir synthesis, the automated lab reactor platforms EasyMax 102 and 402 (Mettler-Toledo AG, AutoChem, Switzerland) were utilised by Merck for reaction scale-up. Although ISL+LEN is currently being evaluated as a fixed-dose oral regimen, future studies may permit LEN to be administered via subcutaneous injection. In this instance, 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

Islatravir: 400 MHz Briker AVANCE III and 500MHz Bruker Ultrashield spectrometer (or equivalent) for 1H, 19F, 31P and 13C NMR. An Accurate-Mass Time-of-Flight (TOF) high resolution mass spectrometer. Molecular Devices plate reader Spectra Max Plus for Spectrophotomeric analyses, alongside a Perkin Elmer polarimeter with a PCB 1500

water Peltier system for optical rotation measurements. Lenacapavir: Proton nuclear magnetic resonance (1H NMR), High-performance liquid chromatography (HPLC), Ultra-Performance Liquid Chromatography (UPLC).

Clinical trials

GS-US-563-6041

Identifier

NCT05052996

Link

https://clinicaltrials.gov/study/NCT05052996

Phase

Phase II

Status

Completed

Sponsor

Gilead Sciences

More details

The primary objective of this study is to evaluate the efficacy of oral weekly islatravir (ISL) in combination with lenacapavir (LEN) in virologically suppressed people with HIV (PWH) at Week 24.

Purpose

Study Evaluating the Safety and Efficacy of Islatravir in Combination With Lenacapavir in Virologically Suppressed People With HIV

Interventions

Intervention 1

Biktarvy®

Dosage: Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg daily tablets

Intervention 2

Oral Islatravir (ISL) and lenacapavir (LEN) once weekly tablet

Dosage: 2mg ISL + 300mg LEN

Countries

United States of America

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2021-10-05

Anticipated Date of Last Follow-up

2024-12-19

Estimated Primary Completion Date

Not provided

Estimated Completion Date

2027-11-01

Actual Primary Completion Date

2023-12-19

Actual Completion Date

Not provided

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

Key Inclusion Criteria: - Received bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) for ≥ 24 weeks at screening. - Documented plasma human immunodeficiency virus type 1 (HIV-1) ribonucleic acid (RNA) < 50 copies/mL (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL) for ≥ 24 weeks before and at screening. - Plasma HIV-1 RNA < 50 copies/mL at screening. Key Exclusion Criteria: * History of prior virologic failure while receiving treatment for HIV-1. * Prior use of, or exposure to, islatravir (ISL) or lenacapavir (LEN). * Active, serious infections requiring parenteral therapy < 30 days before randomization.

Health status

Negative to : HBV, HCV

Positive to : HIV

Study type

Interventional (clinical trial)

Enrollment

142

Allocation

Randomized

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Open label

Masking description

None (Open Label)

Frequency of administration

Weekly

Studied LA-formulation(s)

Tablet

Studied route(s) of administration

Oral

Use case

Treatment

Key resources

Not provided

ISLEND-1

Identifier

NCT06630286

Link

https://clinicaltrials.gov/study/NCT06630286

Phase

Phase III

Status

Completed

Sponsor

Gilead Sciences

More details

Recruitment complete. MSD reported on April 24, 2025 "partial clinical hold for higher doses of islatravir than those used in current clinical trials". The goal of this clinical study is to learn about the safety and efficacy of switching to once weekly tablet of islatravir/lenacapavir (ISL/LEN) regimen versus continuing standard treatment of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in people with human immunodeficiency virus (PWH) who are virologically suppressed (HIV-1 RNA levels \< 50 copies/mL) on B/F/TAF for ≥ 6 months prior to screening. The primary objective is to evaluate the efficacy of switching to oral weekly ISL/LEN tablet regimen versus continuing B/F/TAF in virologically suppressed PWH at Week 48.

Purpose

Study to Compare an Oral Weekly Islatravir/Lenacapavir Regimen With

Bictegravir/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed People With HIV-1

Interventions

Intervention 1

Drug: ISL/LEN

Dosage: ISL 2mg + LEN 300mg once weekly

Intervention 2

Drug: PTM B/F/TAF

Dosage: 50/200/25mg once daily

Countries

Puerto Rico

United States of America

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2024-10-09

Anticipated Date of Last Follow-up

2025-03-31

Estimated Primary Completion Date

2026-06-01

Estimated Completion Date

2030-08-01

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

No

Comments about the studied populations

Key Inclusion Criteria: - HIV-1 RNA < 50 copies/mL for ≥ 6 months before screening, as documented by: 1. One HIV-1 RNA < 50 copies/mL immediately preceding the 24 week period prior to screening. 2. Within 24 weeks prior to screening, if HIV-1 RNA results are available, all levels must be < 50 copies/mL. 3. During the 6 to 12 months period prior to screening, transient detectable viremia ≥ 50 copies/mL is acceptable ("blip"), as long as it is not confirmed on 2 consecutive visits. - Plasma HIV-1 RNA levels < 50 copies/mL at screening. - Individuals are receiving B/F/TAF for ≥ 6 months prior to screening and willing to continue until Day 1. - Individuals assigned female at birth and of childbearing potential who engage in heterosexual intercourse must agree to use

contraception.

Health status

Positive to : HIV
Negative to : HBV, HCV

Study type

Interventional (clinical trial)

Enrollment

600

Allocation

Randomized

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Double-blind masking

Masking description

Double (Participant, Investigator)

Frequency of administration

Weekly

Studied LA-formulation(s)

Tablet

Studied route(s) of administration

Oral

Use case

Treatment

Key resources

Not provided

ISLEND-2

Identifier

NCT06630299

Link

https://clinicaltrials.gov/study/NCT06630299

Phase

Phase III

Status

Completed

Sponsor

Gilead Sciences

More details

Recruitment complete. MSD reported on April 24, 2025 "partial clinical hold for higher doses of islatravir than those used in current clinical trials". The goal of this clinical study is to learn more about the safety and efficacy of switching to a once weekly tablet of islatravir/lenacapavir (ISL/LEN) regimen versus continuing standard of care treatment in PWH who are virologically suppressed (HIV-1 RNA levels \< 50 copies/mL) on a stable standard of care regimen for ≥ 6 months prior to screening. The standard of care includes 2 or 3 medicines, antiretroviral agents (ARVs). The primary objective of the study is to evaluate the efficacy of switching to oral weekly ISL/LEN tablet regimen versus continuing standard of care in virologically suppressed

Purpose

Study to Compare an Oral Weekly Islatravir/Lenacapavir Regimen With Standard of

Care in Virologically Suppressed People With HIV-1

Interventions

Intervention 1

Drug: ISL/LEN

Dosage: ISL 2mg + LEN 300mg once weekly

Intervention 2

Drug: Antiretroviral Combinations

Dosage: Variable

Countries

United States of America

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2024-10-08

Anticipated Date of Last Follow-up

2025-04-16

Estimated Primary Completion Date

2027-06-01

Estimated Completion Date

2030-08-01

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

No

Comments about the studied populations

Key Inclusion Criteria: - HIV-1 RNA < 50 copies/mL for ≥ 6 months before screening, as documented by: 1. One HIV-1 RNA < 50 copies/mL immediately preceding the 24 weeks period prior to screening. 2. Within 24 weeks prior to screening, if HIV-1 RNA results are available, all levels must be < 50 copies/mL. 3. During the 6 to 12 months period prior to screening, transient detectable viremia ≥ 50 copies/mL is acceptable ("blip") as long as it is not confirmed on 2 consecutive visits. - Plasma HIV-1 RNA levels < 50 copies/mL at screening. - Are receiving guideline-recommended standard of care treatment such as International Antiviral Society (IAS), Department of Health and Human Services (DHHS), European AIDS Clinical Society (EACS) consisting of 2 or 3 ARVs for ≥ 6 months.

Health status

Positive to : HIV
Negative to : TB, HBV

Study type

Interventional (clinical trial)

Enrollment

600

Allocation

Randomized

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Open label

Masking description

None (Open Label)

Frequency of administration

Weekly

Studied LA-formulation(s)

Tablet

Studied route(s) of administration

Oral

Use case

Treatment

Key resources

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

There are either no relevant patents or these were not yet submitted to LAPaL

Supporting material

Publications

Amy E Colson, Gordon E Crofoot, Peter J Ruane, Moti N Ramgopal, Alexandra W Dretler, Ronald G Nahass, Gary I Sinclair, Mezgebe Berhe, Fadi Shihadeh, Shan-Yu Liu, Stephanie Klopfer, Sharline Madera, Hadas Dvory-Sobol, Martin Rhee, Elizabeth G Rhee, Jared Baeten, Joseph J Eron, 577. Week 48 Results of a Phase 2 Study Evaluating Once-weekly Oral Islatravir Plus Lenacapavir, *Open Forum Infectious Diseases*, Volume 12, Issue Supplement_1, February 2025, ofae631.015, https://doi.org/10.1093/ofid/ofae631.015

Both islatravir (ISL), a nucleotide reverse transcriptase translocation inhibitor, and lenacapavir (LEN), a capsid inhibitor, have potent anti-HIV-1 activity and pharmacokinetic profiles permitting once-weekly oral dosing. Week (W) 24 data (primary endpoint) from the current Phase 2 study were previously reported (CROI 2024); weekly oral ISL 2 mg + LEN 300 mg maintained high rates of viral suppression (HIV-1 RNA < 50 copies/mL) with no clinically relevant decreases in CD4+ T-cells or lymphocytes, which had been previously observed with higher ISL doses. Here, we report W48 results.

In this Phase 2, randomized, open-label, active-controlled study (NCT05052996), virologically suppressed adults on bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) were randomized 1:1 to receive weekly oral ISL 2 mg + LEN 300 mg or to continue daily B/F/TAF. Virologic outcomes (using FDA-defined snapshot algorithm), adverse events (AEs), CD4+ T-cells, and lymphocytes were assessed.

Additional documents

- MSD Q1 2025 Earnings call - 24 April 2025
- Modelling of missed doses of LEN+ISL weekly - poster - CROI 2025

Useful links

- Gilead and Merck Announce Phase 2 Data Showing a Treatment Switch to ISL+LEN Once Weekly.
- Gilead and Merck Announce Phase 2 Data Showing Investigational Oral Once-Weekly ISL+LEN.
- Study to Compare an Oral Weekly Islatravir/Lenacapavir Regimen With Standard of Care in Virologically Suppressed People With HIV-1 (ISLEND-2)

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

Update from MSD, May 2025: MK-8591D is on FDA partial clinical hold for higher doses of islatravir than those used in current clinical trials. (https://www.msd.com/research/product-pipeline/)