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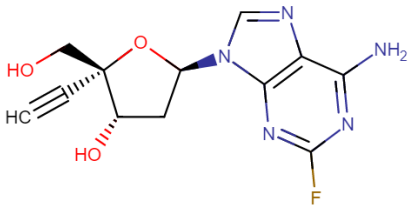


Islatravir (ISL)

Developer(s)

Merck & Co., Inc.

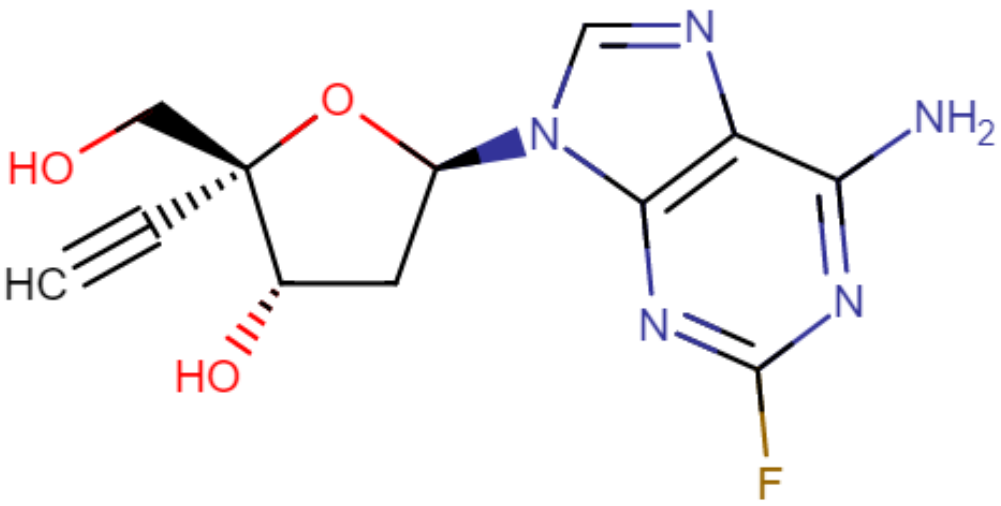
Originator

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)

Treatment

Use of drug

Ease of administration

Administered by a nurse
Administered by a specialty health worker
Self-administered

User acceptance

Not provided

Dosage

Available dose and strength

investigational

Frequency of administration

Not provided

Maximum dose

Not provided

Recommended dosing regimen

Not provided

Additional comments

Not provided

Dosage link(s)

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 (NRTTI) 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 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. Aglient 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 resources

Type	Title	Content	Link
Link	Safety and pharmacokinetics of oral islatravir once monthly for HIV pre-exposure prophylaxis (PrEP): week 24 analysis of a phase 2a trial		https://theprogramme.ias20

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 disproxil 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 resources

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, al 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 resources

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 resources

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 POCBP and uses an acceptable contraception method or is abstinent.

Health status

Negative to : HIV, HBV, HCV
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

Other : "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. "
Yearly

Studied LA-formulation(s)

Implant

Studied route(s) of administration

Subcutaneous

Use case

PrEP

Key resources

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 ≥ 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 ≤ 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 : "Single dose "

Studied LA-formulation(s)

Tablet

Studied route(s) of administration

Oral

Use case

Treatment

Key resources

Type	Title	Content	Link

Link	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/s235 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 : "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 resources

Type	Title	Content	Link
Link	Safety and pharmacokinetics of islatravir subdermal implant for HIV-1 pre-exposure prophylaxis: a randomized, placebo-controlled phase 1 trial		https://www.nature.com/arti 021-01479-3

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	Use		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, Dominican Republic, Belarus, Kazakhstan, Azerbaijan, 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, El Salvador, Nicaragua	Lithuania, Korea, Republic of, Singapore, Taiwan, Province of China, Israel, Hong Kong
Not in force	Argentina, China, Turkmenistan, Tajikistan, Kyrgyzstan, 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		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), Mexico	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 ω-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'-Ethynyl-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 β-anomer from the glycosylation step.

Kageyama M, Nagasawa T, Yoshida M, Ohrui 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 α-alkoxy ketone intermediate.

Fukuyama K, Ohrui 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, Ohrui 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 α-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
- Safety and pharmacokinetics of oral islatravir once monthly for HIV pre-exposure prophylaxis (PrEP): week 24 analysis of a phase 2a trial
- Safety, pharmacokinetics, and antiretroviral activity of islatravir (ISL, MK-8591), a novel nucleoside reverse transcriptase translocation inhibitor, following single-dose administration
- Safety and pharmacokinetics of islatravir subdermal implant for HIV-1 pre-exposure prophylaxis: a randomized, placebo-controlled phase 1 trial

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