Establishing a Controlled Human Infection Model with the Chikungunya live attenuated vaccine VLA1553 in healthy volunteers

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Ethical review	Approved WMO
Status	Pending
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON57290

Source
ToetsingOnline

Brief title
Establishing a Chikungunya CHIM

Condition

- Viral infectious disorders

Synonym
Viral infection

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research

Source(s) of monetary or material Support: CHDR

Intervention

Keyword: Chikungunya, CHIM, immunology, vaccine

Outcome measures

Primary outcome

- Infection rate: number of healthy volunteers developing viremia divided by the number of healthy volunteers receiving the vaccine

- Sumptomatic rate: number of healthy volunteers developing vaccine related symptoms divides by the number of healthy volunteers receiving the vaccine.

Secondary outcome

- Nature, frequency and severity of (serious) adverse events;

- Vital signs;

- Vaccine related symptoms;

- Clinical laboratory tests including hematology and chemistry;

- Physical examination, symptom directed and on indication;

- Concomitant medication;

- Local tolerability of injection site as assessed by a numeric rating scale (NRS).

- Chikungunya viral load (in both blood and urine) over time as determined by qPCR.

- Chikungunya viral culture titer, determined by plaque assay, over time.

- Severity, duration and nature of solicited and unsolicited vaccine related symptoms.

- Occurrence of leukopenia and lymphopenia after administration of the VLA1553

vaccine.

- Seroconversion rate: number of healthy volunteers developing virus

neutralizing antibodies divided by the number of healthy volunteers receiving

the vaccine;

- Titer of virus neutralizing antibodies.

Study description

Background summary

Chikungunya is a vector-borne viral disease, increasing in incidence and expected to spread worldwide in the coming decades.1 Infection with Chikungunya virus (CHIKV) can lead to acute disease, associated with symptoms such as fever, headache, myalgia and skin rash, but seldomly with lethal outcome.2 However, up to 60% of infected patients develop debilitating chronic arthralgias, which can last up to years. Outbreaks of CHIKV are characterized by a rapid spread of the virus, leading to a high disease burden in local populations within a short period of time.1 The intensification of global travel and trade has led to an increase in CHIKV outbreaks; a further increase in the coming decades is expected due to climate change, as well as the emergence of alternative CHIKV transmission vectors beside the Aedes aegypti mosquito, such as Aedes albopticus, which is more tolerant to cold temperatures.1 The current need for prophylactic measures against Chikungunya disease is urgent and will expectedly increase.

Rapid availability of pharmaceuticals targeting e.g. viruses can limit the impact of infectious diseases; in the case of future local outbreaks or pandemics, a health crisis can be mitigated by swift development and testing of vaccines.3,4 The controlled human infection model (CHIM) is an innovative

and effective method for testing pharmaceutics targeting infectious diseases in early clinical phase.
CHIMs involve active exposure of (healthy) volunteers in a controlled setting, facilitating close safety
monitoring, as well as the evaluation of efficacy endpoints and extensive assessment of viral and
immunological endpoints. This allows for an early evaluation and understanding of the efficacy of new
pharmaceuticals, resulting in early assessment of whether these pharmaceuticals will be worth their
investment.5,6 CHIMs are often conducted using respiratory viruses, as these generally cause shortlasting, mild symptoms. Exposing healthy individuals to CHIKV would be accompanied by a significant
risk (up to 60%) of inducing chronic Chikungunya disease, with symptoms that can often not be
effectively managed.

Recently, a live attenuated virus (LAV) was approved by the FDA as a vaccine against Chikungunya.
This vaccine, named VLA1553, showed high effectivity, with immunisation rates of up to 100%.7,8 In
addition, VLA1553 was demonstrated to cause detectable viremia and mild acute Chikungunya
associated symptoms, such as fever, headache or joint pains; however, the LAV did not cause chronic
Chikungunya disease. Passive transfer of VLA1553 induced antibodies to non-human primates
resulted in protection against Chikungunya associated symptoms after exposure to CHIKV,
establishing VLA1553 as an effective prophylaxis against natural CHIKV infection.9 After
revaccination in humans, both viremia and symptoms significantly decreased, confirming the
immunogenic capacity of VLA1553, as well as its suitability as a challenge agent to test new therapies
against CHIKV.8 In this study, we aim to establish a controlled human infection model using the
VLA1553 vaccine as challenge agent, to facilitate efficient and closely monitored testing of newly
developed drugs against Chikungunya disease.

Study objective

The main objective of this study is to establish a controlled human infection model for Chikungunya
using the VLA1553 vaccine.

Primary objectives:
- To assess the infection rate induced by a single administration of the VLA1553 vaccine
- To assess the symptomatic rate induced by a single administration of the VLA1553 vaccine

Secondary objectives:
- To investigate the safety and tolerability of controlled infection after vaccination with the VLA1553 live attenuated Chikungunya virus
- To assess the VLA1553 viral kinetics in blood and urine
- To characterize symptoms after VLA1553 challenge
- To assess the immunological response after VLA1553 challenge

Study design

This is an open-label validation study of the VLA1553 Chikungunya vaccine challenge model. The
study consists of a screening/enrollment period, a baseline visit, a vaccination period, and a followup visit.The subjects will be monitored for vaccine-related symptoms, solicited and unsolicited symptoms, adverse events (AE) and vital signs including tympanic temperature. Routine safety laboratory assessments (hematology and blood chemistry) will be performed; additional safety assessments will be performed if deemed
necessary by the investigator. Chikungunya viral load, viral culture and virus neutralizing antibodies
will be assessed in serum. PBMCs will be collected on timepoints.

Intervention

Subjects will receive the VLA1553 vaccine by intramuscular administration. The VLA1553 vaccine is a registered vaccine, containing 1 x 10^4 50% Tissue Culture Infective Dose (TCID50) of live attenuated virus.

Study burden and risks

VLA1553 has a well-established safety profile, assessed in large clinical trials. Healthy volunteers will receive a single administration containing the approved dose of 1 x 104 TCID50.
Study participants may develop symptoms related to the vaccine administration, such as swelling, redness, pain, induration, tenderness or a rash at the location of administration. In addition, systemic symptoms may emerge in the first week after vaccine administration; possible systemic symptoms include headache, fatigue, muscle pain, nausea, vomiting, or joint pain. In clinical studies, local and systemic symptoms generally subsided after 1-4 days.7 As with any study involving drug administration, other symptoms may arise that are not yet described in literature. Finally, volunteers may experience discomfort

during blood sampling.
As VLA1553 has demonstrated high immunogenicity and signs of clinical protection against Chikungunya disease, volunteers will benefit from receiving the vaccine in this study. However, as Chikungunya is not endemic in The Netherlands, and since the longevity of the VLA1553-induced antibodies is not fully clear, the significance of this benefit remains unclear.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Signed informed consent prior to any study-mandated procedure
- Healthy male or female volunteers, 18 to 64years of age (inclusive) at screening
- A total body weight >=50 kg and body mass index (BMI) >=18.0 and <=32.0 kg/m2 at screening;

- All women of childbearing potential must practice effective contraception during the course of the study and until the last study visit (Day 60);
- Subject is able to communicate well in Dutch with the investigator, has adequate understanding of the procedures of the study and is willing to comply with the study procedures and restrictions;

Exclusion criteria

1. Any history or evidence of any clinically significant or currently active major disease, or condition that, in the opinion of the investigator, may interfere with a subject completing the study and the necessary investigations (following a detailed medical history, physical examination, vital signs (systolic and diastolic blood pressure, and body temperature) and ECG). Minor deviations from the normal range may be accepted, if judged by the investigator to have no clinical relevance;
2. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening;
3. Any confirmed or suspected disease or condition associated with immune system impairment, including auto-immune diseases, HIV, asplenia or recurrent severe infections;
4. (History of) confirmed or suspected rheumatic disease or condition associated with joint inflammation or clinically significant arthritis/arthralgia.
5. Suspected or confirmed history of infection with Chikungunya;
6. Prior participation in another controlled human infection study with Chikungunya, Yellow Fever or Dengue.
7. Participation in an investigational medical product, vaccine or device study within 30 days or 5 half-lives prior to the study period (whichever is longer), or more than 4 times in the past year;
8. Any known history of anaphylaxis or any significant allergy against vaccines;
9. Use of any medications (prescription or over-the-counter [OTC]), within 14 days prior to vaccine administration, or less than 5 half-lives (whichever is longer), and during the course of the study. Exceptions are paracetamol (up to 4 gram/day) and contraceptives. Other exceptions will only be made if the rationale is clearly documented and accepted by the investigator.
10. Use of vitamins or dietary supplements, within 7 days prior to inoculation.
11. Use of chronic (more than 14 days) systemic immunosuppressant medications within the 3 months prior to vaccine administration, or isolated (non-chronic) use within 30 days prior to vaccine administration. Incidental use of topical, intranasal or inhalation corticosteroids may be permitted up to 14 days prior to vaccine administration (day 1) at the discretion of the investigator;
12. Receipt of any vaccine within 6 weeks prior to vaccine and during the course of the study;
13. Receipt of blood or blood derived products (including immunoglobulin)

within 180 days prior to vaccine administration;
14. History of abuse of addictive substances (alcohol, illegal substances) or current use of more than 21 units alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquillizers, or any other addictive agent;
15. Positive test for drugs of abuse at screening or prior to vaccine administration;
16. Loss or donation of blood over 500 mL within three months (males) or four months (females)
prior to screening or intention to donate blood or blood products during the study or within 4
weeks after vaccine administration.
17. Females who are pregnant, breastfeeding, or are planning to become pregnant during the study; 18. Any known factor, condition, or disease that might interfere with treatment compliance, study conduct or interpretation of the results, as deemed by the investigator.

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2025
Enrollment:	12
Type:	Anticipated

Ethics review

Approved WMO

Date:	07-02-2025

Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL88062.058.24