LAPaL
THE LONG-ACTING THERAPEUTICS PATENTS AND LICENCES DATABASE

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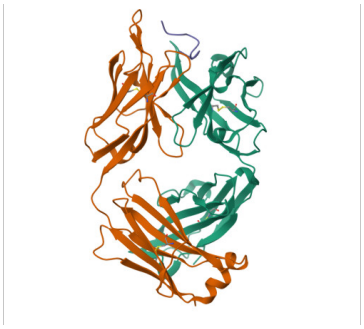


CIS43LS

Developer(s)

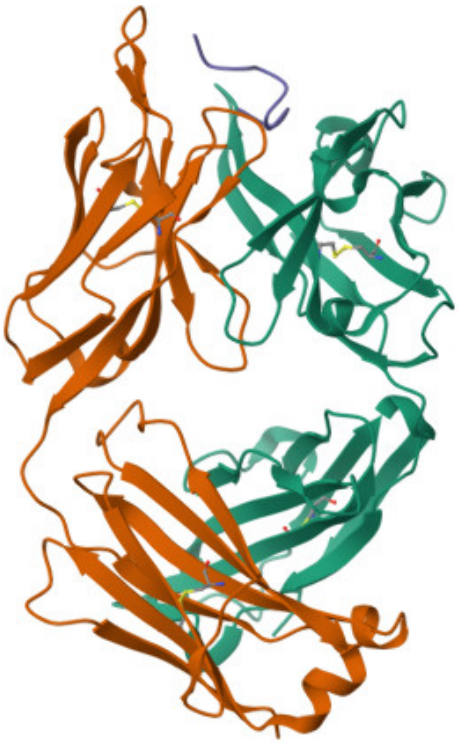
Leidos Biomedical Research

https://www.leidos.com/

United States

Leidos Biomedical Research, Inc. is a research company that operates the Frederick National Laboratory for Cancer Research on behalf of the National Cancer Institute. Based in Frederick, Maryland, the laboratory develops technological solutions for HIV/AIDs, emerging infectious diseases and oncology, in addition to providing scientific support to several national institutes including the NIAID.

Drug structure



Crystal Structure of CIS43 with PfCSP Peptide 20

https://doi.org/10.2210/pdb6B5L/pdb

Drug information

Associated long-acting platforms

Monoclonal Antibody

Administration route

Subcutaneous, Intravenous

Therapeutic area(s)

Malaria

Use case(s)

Pre-Exposure Prophylaxis (PrEP)

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)

Not provided

Generic name

CIS43LS

Brand name

Not provided

Compound type

Biotherapeutic

Summary

CIS43LS (VRC-MALMAB0100-00-AB) is a long-acting human IgG1 monoclonal antibody in clinical development for the prevention of P. falciparum malaria. The Fc region of CIS43LS contains two site-directed mutagenesis substitutions at amino acid residues N457S and M451L (termed “LS”) to extend its efficacy and half-life. CIS43 was originally isolated from a clinical trial participant inoculated with an attenuated P. falciparum whole-sporozoite vaccine, and functions by targeting the highly conserved junctional NPDP epitope of the P. falciparum circumsporozoite protein essential for hepatocyte infection and parasite motility. Recent studies have shown that a single dose of CIS43LS provides high levels of malarial prophylaxis for 8 weeks, and may offer additional protection for up to 6 months.

Approval status

Unknown

Regulatory authorities

Unknown

Delivery device(s)

No delivery device

Scale-up and manufacturing prospects

Scale-up prospects

Manufacturing requirements and production scale-up for therapeutic monoclonal antibodies (mAbs) is primarily focused on pharmacokinetic suitability, formulation stability and overall maintenance of product quality. In addition, industrial bioprocessing steps can introduce further challenges regarding mAb formulation 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

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 resulting from a wide range of processes, including: N-linked glycosylation, isomerisation, fragmentation, deamidation, oxidation and C-terminal lysine clipping. Additionally prior to packaging, the final product requires close monitoring for the presence of residual contaminants such as endotoxins and pro-inflammatory peptidoglycans.

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, and (3) Antibody clipping and fragmentation detection by capillary electrophoresis.

Clinical trials

VRC 612

Identifier

NCT04206332

Link

https://www.clinicaltrials.gov/study/NCT04206332

Phase

Phase I

Status

Completed

Sponsor

National Institute of Allergy and Infectious Diseases (NIAID)

More details

Not provided

Purpose

Evaluate the protective efficacy, tolerability, safety and dose of the anti-malarial human monoclonal antibody CIS43LS (VRC-MALMAB0100-00-AB).

Interventions

Intervention 1

Drug: VRC-MALMAB0100-00-AB

Intervention 2

Other: Plasmodium falciparum (P. falciparum) sporozoite challenge

Countries

United States of America

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2020-01-07

Anticipated Date of Last Follow-up

Not provided

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2022-02-28

Actual Completion Date

2022-02-28

Studied populations

Age Cohort

- Adults

Genders

- All

Accepts pregnant individuals

No

Accepts lactating individuals

No

Accepts healthy individuals

Yes

Comments about the studied populations

Study participants aged between 18 to 50 years and in good general health without clinically significant medical history. Exclusion criteria includes previous receipt of a malaria vaccine.

Health status

Negative to : Malaria, COVID 19, HIV

Study type

Interventional (clinical trial)

Enrollment

71

Allocation

Non-randomized

Intervention model

Sequential 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)

Injectable

Studied route(s) of administration

Subcutaneous
Intravenous

Use case

PrEP

Key results

Type of key results	Title	Website link
Article	A Monoclonal Antibody for Malaria Prevention	https://doi.org/10.1056/nejmoa2034031

Type of key results	Title	Website link
Article	Low-dose intravenous and subcutaneous CIS43LS monoclonal antibody for protection against malaria (VRC 612 Part C): a phase 1, adaptive trial	https://doi.org/10.1016/s1473-3099(22)00793-9

2020/32/CE/FMOS/FAPH

Identifier

NCT04329104

Link

https://www.clinicaltrials.gov/study/NCT04329104

Phase

Phase II

Status

Completed

Sponsor

National Institute of Allergy and Infectious Diseases (NIAID)

More details

Not provided

Purpose

Evaluate the safety, tolerability, and efficacy of VRC MALMAB0100-00-AB (CIS43LS), a human monoclonal antibody, against naturally occurring Plasmodium falciparum (Pf) infection.

Interventions

Intervention 1

Biological: VRC-MALMAB0100-00-AB (CIS43LS)

Intervention 2

Other: Normal saline

Countries

Mali

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2021-02-15

Anticipated Date of Last Follow-up

Not provided

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2022-01-26

Actual Completion Date

2023-07-05

Studied populations

Age Cohort

- Adults

Genders

All

Accepts pregnant individuals

No

Accepts lactating individuals

No

Accepts healthy individuals

Yes

Comments about the studied populations

Participants aged ≥18 and ≤55 years and in good general health and without clinically significant medical history.

Health status

Negative to : HIV, HCV, HBV

Study type

Interventional (clinical trial)

Enrollment

348

Allocation

Randomized

Intervention model

Sequential assignment

Intervention model description

Not provided

Masking

Double-blind masking

Masking description

Double (Participant, Investigator)

Frequency of administration

Other(s) : "Single dose "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Intravenous

Use case

PrEP

Key results

Type of key results	Title	Website link
Article	Safety and Efficacy of a Monoclonal Antibody against Malaria in Mali	https://doi.org/10.1056/nejmoa2206966

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

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

Supporting material

Publications

Kisalu NK, Pereira LD, Ernste K, Flores-Garcia Y, Idris AH, Asokan M, Dillon M, MacDonald S, Shi W, Chen X, Pegu A, Schön A, Zavala F, Balazs AB, Francica JR, Seder RA. Enhancing durability of CIS43 monoclonal antibody by Fc mutation or AAV delivery for malaria prevention. JCI Insight. 2021 Feb 8;6(3):e143958. DOI: 10.1172/jci.insight.143958. PMID: 33332286; PMCID: PMC7934869.

CIS43 is a potent neutralizing human mAb that targets a highly conserved “junctional” epitope in the *Plasmodium falciparum* (Pf) circumsporozoite protein (PfCSP). Enhancing the durability of CIS43 in vivo will be important for clinical translation. Here, 2 approaches were used to improve the durability of CIS43 in vivo while maintaining potent neutralization. First, the Fc domain was modified with the LS mutations (CIS43LS) to increase CIS43 binding affinity for the neonatal Fc receptor (FcRn). CIS43LS and CIS43 showed comparable in vivo protective efficacy. CIS43LS had 9- to 13-fold increased binding affinity for human (6.2 nM versus 54.2 nM) and rhesus (25.1 nM versus 325.8 nM) FcRn at endosomal pH 6.0 compared with CIS43. Importantly, the half-life of CIS43LS in rhesus macaques increased from 22 days to 39 days compared with CIS43. The second approach for sustaining antibody levels of CIS43 in vivo is through adeno-associated virus (AAV) expression. Mice administered once with AAV-expressing CIS43 had sustained antibody levels of approximately 300 μg/mL and mediated protection against sequential malaria challenges up to 36 weeks. Based on these data, CIS43LS has advanced to phase I clinical trials, and AAV delivery provides a potential next-generation approach for malaria prevention.

Additional documents

No documents were uploaded

Useful links

There are no additional links

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