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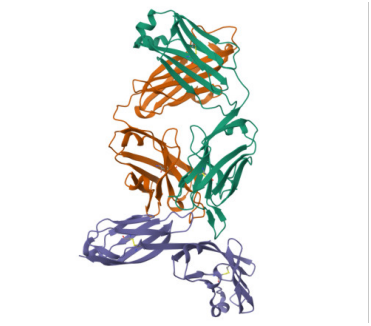


Ibalizumab

Developer(s)

Theratechnologies Inc.

Originator

https://www.theratech.com/

Canada

Ibalizumab was initially developed by Biogen. In the late 1990s, Tanox acquired the exclusive global rights. Subsequently, Genentech acquired Tanox inheriting the ibalizumab license and later partnering with TaiMed Biologics. In 2012, TaiMed contracted WuXi PharmaTech to manufacture ibalizumab. Finally, in 2016, TaiMed established a collaboration with Theratechnologies for commercialization.

TaiMed Biologics Inc.

Originator

https://www.taimedbiologics.com/

Taiwan

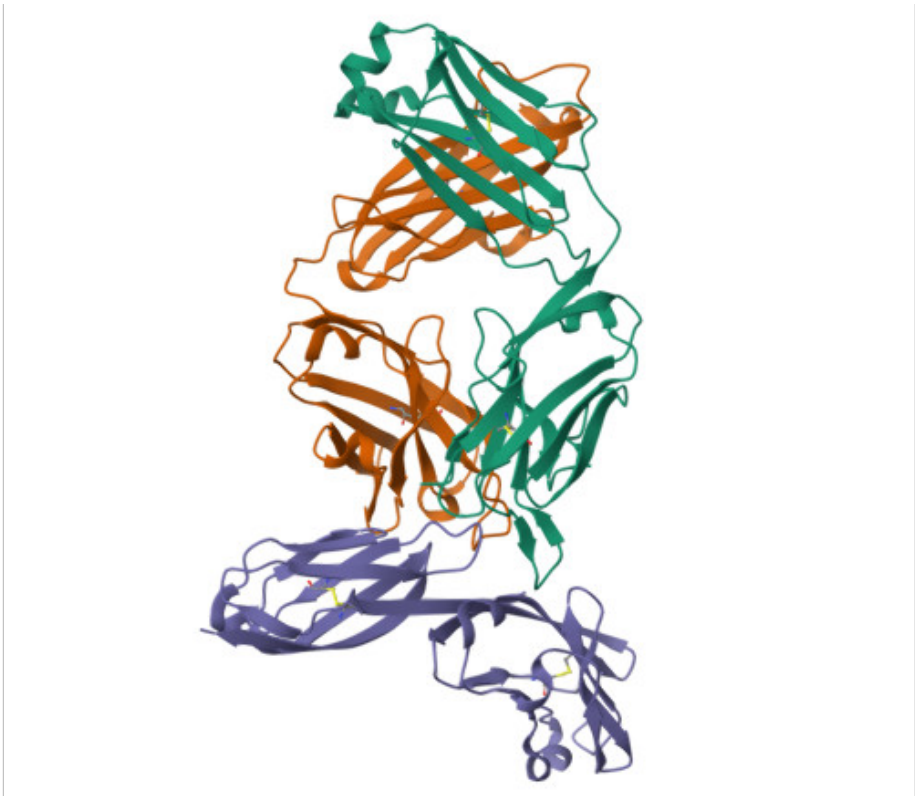
TaiMed Biologics is a highly specialized biopharmaceutical company headquartered in Taiwan that focuses on the development and commercialization of HIV therapeutics. TaiMed was originally founded in Sep 2007 after securing an exclusive license agreement with Genentech for the anti-cd4 antibody Ibalizumab (TMB-355). In March 2018, TMB-355 was approved by the U.S FDA under the brand name Trogarzo®.

Theratechnologies/TaiMed Biologics

Originator

https://www.taimedbiologics.com/

Drug structure



Crystal structure of HIV-1 primary receptor CD4 in complex with Ibalizumab

https://doi.org/10.2210/pdb3O2D/pdb

Drug information

Associated long-acting platforms

Recombinant humanized monoclonal antibody

Administration route

Subcutaneous, Intramuscular, Intravenous

Therapeutic area(s)

HIV

Use case(s)

Treatment

Use of drug

Ease of administration

Administered by a nurse
Administered by a specialty health worker

User acceptance

Not provided

Dosage

Available dose and strength

Not provided

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/DB12698

Generic name

Ibalizumab

Brand name

Trogarzo

Compound type

Biotherapeutic

Summary

Ibalizumab (ibalizumab-uiyk; TMB-355; TNX-355) is a first-in-class humanised IgG4 monoclonal antibody indicated for use in heavily treatment experienced individuals with multidrug-resistant HIV-1 infection. Ibalizumab functions as a post-attachment inhibitor, specifically disrupting HIV-1 viral entry into CD4 cells through targeting of the gp120-CD4 complex. It binds to an epitope within domain 2 of the CD4 receptor, preventing the conformational changes necessary for co-receptor binding and subsequent fusion. Notably, Ibalizumab's binding site is distinct from both the gp120 and MHC-II binding regions, ensuring that it does not disrupt MHC-II mediated immune function. Additionally, Ibalizumab also acts to directly inhibit HIV-1 induced syncytium formation, further limiting viral spread.

Approval status

Ibalizumab-uiyk (TROGARZO) 300mg/2mL (delivers 1.33ml) intravenous injection was approved for the treatment of heavily treated, multi-drug resistant HIV-1 infection in combination with other antiretroviral therapies. TROGARZO is currently approved only

in the United States of America. Ibalizumab-uiyk (TROGARZO) was initially approved in the European Union, but later it was withdrawn from the EU market by the Marketing Authorization Holder for commercial reasons.

Regulatory authorities

Ibalizumab-uiyk (TROGARZO) 300 mg/2 mL vial has received the Orphan Drug designation from the US FDA.

Delivery device(s)

No delivery device

Scale-up and manufacturing prospects

Scale-up prospects

Ibalizumab is a humanised IgG4, κ monoclonal antibody produced in a NS0 cell line. The successful scale-up of therapeutic monoclonal antibody (mAb) products involves achieving favourable pharmacokinetic profiles, maintaining formulation stability and ensuring consistency of the overall product quality. However, industrial bioprocessing steps can potentially introduce additional complexities regarding mAb solution viscosity and aggregation propensity.

Tentative equipment list for manufacturing

Industrial bioreactor vessel with a production volume capacity of between 5-25kL. Continuous disc stack centrifuges for bioreactor harvesting with subsequent membrane and depth filtration for supernatant clarification. Recombinant protein-A chromatography or other suitable affinity capture apparatus followed by two chromatographic polishing steps such as cation- and anion-exchange. Ultrafiltration membrane system to concentrate and formulate the final product.

Manufacturing

Store in a refrigerator at 2˚C to 8˚C (36˚F to 46˚F). Protect from light until use. Do not freeze. Ibalizumab is supplied in a single 2 mL (200mg/1.33 mL) glass vial with a rubber stopper and aluminum flip-off seal. MAbs are highly dependent on their structural, chemical and conformational stability for biological activity. Chemical degradation of mAbs during manufacture can lead to the generation of product variants and complex impurity profiles. Additionally prior to packaging, the final product requires close monitoring for the presence of residual contaminants such as endotoxins.

Specific analytical instrument required for characterization of formulation

Formulation characterisation steps for therapeutic mAb products include (but are not limited to): (1) Identification of post-translational modifications using ion-exchange chromatography and capillary isoelectric focusing. (2) Measurement of concentration dependent aggregation rates via thermal differential scanning calorimetry, sub-visible particle quantitation and size-exclusion chromatography. (3) Antibody clipping and

fragmentation detection by capillary electrophoresis.

Clinical trials

TMB-202

Identifier

NCT00784147

Link

https://clinicaltrials.gov/study/NCT00784147

Phase

Phase II

Status

Completed

Sponsor

TaiMed Biologics Inc.

More details

The investigational product, ibalizumab, is a humanized IgG4 monoclonal antibody administered via intravenous infusion at 800 mg every 2 weeks or at 2000 mg every 4 weeks. In addition to study drug, all patients will receive an optimized background regimen (OBR), which is a standard-of-care regimen selected by the investigator prior to randomization that is comprised of 2-4 antiretroviral agents. These agents must have been approved by the local regulatory agency or be available through expanded-access programs for treatment of human immunodeficiency virus (HIV).

Purpose

Dose-Response Study of Ibalizumab (Monoclonal Antibody) Plus Optimized Background Regimen in Patients With HIV-1

Interventions

Intervention 1

Ibalizumab

Intervention 2

Ibalizumab

Countries

Puerto Rico

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2008-08-01

Anticipated Date of Last Follow-up

2014-04-17

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2011-04-01

Actual Completion Date

2011-04-01

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

Inclusion Criteria: 1. Are capable of understanding and have voluntarily signed the informed consent document 2. Have documented HIV-1 infection by official, signed, written history (eg, laboratory report), otherwise an HIV-antibody test will be performed 3. Have no acquired immunodeficiency syndrome (AIDS)-defining events in the 3 months before screening, other than cutaneous Kaposi's sarcoma or wasting syndrome due to HIV 4. Are able and willing to comply with all protocol requirements and procedures 5. Are 18 years of age or older 6. Have a life expectancy that is \>6 months. 7. Have a viral load \>1,000 copies/mL and documented decreased susceptibility to at least one NRTI, one NNRTI, and one PI, as measured by resistance testing 8. Are receiving a stable highly active antiretroviral

Health status

Positive to : HIV

Study type

Interventional (clinical trial)

Enrollment

113

Allocation

Randomized

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Quadruple-blind masking

Masking description

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

Frequency of administration

Other : "Once every 2 weeks (800 mg) or Once every 4 weeks (2000 mg) "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Intravenous

Use case

Treatment

Key resources

Not provided

TMB-302

Identifier

NCT03913195

Link

https://clinicaltrials.gov/study/NCT03913195

Phase

Phase III

Status

Completed

Sponsor

TaiMed Biologics Inc.

More details

This study is designed to assess the safety and pharmacokinetic profile of 800 mg Trogarzo once every two weeks administered via "IV Push" or intramuscular injection. An initial "Sentinel Group" of 5 participants will begin receiving 800mg Trogarzo on a gradual schedule of increasing concentration and decreasing administration time until undiluted IV Push over 30 seconds is achieved, while safety and pharmacokinetics are evaluated. If no safety signals are seen, the Core Group of 15 participants will be enrolled. The Core Group will receive 800mg Trogarzo via undiluted IV Push over 30 seconds while safety and pharmacokinetics are monitored. After completion of the IV Push portion of the study, a second group of 20 participants will be enrolled to evaluate the safety and pharmacokinetics of

Purpose

Study of the Safety of Trogarzo™ Administered as an Undiluted "IV Push" or an Intramuscular Injection

Interventions

Intervention 1

ibalizumab-uiyk

Countries

Not provided

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2019-05-30

Anticipated Date of Last Follow-up

2023-09-14

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2022-10-17

Actual Completion Date

2022-10-31

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 - HIV-infected participants (all groups): 1. Are capable of understanding and have voluntarily signed the informed consent document 2. Currently receiving a stable Trogarzo-containing ARV regimen for a minimum of 3 months, and no change in background ARVs anticipated over the period of study participation; a stable regimen is defined as having no changes in dose or frequency and no interruptions greater than or equal to 2 weeks during the 3 month period 3. Have no acquired immunodeficiency syndrome (AIDS)-defining events in the 3 months before Screening, other than cutaneous Kaposi's sarcoma or wasting syndrome due to HIV 4. Are able and willing to comply with all protocol requirements and procedures 5. Are 18 years of age or older 6. Have a life expectancy that is \>6

Health status

Not provided

Study type

Interventional (clinical trial)

Enrollment

46

Allocation

Not provided

Intervention model

Sequential assignment

Intervention model description

Not provided

Masking

Open label

Masking description

None (Open label)

Frequency of administration

Other : "Once every two weeks "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Intravenous
Intramuscular

Use case

Treatment

Key resources

Not provided

TMB-311

Identifier

NCT02707861

Link

https://clinicaltrials.gov/study/NCT02707861

Phase

Phase III

Status

Completed

Sponsor

TaiMed Biologics Inc.

More details

Ibalizumab is a monoclonal antibody that works by blocking HIV entry into the immune system cells (CD4+ or T-cells) the virus typically infects. Ibalizumab is intended for use in combination with other anti-HIV drugs in people with multi-drug resistant HIV and limited treatment options. This study will collect further information on the safety and tolerability of intravenously administered (IV) ibalizumab combined with an optimized background regimen for treating multi-drug resistant HIV-1 infection, and will provide continuing access to ibalizumab for patients completing a prior ibalizumab clinical trial.

Purpose

Ibalizumab Plus Optimized Background Regimen in Treatment-Experienced Patients With Multi-Drug Resistant HIV-1

Interventions

Intervention 1

ibalizumab

Intervention 2

Optimized Background Regimen

Countries

Puerto Rico

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2016-03-01

Anticipated Date of Last Follow-up

2021-02-18

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2018-11-01

Actual Completion Date

2018-11-01

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

Inclusion Criteria: (Cohort 1) * Currently receiving ibalizumab via other TaiMed-sponsored or investigator-Sponsored protocol * Are capable of understanding and have voluntarily signed the informed consent document (Cohort 2) * 18 years of age or older * Are capable of understanding and have voluntarily signed the informed consent document * Have documented HIV-1 infection by official, signed, written history (e.g., laboratory report), otherwise an HIV-antibody test will be performed * Are able and willing to comply with all protocol requirements and procedures * Have a viral load \>1,000 copies/mL and documented resistance to at least one antiretroviral medication from each of three classes of antiretroviral medications as measured by previous viral resistance testing (resistance test

Health status

Positive to : HIV

Study type

Interventional (clinical trial)

Enrollment

79

Allocation

Not provided

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Open label

Masking description

None (Open label)

Frequency of administration

Other : "Once every 2 weeks (800 mg) or Once every 4 weeks (2000 mg) "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Intravenous

Use case

Treatment

Key resources

Not provided

TMB-108

Identifier

NCT01292174

Link

https://clinicaltrials.gov/study/NCT01292174

Phase

Phase I

Status

Completed

Sponsor

TaiMed Biologics Inc.

More details

The is a blinded safety study of ibalizumab given by subcutaneous injection in sequentially increasing dose-groups of at-risk, HIV-negative, healthy volunteers. The study involves the administration of four total injections of ibalizumab or matching placebo in each volunteer, given once every week, at one of three dose levels. Drug administration begins at the lowest dose. After 4 of 8 volunteers in the first group have received all study drug injections and have completed 6 additional weeks of follow-up, an independent safety monitoring group will review available data before approving initiation of the next higher dose-group. This process will be repeated prior to initiation of the 3rd and highest dose-group. All volunteers will participate in 2 separate intensive blood sampling periods

Purpose

Safety Study of Ibalizumab Subcutaneous Injection in Healthy Volunteers

Interventions

Intervention 1

ibalizumab (biologic/MAb) for SC Injection or placebo

Intervention 2

ibalizumab (biologic/MAb) for SC Injection or placebo

Intervention 3

ibalizumab (biologic/MAb) for SC Injection or placebo

Countries

United States of America

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2011-02-01

Anticipated Date of Last Follow-up

2012-12-17

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2012-09-01

Actual Completion Date

2012-09-01

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: 1. At-risk adult males and females, as assessed by a medical history, physical exam, and laboratory tests 2. At least 18 years of age and no greater than 40 years on the day of screening 3. Willing to comply with the requirements of the protocol and available for follow-up for the planned duration of the study 4. In the opinion of the principal investigator or designee, has understood the information provided; written informed consent needs to be given before any study-related procedures are performed 5. Willing to undergo HIV Testing and counseling, and receive HIV test results 6. Agrees to use a barrier form of contraception if engaging in sexual activity at any time throughout the study and the follow-up period (males and females) - two reliable forms of contracepti

Health status

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

Study type

Interventional (clinical trial)

Enrollment

25

Allocation

Randomized

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Quadruple-blind masking

Masking description

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

Frequency of administration

Weekly

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Subcutaneous

Use case

PrEP

Key resources

Not provided

TMB-301

Identifier

NCT02475629

Link

https://clinicaltrials.gov/study/NCT02475629

Phase

Phase III

Status

Completed

Sponsor

TaiMed Biologics Inc.

More details

This Phase 3, single arm, multicenter study will evaluate the safety and effectiveness of ibalizumab in treatment-experienced patients infected with multi-drug resistant HIV-1.

Purpose

Ibalizumab Plus Optimized Background Regimen in Patient With Multi-Drug Resistant HIV

Interventions

Intervention 1

ibalizumab

Intervention 2

Optimized Background Regimen (OBR)

Countries

Puerto Rico

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2015-08-01

Anticipated Date of Last Follow-up

2020-03-10

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2016-10-01

Actual Completion Date

2016-12-01

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

Inclusion Criteria: * Are capable of understanding and have voluntarily signed the informed consent document * Have documented HIV-1 infection by official, signed, written history (e.g., laboratory report), otherwise an HIV-antibody test will be performed * Have no acquired immunodeficiency syndrome (AIDS)-defining events in the 3 months before Screening, other than cutaneous Kaposi's sarcoma or wasting syndrome due to HIV * Are able and willing to comply with all protocol requirements and procedures * Have a life expectancy that is \>6 months. * Have a viral load \>1,000 copies/mL and documented resistance to at least one antiretroviral medication from each of three classes of antiretroviral medications as measured by resistance testing * Have a history of at least 6 months on antiretrov

Health status

Positive to : HIV

Study type

Interventional (clinical trial)

Enrollment

40

Allocation

Not provided

Intervention model

Single group assignment

Intervention model description

Not provided

Masking

Open label

Masking description

None (Open label)

Frequency of administration

Other : "Once every two weeks "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Intravenous

Use case

Treatment

Key resources

Not provided

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

Description

Use of ibalizumab for the treatment of HIV-2 infection

Brief description

There are major differences in the susceptibility of human immunodeficiency virus type 1 (HIV-1) and human immunodeficiency virus type 2 (HIV-2) to currently available drugs, and novel approaches for the treatment of HIV-2 are needed. The present application relates to a method for treating infection by several HIV-2 strains/isolates, including multidrug resistant (MDR) HIV-2 strains, comprising administering to a subject in need thereof an effective amount of ibalizumab, or of an antibody or antigen-binding fragment thereof that binds the same antigenic epitope, or an overlapping epitope, as ibalizumab.

Representative patent

WO21062546

Category

Use

Patent holder

Taimed biologics inc.

Exclusivity

Not provided

Expiration date

October 1, 2040

Status

Not provided

Description

Ibalizumab and homologues (anti-CD4 antibodies blocking HIV-induced syncytia)

Brief description

Anti-CD4 antibody homologs, DNA sequences and recombinant DNA molecules encoding them, prophylactic, immunotherapeutic and diagnostic compositions comprising those antibody homologs, and methods for preventing or treating diseases in mammals, including humans, caused by infective agents whose primary targets are CD4+ lymphocytes. Such diseases include acquired immune deficiency syndrome ('AIDS'), AIDS related complex, and human immunodeficiency virus infection.

Representative patent

WO1992009305

Category

Compound patent broad claims and CDR

Patent holder

Biogen

Exclusivity

Not provided

Expiration date

November 27, 2011

Status

Expired

Supporting material

Publications

Chahine EB, Durham SH. Ibalizumab: The First Monoclonal Antibody for the Treatment of HIV-1 Infection. Annals of Pharmacotherapy. 2021;55(2):230-239. DOI: 10.1177/1060028020942218

Objective:

To review the efficacy and safety of ibalizumab (IBA) in the treatment of HIV-1 infection.

Data Sources:

A literature search was performed using PubMed and Google Scholar (2010 to mid-June 2020) with the search terms *TMB-355, TNX-355*, and *ibalizumab*. Other resources included abstracts presented at recent conferences and the manufacturer's website and prescribing information.

Study Selection and Data Extraction:

All relevant English-language articles of studies assessing the efficacy and safety of IBA were included.

Data Synthesis:

IBA is a monoclonal antibody that blocks HIV-1 from infecting CD4+ T cells. IBA is approved by the Food and Drug Administration, in combination with other antiretrovirals (ARVs), for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug-resistant (MDR) HIV-1 infection failing their current ARVs. IBA demonstrated significant and sustained antiviral activity in patients with MDR HIV-1 infection who had advanced disease and limited treatment options. It carries a warning regarding the development of immune reconstitution inflammatory

syndrome. Common adverse reactions include diarrhea, dizziness, nausea, and rash.

Relevance to Patient Care and Clinical Practice:

IBA represents an attractive option for treatment-experienced adults with advanced HIV-1 infection who are no longer able to achieve viral suppression on oral ARV therapy alone and who are able to adhere to an infusion therapy every 2 weeks. As with other biologics, there is a potential for the development of antibodies to IBA that can compromise its efficacy and safety.

Conclusion:

IBA provides a needed treatment option to achieve and maintain viral suppression in heavily treatment-experienced adults with MDR HIV-1 infection.

Bettiker, Robert L.a; Koren, David E.d; Jacobson, Jeffrey M.a,b,c. Ibalizumab. Current Opinion in HIV and AIDS 13(4):p 354-358, July 2018. DOI: 10.1097/COH.0000000000000473

Purpose of review

Antiretroviral options for patients infected with multiclass resistant HIV-1 warrant the development of new agents with unique mechanisms of action and modes of delivery. Here we review one such agent, ibalizumab, a parenteral CD4 postattachment inhibitor that has demonstrated efficacy as part of combination antiretroviral therapy in the treatment of HIV-1.

Recent findings

In a phase III clinical trial in HIV-infected participants with multiclass antiretroviral drug resistance, the intravenous administration of ibalizumab led to declines in plasma HIV-1 RNA more than 0.5 log in 83% of participants at 1 week. An optimized background

antiretroviral regimen was then added, and plasma HIV-1 RNA became less than 50 copies/ml in 43% of participants at 24 weeks. Adverse effects of ibalizumab were uncommon and generally low grade. Ibalizumab was approved by the US Food and Drug Administration on March 16, 2018, under the trade name Trogarzo.

Summary

Ibalizumab has demonstrated both safety and efficacy in the treatment of HIV-1 infection. Its primary use will be in the setting of multidrug resistant virus as part of combination antiretroviral therapy. Further enhancements of ibalizumab to prolong its clearance and broaden its activity are in development.

Additional documents

No documents were uploaded

Useful links

- FDA PRODUCT QUALITY REVIEW(S) - IBALIZUMAB
- FDA PRODUCT SUMMARY REVIEW - IBALIZUMAB

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