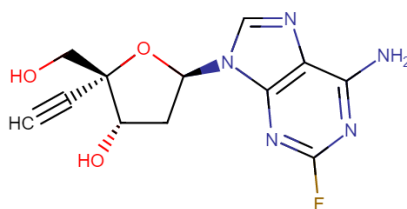


Developed by



Supported by



## Islatravir (ISL)

## Developer(s)

Merck & Co., Inc.

Originator

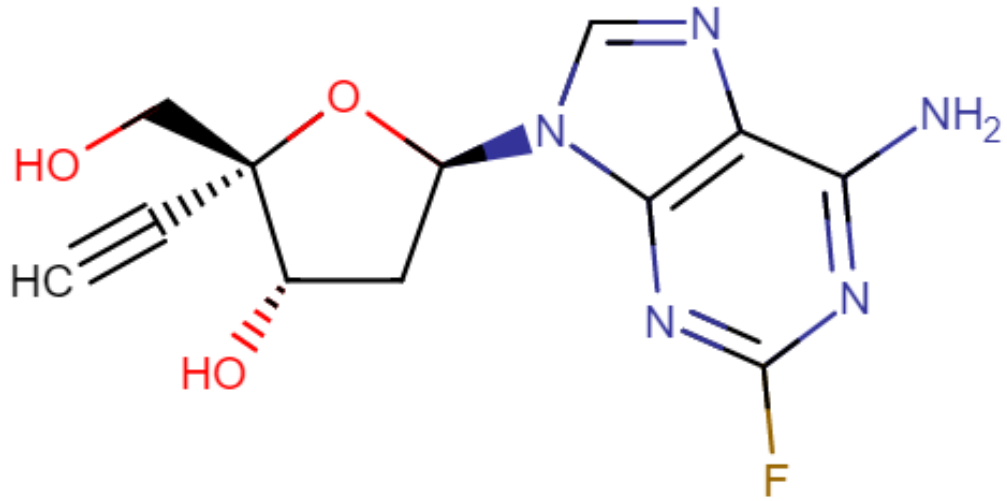
<https://www.msd.com/>

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.

## Drug structure



Islatravir Chemical Structure

Sourced from DrugBank

# Drug information

## Associated long-acting platforms

Polymeric implant, Oral solid form

## Administration route

Oral, Subcutaneous

## Therapeutic area(s)

HIV

## Use case(s)

Pre-Exposure Prophylaxis (PrEP)

Treatment

## Use of drug

### Ease of administration

Administered by a nurse

Administered by a specialty health worker

Self-administered

### User acceptance

Not provided

## Drug information

### Drug's link(s)

<https://go.drugbank.com/drugs/DB15653>

### Generic name

Islatravir

### Brand name

Not provided

### Compound type

Small molecule

### Summary

Islatravir (ISL), also known as MK-8591, is a nucleoside reverse transcriptase translocation inhibitor (NRTI) in clinical development for HIV treatment. ISL is a first-in-class compound with a varied mechanism of action including a strong binding affinity for reverse transcriptase, the ability to block HIV primer translocation and an extended half-life enabling once-weekly oral dosing. ISL is being evaluated in several clinical trials in combination with other antiretroviral therapies including doravirine, lenacapavir and MK-8507. In 2021, the US FDA placed a clinical hold on ISL following a decrease in CD4 T-cell counts in HIV-positive patients, and reduced total lymphocyte counts in HIV-negative trial participants. The FDA clinical hold was lifted after Merck introduced lower ISL dosing.

### Approval status

Unknown

### Regulatory authorities

Unknown

## **Delivery device(s)**

Not provided

## **Scale-up and manufacturing prospects**

## **Scale-up prospects**

The automated lab reactor platforms EasyMax 102 and 402 (Mettler-Toledo AG, AutoChem, Switzerland) were utilised by Merck for the reaction scale-up of Islatravir synthesis. The EasyMax reactors contained integrated measurement probes for pH and temperature, FireStringO2 dissolved oxygen sensors (Pyro-Science GmbH, Germany) and the EasySampler 1210 automated sampling system.

## **Tentative equipment list for manufacturing**

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. Reactions at the 1L scale should be conducted using the Optimal 1001 automated lab reactor platform (Mettler-Toledo) or equivalent, alongside a sintered steel frit for improved 1L gas distribution for the oxidation reactions.

## **Manufacturing**

Several synthetic chemical processes describing the manufacture of ISL have been published, with each approach containing around twelve and eighteen steps. However, it should be noted that 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

## **Specific analytical instrument required for characterization of formulation**

400 MHz Bruker AVANCE III and 500MHz Bruker Ultrashield spectrometer (or equivalent) for <sup>1</sup>H, <sup>19</sup>F, <sup>31</sup>P and <sup>13</sup>C NMR. An Accurate-Mass Time-of-Flight (TOF) high resolution mass spectrometer. Molecular Devices plate reader Spectra Max Plus for Spectrophotometric analyses, alongside a Perkin Elmer polarimeter with a PCB 1500 water Peltier system for optical rotation measurements. Agilent 7890A instrument for gas chromatography. UPLC via Agilent Technologies 1290 Infinity II series or HPLC



through Agilent 1100 Series. Corona Ultra RS detector by Dionex for supercritical fluid chromatography.

# Clinical trials

**MK-8591-016**

## Identifier

NCT04003103

## Link

<https://clinicaltrials.gov/study/NCT04003103>

## Phase

Phase II

## Status

Completed

## Sponsor

Merck Sharp & Dohme LLC

## More details

Not provided

## Purpose

This study will evaluate the safety, tolerability and pharmacokinetics (PK) of 6 once-monthly doses of oral islatravir (60 mg and 120 mg) compared with placebo in adults at low risk of HIV-1 infection

## Interventions

## **Intervention 1**

Drug: Oral Islatravir

Dosage: 30mg oral tablets (for a total 60mg or 120mg once-monthly)

## **Intervention 2**

Drug: Placebo

## **Countries**

United States of America

Israel

South Africa

## **Sites / Institutions**

Not provided

## **Trials dates**

### **Anticipated Start Date**

Not provided

### **Actual Start Date**

2019-09-19

### **Anticipated Date of Last Follow-up**

Not provided

### **Estimated Primary Completion Date**

Not provided

### **Estimated Completion Date**

Not provided

### **Actual Primary Completion Date**

2022-03-18

**Actual Completion Date**

2022-11-24

**Studied populations****Age Cohort**

- Adults
- Older Adults

**Genders**

- All

**Accepts pregnant individuals**

No

**Accepts lactating individuals**

No

**Accepts healthy individuals**

Yes

**Comments about the studied populations**

Inclusion Criteria: - Is in general good health with acceptable laboratory values at screening. - Is confirmed HIV-uninfected based on negative HIV-1/HIV-2 test result before randomization. - Has low risk of HIV infection, within 12 months prior to screening visit or the rescreening visit (if applicable). - Use contraceptives consistent with local regulations. - Female is not pregnant or breastfeeding, and is not a woman of childbearing potential (WOCBP). - A WOCBP is using an acceptable contraceptive method, or is abstinent from heterosexual intercourse as their preferred and usual lifestyle; or has a negative pregnancy test.

**Health status**

Negative to : HIV, HCV, HBV

Considered at low risk of : HIV

**Study type**

Interventional (clinical trial)

**Enrollment**

242

**Allocation**

Randomized

**Intervention model**

Parallel Assignment

**Intervention model description**

Not provided

**Masking**

Double-blind masking

**Masking description**

Double (Participant, Investigator)

**Frequency of administration**

Monthly

**Studied LA-formulation(s)**

Tablet

**Studied route(s) of administration**

Oral

**Use case**

PrEP

## Key results

Type of key results	Title	Website link
Abstract	Safety and pharmacokinetics of oral islatravir once monthly for HIV pre-exposure prophylaxis (PrEP): week 24 analysis of a phase 2a trial	<a href="https://theprogramme.ias2021.org/Abst">https://theprogramme.ias2021.org/Abst</a>

# IMPOWER-022

## Identifier

NCT04644029

## Link

<https://clinicaltrials.gov/study/NCT04644029>

## Phase

Phase III

## Status

Terminated

## Sponsor

Merck Sharp & Dohme LLC

## More details

Voluntarily terminated due to benefit/risk assessment.

## Purpose

This study will evaluate whether oral islatravir (ISL) is effective in preventing Human Immunodeficiency Virus Type 1 (HIV-1) infection in women at high-risk for HIV-1 infection.

## Interventions

### Intervention 1

Drug: Oral Islatravir

Dosage: 60 mg tablet administered once monthly

## **Intervention 2**

Drug: Placebo to FTC/TDF

## **Intervention 3**

Drug: FTC/TDF

Dosage: 200 mg emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300 mg tenofovir disoproxil fumarate or 201.22 mg tenofovir disoproxil phosphate), administered orally once daily

## **Intervention 4**

Drug: Placebo to ISL

## **Countries**

United States of America

South Africa

Uganda

## **Sites / Institutions**

Not provided

## **Trials dates**

### **Anticipated Start Date**

Not provided

### **Actual Start Date**

2021-02-24

### **Anticipated Date of Last Follow-up**

2024-08-06

### **Estimated Primary Completion Date**

Not provided

### **Estimated Completion Date**

2024-07-01



**Actual Primary Completion Date**

2023-07-18

**Actual Completion Date**

2024-06-11

**Studied populations****Age Cohort**

- Adolescents
- Adults

**Genders**

- Cisgender female

**Accepts pregnant individuals**

No

**Accepts lactating individuals**

No

**Accepts healthy individuals**

Yes

**Comments about the studied populations**

Inclusion Criteria: - Confirmed HIV-uninfected based on negative HIV-1/HIV-2 test results before randomization. - Sexually active (vaginal and/or anal sex) with a male sexual partner in the 30 days prior to screening. - High risk for HIV-1 infection. - Not pregnant or breastfeeding, and one of the following conditions applies: - Not a woman of childbearing potential (WOCBP) or is a WOCBP and is using an acceptable contraceptive method during the intervention period and for at least 42 days after the last dose. - A WOCBP must have a negative pregnancy test within 24 hours prior to the first dose of study intervention.

**Health status**

Negative to : HIV, HBV

Considered high risk to : HIV

## **Study type**

Interventional (clinical trial)

## **Enrollment**

730

## **Allocation**

Randomized

## **Intervention model**

Parallel Assignment

## **Intervention model description**

Not provided

## **Masking**

Triple-blind masking

## **Masking description**

Triple (Participant, Care Provider, Investigator)

## **Frequency of administration**

Monthly

## **Studied LA-formulation(s)**

Tablet

## **Studied route(s) of administration**

Oral

**Use case**

PrEP

**Key results**

Not provided

# IMPOWER-024

## Identifier

NCT04652700

## Link

<https://clinicaltrials.gov/study/NCT04652700>

## Phase

Phase III

## Status

Completed

## Sponsor

Merck Sharp & Dohme LLC

## More details

Voluntarily terminated due to benefit/risk assessment.

## Purpose

Evaluate the safety and tolerability of oral Islatravir (ISL) once monthly as Preexposure Prophylaxis.

## Interventions

### Intervention 1

Drug: Oral Islatravir

Dosage: ISL 60 mg tablet, QM, orally for up to 24 months

### Intervention 2

Drug: FTC/TDF

Dosage: 200/245 mg of FTC/TDF combination tablet, QD, orally for up to 24 months

### **Intervention 3**

Drug: FTC/TAF

Dosage: 200/25 mg of FTC/TAF combination tablet, QD, orally for up to 24 months

### **Intervention 4**

Drug: Placebo

### **Countries**

United States of America

Brazil

France

Japan

Peru

South Africa

Thailand

### **Sites / Institutions**

Not provided

### **Trials dates**

#### **Anticipated Start Date**

Not provided

#### **Actual Start Date**

2021-03-15

#### **Anticipated Date of Last Follow-up**

Not provided

#### **Estimated Primary Completion Date**

Not provided

**Estimated Completion Date**

Not provided

**Actual Primary Completion Date**

2023-08-04

**Actual Completion Date**

2023-08-04

**Studied populations****Age Cohort**

- Adolescents
- Adults
- Older Adults

**Genders**

- Cisgender male
- Transgender female

**Accepts pregnant individuals**

Unspecified

**Accepts lactating individuals**

Unspecified

**Accepts healthy individuals**

Yes

**Comments about the studied populations**

Cisgender men who have sex with men (MSM) and transgender women (TGW) who have sex with men.

**Health status**

Negative to : HIV, HBV

Considered high risk to : HIV

## **Study type**

Interventional (clinical trial)

## **Enrollment**

494

## **Allocation**

Randomized

## **Intervention model**

Parallel Assignment

## **Intervention model description**

Not provided

## **Masking**

Double-blind masking

## **Masking description**

In Study Part 1, double-blind with in-house blinding is used. In Study Part 2, sponsor personnel not directly involved with blinded safety monitoring will be unblinded to participants' randomized study intervention in Part 1 (personnel involved with Part 2 will remain blinded). In Study Part 3, all participants, investigators, and Sponsor personnel are unblinded as to the participant's original randomized intervention group.

## **Frequency of administration**

Monthly

## **Studied LA-formulation(s)**

Tablet

**Studied route(s) of administration**

Oral

**Use case**

PrEP

**Key results**

Not provided



## **MK-8591-035**

### **Identifier**

NCT05130086

### **Link**

<https://clinicaltrials.gov/study/NCT05130086>

### **Phase**

Phase II

### **Status**

Withdrawn

### **Sponsor**

Merck Sharp & Dohme LLC

### **More details**

Withdrawn due to Business Reasons.

### **Purpose**

Evaluate the safety and tolerability of Islatravir (ISL) in trans and gender diverse participants who are receiving gender-affirming hormone therapy and are at low-risk for HIV-1 infection.

### **Interventions**

#### **Intervention 1**

Drug: Islatravir

Dosage: 60 mg taken orally in tablet form once monthly for up to 24 weeks

## **Countries**

Not provided

## **Sites / Institutions**

Not provided

## **Trials dates**

### **Anticipated Start Date**

2022-10-17

### **Actual Start Date**

Not provided

### **Anticipated Date of Last Follow-up**

2022-10-13

### **Estimated Primary Completion Date**

2024-03-25

### **Estimated Completion Date**

2024-03-25

### **Actual Primary Completion Date**

Not provided

### **Actual Completion Date**

Not provided

## **Studied populations**

### **Age Cohort**

- Adults
- Older Adults

### **Genders**

- Transgender female
- Transgender male
- Intersex
- Gender non-binary

**Accepts pregnant individuals**

No

**Accepts lactating individuals**

No

**Accepts healthy individuals**

Yes

**Comments about the studied populations**

Study participants must identify with a gender that is different from that assigned at birth.

**Health status**

Negative to : HIV

Considered at low risk of : HIV

**Study type**

Interventional (clinical trial)

**Enrollment**

Not provided

**Allocation**

Not provided

**Intervention model**

Single group assignment

## **Intervention model description**

Not provided

## **Masking**

Open label

## **Masking description**

None (Open Label)

## **Frequency of administration**

Monthly

## **Studied LA-formulation(s)**

Tablet

## **Studied route(s) of administration**

Oral

## **Use case**

PrEP

## **Key results**

Not provided

# MK-8591-043

## Identifier

NCT05115838

## Link

<https://clinicaltrials.gov/study/NCT05115838>

## Phase

Phase II

## Status

Withdrawn

## Sponsor

Merck Sharp & Dohme LLC

## More details

Withdrawn for business reasons.

## Purpose

Evaluate the safety, tolerability, and pharmacokinetics (PK) of an islatravir (ISL)-eluting implant

## Interventions

### Intervention 1

Drug: Islatravir (ISL)-eluting implant

Dosage: ISL 47, 52, or 57 mg implantable rod placed subdermally on the upper arm.

### Intervention 2

Drug: Placebo

## **Countries**

Not provided

## **Sites / Institutions**

Not provided

## **Trials dates**

### **Anticipated Start Date**

2024-01-04

### **Actual Start Date**

Not provided

### **Anticipated Date of Last Follow-up**

Not provided

### **Estimated Primary Completion Date**

2025-10-02

### **Estimated Completion Date**

2025-10-02

### **Actual Primary Completion Date**

Not provided

### **Actual Completion Date**

Not provided

## **Studied populations**

### **Age Cohort**

- Adults

## **Genders**

- All

## **Accepts pregnant individuals**

No

## **Accepts lactating individuals**

No

## **Accepts healthy individuals**

Yes

## **Comments about the studied populations**

Inclusion Criteria: - Is in good health. - Is confirmed human immunodeficiency virus (HIV)-uninfected. - Is at low risk of HIV infection. - For males, uses contraception in accordance with local regulations regarding contraception use for those participating in clinical trials. - For females, is not pregnant or breastfeeding and one of the following applies: (i) Is not a participant of childbearing potential (POCBP). (ii) Is a POCPBP and uses an acceptable contraception method or is abstinent.

## **Health status**

Negative to : HIV, HCV, HBV

Considered at low risk of : HIV

## **Study type**

Interventional (clinical trial)

## **Enrollment**

Not provided

## **Allocation**

Randomized

## **Intervention model**

Parallel Assignment

## **Intervention model description**

Not provided

## **Masking**

Triple-blind masking

## **Masking description**

Triple (Participant, Investigator, Outcomes Assessor)

## **Frequency of administration**

Yearly

Other(s) : "Participants receive an ISL 47 mg implant for approximately 52 weeks. A subset of participants will receive a second implant for 12 weeks after removal of the first implant. "

## **Studied LA-formulation(s)**

Implant

## **Studied route(s) of administration**

Subcutaneous

## **Use case**

PrEP

## **Key results**

Not provided



**MK-8591-003**

**Identifier**

NCT02217904

**Link**

<https://clinicaltrials.gov/study/NCT02217904>

**Phase**

Phase I

**Status**

Completed

**Sponsor**

Merck Sharp & Dohme LLC

**More details**

Not provided

**Purpose**

Evaluate the safety, tolerability, pharmacokinetics, and anti-retroviral therapy activity of Islatravir (MK-8591) monotherapy in ART-naive, HIV-1 infected participants.

**Interventions**

**Intervention 1**

Drug: Oral Islatravir

Dosage: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 10 mg, 30 mg.

**Countries**

Not provided

## **Sites / Institutions**

Not provided

## **Trials dates**

### **Anticipated Start Date**

Not provided

### **Actual Start Date**

2015-09-17

### **Anticipated Date of Last Follow-up**

2019-07-24

### **Estimated Primary Completion Date**

Not provided

### **Estimated Completion Date**

Not provided

### **Actual Primary Completion Date**

2017-05-11

### **Actual Completion Date**

2017-05-11

## **Studied populations**

### **Age Cohort**

- Adults

### **Genders**

- All

### **Accepts pregnant individuals**

No

**Accepts lactating individuals**

No

**Accepts healthy individuals**

No

**Comments about the studied populations**

Inclusion Criteria: - Non-pregnant, non-breast feeding, postmenopausal or surgically sterile female. - Female with reproductive potential agrees to use (or have male partner use) two acceptable methods of birth control. - Male agrees to use acceptable method of contraception during study and for 90 days after last dose of trial drug. - Has stable baseline health, other than HIV infection. - Has no significantly abnormal electrocardiogram. - Is HIV-1 positive. - Have a screening plasma HIV-1 RNA  $\geq$  10,000 copies/mL within 30 days prior to the treatment phase of this study. For inclusion in Panel Islatravir Extended Observation, participants must also have a screening plasma HIV-1 RNA  $\leq$  25,000 copies/mL within 30 days prior to the treatment phase. - Is ART naive.

**Health status**

Positive to : HIV

Negative to : HBV

**Study type**

Interventional (clinical trial)

**Enrollment**

30

**Allocation**

Randomized

## **Intervention model**

Parallel Assignment

## **Intervention model description**

Not provided

## **Masking**

Open label

## **Masking description**

None (Open Label)

## **Frequency of administration**

Other(s) : "Single dose "

## **Studied LA-formulation(s)**

Tablet

## **Studied route(s) of administration**

Oral

## **Use case**

Treatment

## **Key results**

**Type of key  
results**

**Title**

**Website link**

---

---

Article

Safety, pharmacokinetics, and antiretroviral activity of islatravir (ISL, MK-8591), a novel nucleoside reverse transcriptase translocation inhibitor, following single-dose administration

[https://doi.org/10.1016/s2352-3018\(19\)30372-8](https://doi.org/10.1016/s2352-3018(19)30372-8)

**MK-8591-007**

**Identifier**

EudraCT: 2018-001329-18

**Link**

<https://www.nature.com/articles/s41591-021-01479-3>

**Phase**

Phase I

**Status**

Completed

**Sponsor**

Merck Sharp & Dohme LLC

**More details**

Not provided

**Purpose**

Safety and pharmacokinetics of islatravir subdermal implant for HIV-1 pre-exposure prophylaxis: a randomized, placebo-controlled phase 1 trial

**Interventions**

**Intervention 1**

Drug: Islatravir subdermal implant

Dosage: 54 mg and 62 mg.

**Intervention 2**

Drug: Placebo subdermal implant

## **Countries**

Belgium

## **Sites / Institutions**

Not provided

## **Trials dates**

### **Anticipated Start Date**

Not provided

### **Actual Start Date**

2018-06-04

### **Anticipated Date of Last Follow-up**

Not provided

### **Estimated Primary Completion Date**

Not provided

### **Estimated Completion Date**

Not provided

### **Actual Primary Completion Date**

2018-07-05

### **Actual Completion Date**

2019-01-25

## **Studied populations**

### **Age Cohort**

- Adults

### **Genders**

All

**Accepts pregnant individuals**

No

**Accepts lactating individuals**

No

**Accepts healthy individuals**

Yes

**Comments about the studied populations**

Not provided

**Health status**

Negative to : HIV

**Study type**

Interventional (clinical trial)

**Enrollment**

16

**Allocation**

Randomized

**Intervention model**

Parallel Assignment

**Intervention model description**

Not provided

**Masking**



Double-blind masking

## Masking description

Not provided

## Frequency of administration

Other(s) : "Study participants received subdermal Islatravir implants or placebo implants for a duration of twelve weeks. "

## Studied LA-formulation(s)

Implant

## Studied route(s) of administration

Subcutaneous

## Use case

PrEP

## Key results

Type of key results	Title	Website link
Article	Safety and pharmacokinetics of islatravir subdermal implant for HIV-1 pre-exposure prophylaxis: a randomized, placebo-controlled phase 1 trial	<a href="https://www.nature.com/articles/s41591-021-01479-3">https://www.nature.com/articles/s41591-021-01479-3</a>

# Excipients

## **Proprietary excipients used**

Not provided

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

Not provided

## **Residual solvents used**

Not provided

## Patent info

# Compound patent families

## Patent informations

Patent description	Representative patent	Categories Patent holder	Licence with MPP	Patent source
Islatravir for the treatment or prophylaxis of HIV (dosing regimen less frequent than once-daily) Expiry date: 2037-02-10	WO2017139519		No	

## Patent status

Patent status/countries	Low, Low- middle and upper-middle	High income
Granted	Türkiye, North Macedonia, Albania, Bosnia and Herzegovina, Montenegro, Serbia, Moldova, Republic of, Morocco, Turkmenistan, Belarus, Tajikistan, Kazakhstan, Azerbaijan, Kyrgyzstan, Armenia, Mexico, South Africa, Georgia, Iran (Islamic Republic of), Ukraine, Malaysia, Botswana, Ghana, Kenya, Namibia, Tunisia, Jordan	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, Japan, Korea, Republic of, United States of America, New Zealand
Filed	China, Dominican Republic, El Salvador, Nicaragua	Lithuania, Korea, Republic of, Singapore, Taiwan, Province of China, Israel, Hong Kong
Not in force	Argentina, China, Philippines, World Intellectual Property Organization (WIPO), Gambia (the), Lesotho, Malawi, Mozambique, Sierra Leone, Liberia, Rwanda, Sao Tome and Principe, Sudan, Eswatini, Tanzania, United Republic of, Uganda, Zambia, Zimbabwe, Brazil	Monaco, San Marino, Chile, Japan, Korea, Republic of, World Intellectual Property Organization (WIPO)

## Patent informations

Patent description	Representative patent	Categories	Patent holder	Licence with MPP	Patent source
Islatravir compound and use for treating HIV Expiry date: 2025-03-24	WO2005090349	Compound		No	

## Patent status

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



## **Supporting material**

## Publications

Derbalah, Abdallaha,b; Karpick, Hayley Christineb,\*; Maize, Hollyb,\*; Skersick, Prestonb,\*; Cottrell, Mackenzieb; Rao, Gauri G.b. Role of islatravir in HIV treatment and prevention: an update. *Current Opinion in HIV and AIDS*: July 2022 - Volume 17 - Issue 4 - p 240-246

doi: <https://doi.org/10.1097/COH.0000000000000740>

## Purpose of review

To summarize recent updates on the potential role of islatravir for HIV treatment and prevention.

## Recent findings

Islatravir is an investigational antiretroviral agent with unique pharmacologic properties that facilitate flexible dosing regimens. Islatravir has demonstrated potent antiviral activity and a high barrier to resistance when combined with doravirine and lamivudine. A simplified two-drug HIV treatment regimen of islatravir combined with doravirine has also demonstrated comparable efficacy to standard of care three-drug regimens. The long half-life and high potency of islatravir's active metabolite may support its use as a long-acting option for HIV preexposure prophylaxis (PrEP). A once monthly oral dose of islatravir maintains effective concentrations of its active metabolite over the entire dosing interval. Furthermore, an investigational implantable formulation has been projected to provide efficacious concentrations for at least a year and exhibits comparable distribution into vaginal and rectal tissues making it a promising PrEP option for male and female individuals. Islatravir has minimal risks of drug interactions as it is not a substrate, inducer, or inhibitor of major drug metabolizers and transporters. Finally, clinical trials demonstrate islatravir's favorable



safety profile revealing only mild and transient adverse events.

## Summary

Leveraging the unique pharmacological properties of islatravir offers opportunities for simplified HIV treatment regimens and long-acting PrEP making it a valuable addition to the antiretroviral arsenal.

Beloor J, Kudalkar SN, Buzzelli G, Yang F, Mandl HK, Rajashekar JK, Spasov KA, Jorgensen WL, Saltzman WM, Anderson KS, Kumar P. Long-acting and extended-release implant and nanoformulations with a synergistic antiretroviral two-drug combination controls HIV-1 infection in a humanized mouse model. *Bioeng Transl Med*. 2021 Jun 26;7(1):e10237. DOI: <https://doi.org/10.1002/btm2.10237>. PMID: 35079625; PMCID: PMC8780078.

The HIV pandemic has affected over 38 million people worldwide with close to 26 million currently accessing antiretroviral therapy (ART). A major challenge in the long-term treatment of HIV-1 infection is nonadherence to ART. Long-acting antiretroviral (LA-ARV) formulations, that reduce dosing frequency to less than once a day, are an urgent need that could tackle the adherence issue. Here, we have developed two LA-ART interventions, one an injectable nanoformulation, and the other, a removable implant, for the delivery of a synergistic two-drug ARV combination comprising a pre-clinical nonnucleoside reverse transcriptase inhibitor (NNRTI), Compound I, and the nucleoside reverse transcriptase inhibitor (NRTI), 4'-ethynyl-2-fluoro-2'-deoxyadenosine. The nanoformulation is poly(lactide-co-glycolide)-based and the implant is a copolymer of  $\omega$ -pentadecalactone and *p*-dioxanone, poly(PDL-co-DO), a novel class of biocompatible, biodegradable materials. Both the interventions, packaged independently with each ARV, released sustained levels of the drugs, maintaining plasma therapeutic indices for over a month, and suppressed viremia in HIV-1-infected humanized mice for up to 42 days with maintenance of CD4+ T cells. These data suggest promise in the use of these new drugs as LA-ART formulations in

subdermal implant and injectable mode.

Huffman, M.A., Fryszkowska, A., Alvizo, O., Borra-Garske, M., Campos, K.R., Canada, K.A., Devine, P.N., Duan, D., Forstater, J.H., Grosser, S.T., Halsey, H.M., Hughes, G.J., Jo, J., Joyce, L.A., Kolev, J.N., Liang, J., Maloney, K.M., Mann, B.F., Marshall, N.M. and McLaughlin, M. (2019). Design of an in vitro biocatalytic cascade for the manufacture of islatravir. *Science*, 366(6470), pp.1255–1259. doi:

<https://doi.org/10.1126/science.aay8484>.

Enzyme-catalyzed reactions have begun to transform pharmaceutical manufacturing, offering levels of selectivity and tunability that can dramatically improve chemical synthesis. Combining enzymatic reactions into multistep biocatalytic cascades brings additional benefits. Cascades avoid the waste generated by purification of intermediates. They also allow reactions to be linked together to overcome an unfavorable equilibrium or avoid the accumulation of unstable or inhibitory intermediates. We report an in vitro biocatalytic cascade synthesis of the investigational HIV treatment islatravir. Five enzymes were engineered through directed evolution to act on non-natural substrates. These were combined with four auxiliary enzymes to construct islatravir from simple building blocks in a three-step biocatalytic cascade. The overall synthesis requires fewer than half the number of steps of the previously reported routes.

McLaughlin M, Kong J, Belyk KM, Chen B, Gibson AW, Keen SP, Lieberman DR, Milczek EM, Moore JC, Murray D, Peng F, Qi J, Reamer RA, Song ZJ, Tan L, Wang L, Williams MJ. Enantioselective Synthesis of 4'-Ethyne-2-fluoro-2'-deoxyadenosine (EFdA) via Enzymatic Desymmetrization. *Org Lett*. 2017 Feb 17;19(4):926-929. doi: <https://doi.org/10.1021/acs.orglett.7b00091>. Epub 2017 Feb 6. PMID: 28165251.

An enantioselective synthesis of the potent anti-HIV nucleoside EFdA is presented. Key features of stereocontrol include construction of the fully substituted 4'-carbon via a biocatalytic desymmetrization of 2-hydroxy-2-((triisopropylsilyl)ethynyl)propane-1,3-diyl diacetate and a Noyori-type asymmetric transfer hydrogenation to control the

stereochemistry of the 3'-hydroxyl bearing carbon. The discovery of a selective crystallization of an N-silyl nucleoside intermediate enabled isolation of the desired  $\beta$ -anomer from the glycosylation step.

Kageyama M, Nagasawa T, Yoshida M, Ohruai H, Kuwahara S. Enantioselective total synthesis of the potent anti-HIV nucleoside EFdA. *Org Lett*. 2011 Oct 7;13(19):5264-6. doi: <https://doi.org/10.1021/ol202116k>. Epub 2011 Sep 2. PMID: 21888325.

A concise enantioselective total synthesis of 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA), an extremely potent anti-HIV agent, has been accomplished from (R)-glyceraldehyde acetonide in 18% overall yield by a 12-step sequence involving a highly diastereoselective ethynylation of an  $\alpha$ -alkoxy ketone intermediate.

Fukuyama K, Ohruai H, Kuwahara S. Synthesis of EFdA via a diastereoselective aldol reaction of a protected 3-keto furanose. *Org Lett*. 2015 Feb 20;17(4):828-31. doi: <https://doi.org/10.1021/ol5036535>. Epub 2015 Feb 2. PMID: 25642994.

An efficient enantioselective total synthesis of EFdA, a remarkably potent anti-HIV nucleoside analogue with various favorable pharmacological profiles, has been achieved in 37% overall yield from diacetone-D-glucose by a 14-step sequence that features a highly diastereoselective installation of the tetrasubstituted stereogenic center at the C4' position, direct oxidative cleavage of an acetonide-protected diol derivative to an aldehyde, and one-pot 2'-deoxygenation of a ribonucleoside intermediate.

Kageyama M, Miyagi T, Yoshida M, Nagasawa T, Ohruai H, Kuwahara S. Concise synthesis of the anti-HIV nucleoside EFdA. *Biosci Biotechnol Biochem*. 2012;76(6):1219-25. doi: <https://doi.org/10.1271/bbb.120134>. Epub 2012 Jun 7. PMID: 22790950.

EFdA (4'-ethynyl-2-fluoro-2'-deoxyadenosine), a nucleoside reverse transcriptase

inhibitor with extremely potent anti-HIV activity, was concisely synthesized from (R)-glyceraldehyde acetonide in an 18% overall yield by a 12-step sequence involving highly diastereoselective ethynylation of an  $\alpha$ -alkoxy ketone intermediate. The present synthesis is superior, both in overall yield and in the number of steps, to the previous one which required 18 steps from an expensive starting material and resulted in a modest overall yield of 2.5%.

Kinvig, H., Cottura, N., Lloyd, A. *et al.* Evaluating Islatravir Administered Via Microneedle Array Patch for Long-Acting HIV Pre-exposure Prophylaxis Using Physiologically Based Pharmacokinetic Modelling. *Eur J Drug Metab Pharmacokinet* 47, 855–868 (2022). <https://doi.org/10.1007/s13318-022-00793-6>

Technologies for long-acting administration of antiretrovirals (ARVs) for the prevention and treatment of HIV are at the forefront of research initiatives aiming to tackle issues surrounding drug adherence with the current standard of once-daily oral administration. Islatravir (ISL) is an emerging ARV that shows promising characteristics for long-acting prevention and treatment both orally as well as through alternative routes of administration. Microneedle array patches (MAPs) are a pain-free and discreet transdermal delivery technology that offer extended-release administration of nanoparticulate drugs. This study aimed to utilise physiologically based pharmacokinetic (PBPK) modelling to predict the pharmacokinetics resulting from ISL administered via MAP and to identify key MAP characteristics required to sustain effective concentrations over extended dosing intervals.

## Additional documents

No documents were uploaded

## Useful links

- [Merck Announces Clinical Holds on Studies Evaluating ISL for the Treatment and Prevention of HIV-1](#)
- [Merck to Initiate New Phase 3 Clinical Program with Lower Dose of Daily Oral Islatravir](#)
- [Merck restarts islatravir HIV treatment studies, but abandons monthly PrEP](#)
- [Merck Announces Topline Results from Pivotal Phase 3 Trials Evaluating Doravirine/Islatravir](#)

# 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