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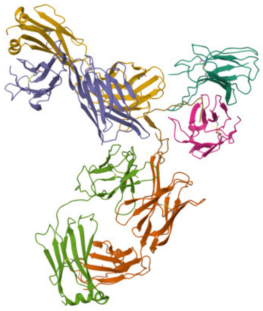


L9LS

Developer(s)

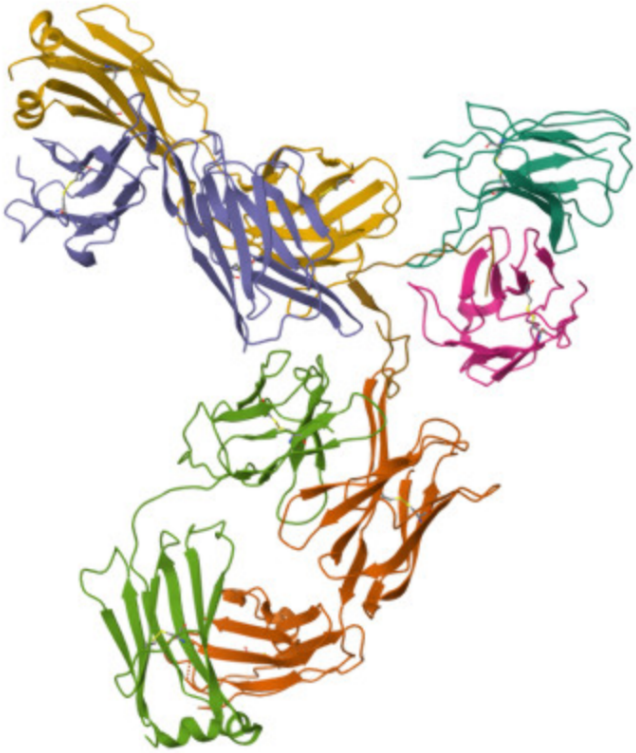
Leidos Biomedical Research

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 L9 with PfCSP (dominant class)

https://doi.org/10.2210/pdb8EK1/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

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)

Not provided

Generic name

L9LS

Brand name

Not provided

Compound type

Biotherapeutic

Summary

L9LS (VRC-MALMAB0114-00-AB) is a long-acting monoclonal antibody currently in clinical development as P. falciparum malaria prophylaxis. The Fc region of L9LS contains two site-directed mutagenesis substitutions (termed “LS”) which enhance neonatal Fc receptor binding affinity and extend its effective half-life to ~56 days. L9LS functions by targeting the highly conserved minor NVDP motifs present on the P. falciparum circumsporozoite protein, thereby disrupting malarial hepatocyte infection and parasite motility. The original L9 antibody was initially isolated from a CHMI study participant who displayed high antibody titres against a junctional epitope mimic (S02). Recent studies have indicated that L9LS may be administered subcutaneously rather than intravenously due to its high potency.

Approval status

Unknown

Regulatory authorities

Unknown

Delivery device(s)

No delivery device

Scale-up and manufacturing prospects

Scale-up prospects

L9LS has been manufactured as a clinical trial product by Leidos Biomedical Research following good manufacturing practices and vialled at a concentration of 150mg/mL within a buffered solution. General manufacturing requirements and production scale-up for therapeutic monoclonal antibody (mAb) products is primarily focused on pharmacokinetic suitability, formulation stability and the overall maintenance of product quality. Industrial bioprocessing steps can also potentially introduce additional 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

2022/34/CE/USTTB

Identifier

NCT05304611

Link

https://www.clinicaltrials.gov/study/NCT05304611

Phase

Phase II

Status

Completed

Sponsor

National Institute of Allergy and Infectious Diseases (NIAID)

More details

Not provided

Purpose

Evaluate the safety and tolerability of L9LS in healthy Malian adults and children, in addition to assessing its protective efficacy during a 7-month malaria season in healthy Malian children.

Interventions

Intervention 1

Biological: L9LS (VRC-MALMAB0114-00-AB)

Intervention 2

Other: Normal saline

Countries

Mali

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2022-03-18

Anticipated Date of Last Follow-up

2024-06-12

Estimated Primary Completion Date

Not provided

Estimated Completion Date

2024-04-01

Actual Primary Completion Date

2023-01-31

Actual Completion Date

2024-04-20

Studied populations

Age Cohort

- Children
- Adults

Genders

- All

Accepts pregnant individuals

No

Accepts lactating individuals

Unspecified

Accepts healthy individuals

Yes

Comments about the studied populations

Adults: Aged ≥18 years. Children: Aged ≥6 years and <11 years. Participants are required to be in good general health and without clinically significant medical history. Any participants that have been previously in receipt of an investigational malaria vaccine or monoclonal antibody in the last 5 years are excluded.

Health status

Negative to : HIV, HBV, HCV

Study type

Interventional (clinical trial)

Enrollment

365

Allocation

Randomized

Intervention model

Sequential assignment

Intervention model description

Not provided

Masking

Triple-blind masking

Masking description

Triple (Participant, Care Provider, Investigator)

Frequency of administration

Other : "Single dose "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Subcutaneous
Intravenous

Use case

PrEP

Key results

Not provided

2023/109/CE/USTTB

Identifier

NCT05816330

Link

https://www.clinicaltrials.gov/study/NCT05816330

Phase

Phase II

Status

Completed

Sponsor

National Institute of Allergy and Infectious Diseases (NIAID)

More details

Not provided

Purpose

Evaluate the safety and tolerability of a one time subcutaneous (SC) administration of L9LS, as well its protective efficacy against naturally occurring Pf infection over a 6-month malaria season.

Interventions

Intervention 1

Biological: L9LS (VRC-MALMAB0114-00-AB)

Intervention 2

Other: Normal saline

Countries

Mali

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2023-05-25

Anticipated Date of Last Follow-up

2024-04-16

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2024-02-11

Actual Completion Date

2024-02-11

Studied populations

Age Cohort

- Adults

Genders

- All

Accepts pregnant individuals

No

Accepts lactating individuals

No

Accepts healthy individuals

Yes

Comments about the studied populations

Females aged ≥18 and ≤49 years and weighing ≥ 45.0 and ≤ 90.0 kg. Males aged ≥18 and ≤55 years and weighing ≥ 50.0 and ≤ 100.0 kg. Exclusion criteria includes prior receipt of an investigational malaria vaccine or monoclonal antibody within the last 5 years.

Health status

Negative to : HIV, HBV, HCV

Study type

Interventional (clinical trial)

Enrollment

288

Allocation

Randomized

Intervention model

Sequential assignment

Intervention model description

Not provided

Masking

Triple-blind masking

Masking description

Triple (Participant, Care Provider, Investigator)

Frequency of administration

Other : "Single dose "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Subcutaneous

Use case

PrEP

Key results

Not provided

VRC 614

Identifier

NCT05019729

Link

https://www.clinicaltrials.gov/study/NCT05019729

Phase

Phase I

Status

Completed

Sponsor

National Institute of Allergy and Infectious Diseases (NIAID)

More details

Not provided

Purpose

Evaluate the safety, tolerability, pharmacokinetics and protective efficacy of the anti-malaria human monoclonal antibody, VRC-MALMAB0114-00-AB (L9LS).

Interventions

Intervention 1

Drug: VRC-MALMAB0114-00-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

2021-09-13

Anticipated Date of Last Follow-up

2024-07-19

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2022-09-19

Actual Completion Date

2022-09-19

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 18-50 years.

Health status

Negative to : HIV, Malaria

Study type

Interventional (clinical trial)

Enrollment

32

Allocation

Non-randomized

Intervention model

Sequential assignment

Intervention model description

Not provided

Masking

Open label

Masking description

None (Open Label)

Frequency of administration

Other : "Single dose "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Subcutaneous
Intramuscular
Intravenous

Use case

PrEP

Key results

Type of key results	Title	Website link
Article	Low-Dose Subcutaneous or Intravenous Monoclonal Antibody to Prevent Malaria	https://doi.org/10.1056/nejmoa2203067

SERU 4413

Identifier

NCT05400655

Link

https://www.clinicaltrials.gov/study/NCT05400655

Phase

Phase II

Status

Completed

Sponsor

National Institute of Allergy and Infectious Diseases (NIAID)

More details

Not provided

Purpose

Evaluate the safety and tolerability of L9LS in healthy Kenyan children; Determining the protective efficacy of one or two doses of L9LS against P. falciparum infection in a high transmission setting.

Interventions

Intervention 1

Drug: L9LS

Intervention 2

Other: Normal Saline

Countries

Kenya

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2022-09-14

Anticipated Date of Last Follow-up

2024-09-11

Estimated Primary Completion Date

2024-06-30

Estimated Completion Date

2024-06-30

Actual Primary Completion Date

2024-06-02

Actual Completion Date

2024-06-02

Studied populations

Age Cohort

- Children

Genders

- All

Accepts pregnant individuals

No

Accepts lactating individuals

No

Accepts healthy individuals

Yes

Comments about the studied populations

Healthy children aged 5 months to 10 years (Part 1) or 5-59 months (Part 2). Weight ≥5 kg and weight ≤30 kg (Part 1) or weight ≥5 kg and ≤22.5 kg (Part 2). Study participants are excluded if they have received any doses of any malaria vaccine.

Health status

Negative to : HIV
Considered high risk to : Malaria

Study type

Interventional (clinical trial)

Enrollment

420

Allocation

Randomized

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Double-blind masking

Masking description

Double (Participant, Investigator)

Frequency of administration

Other : "Part 1: One-time subcutaneous (Sc) dose of L9LS in healthy Kenyan children aged 5 months to 10 years, Part 2: one or two Sc doses of L9LS in Kenyan children aged 5 to 59 months. "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Subcutaneous

Use case

PrEP

Key results

Not provided

2024/158/CE/USTTB

Identifier

NCT06461026

Link

https://clinicaltrials.gov/study/NCT06461026

Phase

Phase I

Status

Recruiting

Sponsor

National Institute of Allergy and Infectious Diseases (NIAID)

More details

The purpose of this study is to assess the safety, tolerability, and pharmacokinetics of L9LS in infants in Mali and to evaluate the impact of L9LS on subsequent R21/Matrix-MTM vaccine immunogenicity.

Purpose

L9LS MAb in Malian Infants

Interventions

Not provided

Countries

Not provided

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2024-08-19

Anticipated Date of Last Follow-up

2024-08-26

Estimated Primary Completion Date

2025-08-01

Estimated Completion Date

2025-08-01

Actual Primary Completion Date

Not provided

Actual Completion Date

Not provided

Studied populations

Age Cohort

- Children

Genders

- All

Accepts pregnant individuals

Unspecified

Accepts lactating individuals

Unspecified

Accepts healthy individuals

Yes

Comments about the studied populations

Inclusion Criteria: 1. Age ≥1 to ≤12 months at enrollment. 2. Born at ≥37 weeks gestation. 3. Parent and/or guardian able to provide proof of identity to the satisfaction of the study clinician completing the enrollment process. 4. In good general health and without clinically significant medical history. 5. Parent and/or guardian able to provide informed consent. 6. Willing to have blood samples and data stored for future research. 7. Resides in or near Kalifabougou, Faladje, or Torodo, Mali, and available for the duration of the study. Exclusion Criteria: 1. Body weight \<3.5 kg. 2. Behavioral, cognitive, or psychiatric disease in the parent and/or guardian that in the opinion of the investigator affects the ability of the parent and/or guardian to understand and comply with the study

Health status

Not provided

Study type

Interventional (clinical trial)

Enrollment

180

Allocation

Randomized

Intervention model

Sequential assignment

Intervention model description

Not provided

Masking

Quadruple-blind masking

Masking description

Not provided

Frequency of administration

Not provided

Studied LA-formulation(s)

Not provided

Studied route(s) of administration

Not provided

Use case

Not provided

Key results

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

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

Supporting material

Publications

Wang LT, Pereira LS, Flores-Garcia Y, O'Connor J, Flynn BJ, Schön A, Hurlburt NK, Dillon M, Yang ASP, Fabra-García A, Idris AH, Mayer BT, Gerber MW, Gottardo R, Mason RD, Cavett N, Ballard RB, Kisalu NK, Molina-Cruz A, Nelson J, Vistein R, Barillas-Mury C, Amino R, Baker D, King NP, Sauerwein RW, Pancera M, Cockburn IA, Zavala F, Francica JR, Seder RA. A Potent Anti-Malarial Human Monoclonal Antibody Targets Circumsporozoite Protein Minor Repeats and Neutralizes Sporozoites in the Liver. Immunity. 2020 Oct 13;53(4):733-744.e8. doi: 10.1016/j.immuni.2020.08.014. Epub 2020 Sep 17. PMID: 32946741; PMCID: PMC7572793.

Discovering potent human monoclonal antibodies (mAbs) targeting the Plasmodium falciparum circumsporozoite protein (PfCSP) on sporozoites (SPZ) and elucidating their mechanisms of neutralization will facilitate translation for passive prophylaxis and aid next-generation vaccine development. Here, we isolated a neutralizing human mAb, L9 that preferentially bound NVDP minor repeats of PfCSP with high affinity while cross-reacting with NANP major repeats. L9 was more potent than six published neutralizing human PfCSP mAbs at mediating protection against mosquito bite challenge in mice. Isothermal titration calorimetry and multiphoton microscopy showed that L9 and the other most protective mAbs bound PfCSP with two binding events and mediated protection by killing SPZ in the liver and by preventing their egress from sinusoids and traversal of hepatocytes. This study defines the subdominant PfCSP minor repeats as neutralizing epitopes, identifies an in vitro biophysical correlate of SPZ neutralization, and demonstrates that the liver is an important site for antibodies to prevent malaria.

Wu, R.L. *et al.* (2022) ‘Low-dose subcutaneous or intravenous monoclonal antibody to prevent malaria’, *New England Journal of Medicine*, 387(5), pp. 397–407. doi: 10.1056/nejmoa2203067.

BACKGROUND

New approaches for the prevention and elimination of malaria, a leading cause of illness and death among infants and young children globally, are needed.

METHODS

We conducted a phase 1 clinical trial to assess the safety and pharmacokinetics of L9LS, a next-generation antimalarial monoclonal antibody, and its protective efficacy against controlled human malaria infection in healthy adults who had never had malaria or received a vaccine for malaria. The participants received L9LS either intravenously or subcutaneously at a dose of 1 mg, 5 mg, or 20 mg per kilogram of body weight. Within 2 to 6 weeks after the administration of L9LS, both the participants who received L9LS and the control participants underwent controlled human malaria infection in which they were exposed to mosquitoes carrying *Plasmodium falciparum* (3D7 strain).

RESULTS

No safety concerns were identified. L9LS had an estimated half-life of 56 days, and it had dose linearity, with the highest mean (±SD) maximum serum concentration (Cmax) of 914.2±146.5 μg per milliliter observed in participants who had received 20 mg per kilogram intravenously and the lowest mean Cmax of 41.5±4.7 μg per milliliter observed in those who had received 1 mg per kilogram intravenously; the mean Cmax was 164.8±31.1 in the participants who had received 5 mg per kilogram intravenously and 68.9±22.3 in those who had received 5 mg per kilogram subcutaneously. A total of 17 L9LS recipients and 6 control participants underwent controlled human malaria infection. Of the 17 participants who received a single dose of L9LS, 15 (88%) were protected after controlled human malaria infection. Parasitemia did not develop in any of the participants who received 5 or 20 mg per kilogram of intravenous L9LS. Parasitemia developed in 1 of 5 participants who received 1 mg per kilogram intravenously, 1 of 5 participants who received 5 mg per kilogram subcutaneously, and all 6 control participants through 21 days after the controlled human malaria infection. Protection conferred by L9LS was seen at serum concentrations as low as 9.2 μg per milliliter.

CONCLUSIONS

In this small trial, L9LS administered intravenously or subcutaneously protected recipients against malaria after controlled infection, without evident safety concerns. (Funded by the National Institute of Allergy and Infectious Diseases; VRC 614 ClinicalTrials.gov number, NCT05019729)

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