



Chikungunya virus virus-like particle vaccine safety and immunogenicity in adolescents and adults in the USA: a phase 3, randomised, double-blind, placebo-controlled trial

Jason S Richardson, Deborah M Anderson, Jason Mendy, Lauren C Tindale, Sufia Muhammad, Tobi Loreth, Sarah Royalty Tredo, Kelly L Warfield, Roshan Ramanathan, Jorge T Caso, Victoria A Jenkins, Patrick Ajiboye, Lisa Bedell, on behalf of the EBSI-CV-317-004 Study Group*

Summary

Background Chikungunya disease is a growing global public health concern. Vimkunya (previously chikungunya virus virus-like particle vaccine, previously PXVX0317) is a single-dose, pre-filled syringe for intramuscular injection. Here, we report safety, tolerability, and immunogenicity data for Vimkunya versus placebo in healthy adolescents and adults aged 12–64 years, and evaluate lot-to-lot consistency.

Methods This pivotal phase 3, randomised, double-blind, placebo-controlled, parallel-group trial was done at 47 clinical trial sites in the USA. Eligible participants were healthy adolescents and adults aged 12–64 years. Participants were divided into three age strata (12–17 years, 18–45 years, and 46–64 years) within each site and randomly assigned (2:2:2:1) to receive one of three consecutively manufactured lots of Vimkunya or placebo (same excipient composition without chikungunya virus virus-like particle or aluminium hydroxide components) on study day 1. Neither participants, nor clinical site personnel, nor the funder knew participants' individual treatment assignments until all participants completed their involvement in the trial and the database was cleaned and locked. Participants attended a screening visit, followed by a day 1 visit that included random assignment, blood sample collection, and administration of a single dose of Vimkunya or placebo by intramuscular injection in the deltoid muscle. The coprimary endpoints were: the difference in chikungunya virus serum neutralising antibody seroreponse rate (vaccine minus placebo) at day 22; chikungunya virus serum neutralising antibody geometric mean titre (GMT) at day 22 for vaccine and placebo; and chikungunya virus serum neutralising GMT ratio at day 22 between all three pairs of vaccine lots (A:B, B:C, and A:C) in adults aged 18–45 years. The trial is registered with ClinicalTrials.gov, NCT05072080 and EudraCT, 2023-001124-42.

Findings Between Sept 29, 2021, and Sept 23, 2022, 4215 participants were screened, of whom 3258 were eligible and enrolled (1667 [51.2%] female and 1591 [48.8%] male), and 3254 (99.9%) received either Vimkunya (n=2790) or placebo (n=464). The immunogenicity evaluable population included 2983 participants, of whom 2559 received Vimkunya and 424 received placebo. At day 22, 2503 (97.8%) of 2559 participants in the Vimkunya group had a seroreponse, compared with five (1.2%) of 424 participants in the placebo group for the immunogenicity evaluable population. The seroreponse rate difference was 96.6% (95% CI 95.0–97.5; $p<0.0001$). In the immunogenicity evaluable population, chikungunya virus serum neutralising antibody GMT at day 22 for the vaccine group was 1618 and for the placebo group was 7.9 ($p<0.0001$). At day 22, the serum neutralising GMT ratios for the pairs of lots (A:B, B:C, and A:C) were 0.98 (95% CI 0.85–1.14), 0.97 (0.84–1.12), and 0.95 (0.82–1.10), respectively. Vimkunya had a favourable safety profile; most adverse events were self-limiting and grade 1 or 2 in severity. The most common adverse events were injection site pain (656 [23.7%] of 2764 participants in the vaccine group), fatigue (551 [19.9%] of 2764), headache (498 [18.0%] of 2765), and myalgia (486 [17.6%] of 2764).

Interpretation Vimkunya induces a rapid and robust immune response. These findings support the potential for this vaccine to protect individuals aged 12–64 years from disease caused by chikungunya virus.

Funding Emergent BioSolutions and Bavarian Nordic.

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Introduction

Chikungunya disease, caused by chikungunya virus, is transmitted to humans through the bite of infected mosquitoes.¹ The classic symptom of acute chikungunya disease, which is present in more than 90% of cases, is debilitating polyarthralgia.¹ Other acute clinical manifestations of infection include high fever, rash, headache,

nausea, fatigue, and myalgia.^{2–4} Acute symptoms can persist for 1–2 weeks after infection and can substantially impact daily productivity, primarily due to reduced mobility associated with joint pain.⁵ In some cases, chronic symptoms persist for months or years, with a serious impact on quality of life.^{6,7} One live-attenuated vaccine (IXCHIQ) is licensed for the prevention of disease caused

Published Online
March 27, 2025
[https://doi.org/10.1016/S0140-6736\(25\)00345-9](https://doi.org/10.1016/S0140-6736(25)00345-9)

*Members are listed in the appendix (pp 2–3)

Bavarian Nordic Canada, Toronto, ON, Canada (J S Richardson PhD, D M Anderson MS, L C Tindale PhD, T Loreth BA); Bavarian Nordic, San Diego, CA, USA (J Mendy MS, S Muhammad MD, P Ajiboye MD, L Bedell MA); Emergent BioSolutions, Gaithersburg, MD, USA (S R Tredo MBA, K L Warfield PhD, R Ramanathan MD MPH); Suncoast Research Associates, Miami, FL, USA (J T Caso MD); Bavarian Nordic Belgium, Brussels, Belgium (V A Jenkins PhD)

Correspondence to: Dr Jason Richardson, Bavarian Nordic Canada, Toronto, ON M5X 1B8, Canada jari@bavarian-nordic.com
See Online for appendix

Research in context

Evidence before this study

Before we undertook this trial, there were no licensed vaccines to prevent chikungunya virus infection or disease. To ensure a thorough understanding of the available evidence, we conducted an extensive literature review. The following database sources were searched for relevant studies: PubMed, Scopus, Web of Science, and ClinicalTrials.gov. Additionally, we reviewed reference lists from recent reviews, meta-analyses, and primary research articles on chikungunya virus and vaccine development. We included studies that focused on vaccine candidates for chikungunya virus, including preclinical and clinical trials; studies published in peer-reviewed journals; and trials involving participants aged 12 years and older. Studies were excluded if they: were not published in English or if translation was not available; focused on non-vaccine interventions for chikungunya virus; or were not relevant to vaccine development or immunisation strategies for chikungunya virus. Search terms used included combinations of the following keywords: “chikungunya virus”, “vaccine”, “vaccine candidates”, “clinical trials”, “immunization”, “vaccine development”, and “chikungunya disease prevention”. The search was conducted using studies published from Jan 19, 2000, to Sept 17, 2021. Studies published before this period were excluded due to the rapid advances in vaccine research in the past two decades. We included all studies regardless of geographical location, given the global impact of chikungunya. Based on this review, we concluded that although several vaccine candidates had entered clinical trials, there were no licensed vaccines at the time to prevent chikungunya virus infection or disease. This informed the rationale for our study, which aimed to address the unmet need for an effective and licensed vaccine. Since our study, IXCHIQ, a live-attenuated vaccine delivered as a single dose after reconstitution, was approved by the US Food and Drug Administration (FDA) in November, 2023, Health Canada in June, 2024, and the European Medicines Agency in July, 2024 for the prevention of chikungunya virus disease in individuals aged 18 years and older who are at increased risk of exposure. Since February, 2024, the US Advisory Committee on Immunization Practices recommends chikungunya vaccination for people aged 18 years and older travelling to countries or territories with ongoing chikungunya outbreaks, as well as for laboratory workers with potential exposure to the virus. Before we undertook this trial, no marketed chikungunya virus vaccine was available for children younger than 12 years.

Added value of this study

Two pivotal phase 3 trials in individuals aged 12 years and older have been completed with Bavarian Nordic's Vimkunya vaccine, with positive safety and immunogenicity results in adolescents, adults (NCT05072080), and older adults (NCT05349617). Results from the present trial of adolescents and adults aged 12–64 years show that Vimkunya (previously chikungunya virus virus-like particle vaccine) induced a seroresponse, considered the presumptive seroprotective antibody response, in 97.8% of individuals at day 22 after vaccination, and in 96.8% of individuals at day 15 after vaccination, and persisted with a seroresponse rate of 85.5% at day 183. Vimkunya showed a favourable safety profile in all age strata; most adverse events were self-limiting and grade 1 or 2 in severity. The chikungunya virus virus-like particle component of the vaccine contains proteins from the chikungunya virus Senegal west African strain 37997. The proposed mechanism of action of Vimkunya is to induce antibodies against the chikungunya virus capsid (C), and envelope (E1, E2) proteins contained in the vaccine, resulting in neutralisation of live chikungunya virus.

Implications of all the available evidence

Vimkunya elicits a high seroresponse rate at protective levels of chikungunya virus neutralising antibodies within 2 weeks after vaccination, which is beneficial to individuals receiving immunisation before travel, and displays a favourable safety profile. Compared with IXCHIQ, Vimkunya is offered as a single-dose, prefilled syringe for easy administration and increased dosing accuracy, with the indication including adolescents aged 12 years and older. Virus-like particle vaccines are non-replicating, have been widely used for over 30 years, and generally are not contraindicated for use in immunocompromised populations and pregnant women. Vimkunya offers a robust immunogenic option for a range of travellers due to its virus-like particle platform. The FDA approved Vimkunya (chikungunya vaccine, recombinant) for injection on Feb 14, 2025, making it the first virus-like particle single-dose chikungunya vaccine in the USA for people aged 12 years and older. On Feb 28, 2025, the European Commission granted marketing authorisation in Europe for Vimkunya for active immunisation for the prevention of disease caused by chikungunya virus in individuals aged 12 years and older.

by chikungunya virus in individuals aged 18 years and older who are at increased risk of exposure.^{8,9} Vimkunya (previously known as chikungunya virus virus-like particle vaccine and PXVX0317) is now licensed in the USA (as of Feb 14, 2025) and Europe (as of Feb 28, 2025) for the prevention of disease caused by chikungunya virus in individuals aged 12 years and older.

Vimkunya comprises the E1, E2, and C proteins of the chikungunya virus Senegal west African strain 37997,

which are assembled to form an approximately spherical, highly ordered virus-like particle.¹⁰ Notably, the E1 glycoprotein mediates membrane fusion during virus infection of host cells and the E2 transmembrane glycoprotein is responsible for receptor binding to host cells during viral replication¹¹ and has been shown to be the primary target of chikungunya virus neutralising antibodies induced during natural infection.¹² Protection against subsequent infection has been shown to correlate

with the presence of chikungunya virus antibodies that neutralise the virus *in vitro*.¹³ Additionally, although there are three major lineages of chikungunya virus, data suggest that there is a single chikungunya virus serotype, allowing for cross-protection from all strains of the virus.^{14–16} For instance, a study found that an unadjuvanted version of chikungunya virus virus-like particle vaccine with 10 µg, 20 µg, or 40 µg of chikungunya virus virus-like particle induced serum neutralising antibody responses in participants in a phase 1 trial against nine viral strains representing all three lineages,¹⁴ and another study showed similar serum neutralising antibody concentrations against three viral strains after immunisation with a 20 µg virus-like particle dose of chikungunya virus virus-like particle vaccine.¹⁵ The immunogenicity threshold used in this trial was defined based on a non-human primate passive antibody transfer and challenge study, in which human serum from individuals vaccinated with chikungunya virus virus-like particle was used to prevent viraemia after wild-type chikungunya virus challenge in cynomolgus macaques. In non-human primates, a serum neutralising antibody titre of 23·6 was estimated to be associated with an 80% probability of protection from chikungunya virus. Based on those results, a serum neutralising antibody titre of 100 was conservatively established as a protective threshold in humans (the US Food and Drug Administration [FDA] and European Medicines Agency [EMA] agreed threshold) and was the basis of the seroresponse threshold for phase 3 trial endpoints. A previous phase 2 dose-finding trial established the final dose selected for development and provided preliminary data on long-term durability of protection for up to 2 years after vaccination.¹⁷

Vimkunya (Bavarian Nordic Berna, Thörishaus, Switzerland) is comprised of 40 µg chikungunya virus virus-like particle in buffered solution and adjuvanted with aluminium hydroxide. The product is supplied as a pre-filled syringe for ease of use, increased dosing accuracy, reduced risk of administrative errors, and fast preparation and administration time.^{18,19} Here, we report safety, tolerability, and immunogenicity data for Vimkunya versus placebo in healthy adolescents and adults aged 12–64 years, and evaluate lot-to-lot consistency.

Methods

Study design and participants

This pivotal phase 3, randomised, placebo-controlled, double-blind, parallel-group trial was done at 47 clinical trial sites in the USA. The trial was done in compliance with International Council on Harmonization Good Clinical Practice guidelines and in accordance with the principles set forth in the Declaration of Helsinki. Ethics approval was obtained from the WCG institutional review board and Cincinnati Children's Hospital Medical Center institutional review board (2021-0617). The protocol is available online. The trial is registered with ClinicalTrials.gov, NCT05072080 and EudraCT, 2023-001124-42.

Eligible participants were healthy adolescents and adults aged 12–64 years. Key exclusion criteria included: current pregnancy, breastfeeding, or plans to become pregnant during the trial, BMI 35 kg/m² or higher, history of any known congenital or acquired immunodeficiency, acute disease within 14 days, previous receipt of an investigational chikungunya virus vaccine or product, or any other medical condition that could adversely affect the participant's involvement or the conduct of the trial. Full inclusion and exclusion criteria are provided in the appendix (pp 4–5). Written informed consent and assent from parents or legal guardians (if applicable) was obtained before any trial procedure.

Randomisation and masking

Participants were divided into three age strata (12–17 years, 18–45 years, and 46–64 years) within each site and randomly assigned (2:2:2:1) to receive one of three consecutively manufactured lots of Vimkunya or placebo (same excipient composition without chikungunya virus virus-like particle or aluminium hydroxide components). The randomisation of participants to treatment was performed using third-party computer generated blocks allocated to site-age strata that contained randomisation numbers randomly allocated in a 2:2:2:1 ratio for the three consecutively manufactured lots of Vimkunya vaccine and placebo. When a participant was assessed as eligible for the study, the randomisation module generated a randomisation number that matched a masked vaccine or placebo kit available at the site.

Neither participants, nor clinical site personnel, nor the funder knew participants' individual treatment assignments until all participants completed their involvement in the trial and the database was cleaned and locked. Assays were run in a masked manner as an added precaution; only sample and data management staff of the funder testing laboratory had access to any data pertaining to trial participants and results; the sample testing operators did not have access to data and funder sample testing staff only had access to a randomly assigned barcode. The assay titre results were not delivered to the funder data management and analysis team until after database lock.

Procedures

Participants attended a screening visit, followed by a day 1 visit that included random assignment, blood sample collection, and administration of a single dose of Vimkunya or placebo by intramuscular injection in the deltoid muscle (appendix p 10). Day 8, 15, 22, and 183 visits included a review of adverse events and concomitant medications and blood sample collection. Day 29 and 92 telephone visits included a review of adverse events.

Participants were monitored for signs of acute adverse reactions to vaccination for 30 min after administration. Solicited adverse event data were collected by participants from the point of injection administration on day 1 through

For the protocol see https://cdn.clinicaltrials.gov/large-docs/80/NCT05072080/Prot_000.pdf

to day 8 by use of a diary. Solicited adverse events included local events of pain, redness (erythema), and swelling (oedema) at the injection site and systemic events of oral temperature 38.0°C or higher ($\geq 100.4^{\circ}\text{F}$), chills, fatigue, headache, myalgia, arthralgia, and nausea. Unsolicited adverse event data were collected from day 1 through to day 29. Data on serious adverse events, adverse events of special interest (defined as new-onset or worsening arthralgia that was medically attended), and medically attended adverse events were collected from day 1 after vaccination through to day 183. The site investigator assessed all adverse events for severity as grade 1 (mild), grade 2 (moderate), grade 3 (severe), or grade 4 (potentially life-threatening). When developing this toxicity grading scale, the funders referred to FDA guidance on toxicity grading for healthy participants in vaccine trials²⁰ and adjusted some parameters to close gaps between the toxicity grades. The site investigator assessed adverse event causality. If an association between an adverse event and the trial drug was determined to be possible or probable, the event was considered related.

A planned independent safety monitoring committee masked safety data review was done after the first 300 participants completed the day 29 visit, at which time no safety signals were identified. A second masked safety monitoring committee data review was done after the final participant completed the day 29 visit, and again no safety concerns were raised and no unmasking occurred.

A luciferase-based chikungunya virus human serum neutralising antibody assay (chikungunya virus-luc reporter strain based on Asian strain 181/25) was used to measure the 80% serum neutralising antibody titre (NT_{80}) against chikungunya virus in human serum samples (appendix p 6). The seroresponse rate was defined as the proportion of participants who achieved serum neutralising antibody NT_{80} 100 or higher (the presumptive seroprotection rate agreed with the FDA and EMA).

Protocol deviations were reviewed on an ongoing basis during the trial.

Outcomes

The coprimary endpoints were: the difference in chikungunya virus serum neutralising antibody seroresponse rate (vaccine minus placebo) at day 22; chikungunya virus serum neutralising antibody geometric mean titre (GMT) at day 22 for vaccine and placebo; and chikungunya virus serum neutralising GMT ratio at day 22 between all three pairs of vaccine lots (A:B, B:C, and A:C) in adults aged 18–45 years. The primary endpoints were centrally assessed.

The key secondary endpoints were the difference in chikungunya virus serum neutralising antibody seroresponse rate at day 15, day 183, and day 8, in that order. Other secondary immunogenicity endpoints were chikungunya virus serum neutralising antibody GMTs by trial group at day 8, day 15, and day 183; geometric mean fold increase from day 1 to subsequent collection

timepoints; and the number and percentage of participants with serum neutralising antibody NT_{80} 15 or higher and a 4-fold rise over baseline. All endpoints are described in detail in the appendix (pp 7–9).

Safety endpoints were the incidence of solicited adverse events from vaccination through to day 8; the incidence of unsolicited adverse events from day 1 through to day 29; and incidence of adverse events of special interest, medically attended adverse events, and serious adverse events from day 1 through to day 183 (end of trial).

Statistical analysis

3150 participants were planned for enrolment. The sample size for the trial was based on the regulatory need for a specific number of participants exposed to Vimkunya for safety assessment. With an assumed 10% rate of non-evaluable participants and the difference between Vimkunya and placebo assumed to be 85–90%, the power to show superiority over placebo with 2430 Vimkunya evaluable and 405 placebo evaluable participants was more than 99.9% for the combined age strata. A 70% difference in seroresponse rate between vaccine and placebo groups was considered clinically relevant. With 2430 vaccine-treated participants and a target seroresponse rate of 90% versus a rate of 0 for placebo, the width of a two-sided 95% CI would be $\pm 1.2\%$. The difference in seroresponse rate had to be above 72% for the lower bound of the 95% CI for the difference to be 70% or more.

The exposed population included all participants who received Vimkunya or placebo injection. The safety population included all participants from the exposed population who provided safety assessment data. The modified intention-to-treat population included all participants who were vaccinated and had at least one post-injection chikungunya virus serum neutralising antibody titre result. The immunogenicity evaluable population included modified intention-to-treat population participants who had no measurable chikungunya virus serum neutralising antibody at day 1 (below lower limit of quantitation [LLOQ]), had evaluable chikungunya virus serum neutralising antibody at day 22, and had no reason for exclusion as defined before unmasking (primary population for immunogenicity analysis).

The primary objectives of the trial were based on serum neutralising antibody NT_{80} titres calculated to determine the chikungunya virus neutralising antibody response. The difference between treatment groups in seroresponse rate (proportion of participants with serum neutralising antibody $\text{NT}_{80} \geq 100$) was tested using a χ^2 test with two-sided $\alpha=0.05$ in the immunogenicity evaluable population across all age strata combined and the two-sided 95% CI for the difference was computed using the Newcombe hybrid score method. In the computation of GMTs, values below the assay LLOQ of less than 15 were assigned the value $\text{LLOQ}/2=7.5$. GMTs were compared between the Vimkunya and placebo treatment groups and were analysed via a linear model based on



Figure 1: Trial profile

CHIKV VLP=chikungunya virus virus-like particle. IEP=immunogenicity evaluable population. mITT=modified intention-to-treat. SNA=serum neutralising antibody. *Exclusions from the IEP were due to no SNA result in the day 22 window, measurable day 1 SNA (baseline positive), prohibited vaccine or medication use, eligibility criteria not met, missing day 1 SNA sample, or serum processing error.

two-sided $\alpha=0.05$. The primary model was an ANOVA, with logarithmically transformed chikungunya virus serum neutralising antibody titres ($\log_{10}$) as the dependent variable and treatment group and trial site as the fixed effects in the model. The adjusted least square means and their 95% CIs calculated based on the ANOVA were back transformed and reported as group GMT values. The proportion of participants with seropositivity (serum neutralising antibody NT₈₀ ≥ 15 ; above the LLOQ) and

those with a 4-fold rise in titre over baseline were also analysed and summarised descriptively as a secondary endpoint. Lot consistency was assessed using a similar ANOVA to the GMT but using only the chikungunya virus virus-like particle vaccinated participants and vaccine lot, rather than vaccine group, as a factor in the model. Multiplicity was addressed by requiring both coprimary endpoints to be met as a success criterion and via hierarchical testing for the key secondary endpoints.

Safety data and the frequency and proportion of participants with either solicited or unsolicited adverse events were summarised descriptively including duration, severity, and causality of the events observed.

Statistical analyses were done using SAS (version 9.4).

Role of the funding source

Employees of Bavarian Nordic and Emergent BioSolutions (the funders of the study) were responsible for study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between Sept 29, 2021, and Sept 23, 2022, 4215 participants were screened, of whom 3258 were eligible and enrolled, and 3254 (99.9%) received either vaccine or placebo (2790 participants received Vimkungunya and 464 received placebo). The immunogenicity evaluable population included 2983 participants, of whom 2559 received Vimkungunya (841, 860, and 858 received lot A, B, and C, respectively) and 424 received placebo (figure 1). 1150 (35.3%) of 3254 participants had at least one important protocol deviation, including out of window or missed visits (829 [25.5%]), eligibility (233 [7.2%]), and non-compliance (97 [3.0%]). No participants received the wrong treatment, and no emergency or accidental unmasking occurred.

We found no appreciable difference between the Vimkungunya groups and placebo group in terms of demographic characteristics (table 1). In the randomly assigned population, 1667 (51.2%) of 3258 participants were female and 1591 (48.8%) were male. There were 254 adolescent participants aged 12–17 years (217 assigned to vaccine and 37 to placebo), 1906 participants aged 18–45 years (1636 assigned to vaccine and 270 to placebo), and 1098 participants aged 46–64 years (941 assigned to vaccine and 157 to placebo). 2384 (73.2%) of 3258 participants were White and 623 (19.1%) were Black or African American. The study completion rate for the placebo group (430 [92.7%] of 464 participants) was slightly higher than for the vaccinated group (2472 [88.5%] of 2794 participants).

At day 22, 2503 (97.8%) of 2559 participants in the Vimkungunya group had a seroresponse, compared with five (1.2%) of 424 participants in the placebo group for the immunogenicity evaluable population (table 2). The seroresponse rate difference was 96.6% (95% CI 95.0–97.5; $p < 0.0001$) and clinically relevant. Chikungunya virus serum neutralising antibody GMT at day 22 for the vaccine group was 1618 and for the placebo group was 7.9, in the immunogenicity evaluable population (appendix pp 12–13);

	Vimkungunya groups (n=2794)	Placebo group (n=464)	Total (n=3258)
Age, years			
Mean (SD)	39 (14.3)	39 (14.4)	39 (14.3)
Median (IQR)	38.0 (27.0–51.0)	38.0 (26.0–51.0)	38.0 (27.0–51.0)
Range	12–64	12–64	12–64
12–17	217 (7.8%)	37 (8.0%)	254 (7.8%)
18–45	1636 (58.6%)	270 (58.2%)	1906 (58.5%)
46–64	941 (33.7%)	157 (33.8%)	1098 (33.7%)
Sex			
Male	1358 (48.6%)	233 (50.2%)	1591 (48.8%)
Female	1436 (51.4%)	231 (49.8%)	1667 (51.2%)
Female and of childbearing potential	846 (58.9%)	136 (58.9%)	982 (58.9%)
Race			
White	2043 (73.1%)	341 (73.5%)	2384 (73.2%)
American Indian or Alaska Native	30 (1.1%)	2 (0.4%)	32 (1.0%)
Asian	79 (2.8%)	16 (3.4%)	95 (2.9%)
Black or African American	534 (19.1%)	89 (19.2%)	623 (19.1%)
Native Hawaiian or Other Pacific Islander	6 (0.2%)	4 (0.9%)	10 (0.3%)
Multiracial	78 (2.8%)	8 (1.7%)	86 (2.6%)
Not reported	24 (0.9%)	4 (0.9%)	28 (0.9%)
Ethnicity			
Hispanic or Latino	506 (18.1%)	71 (15.3%)	577 (17.7%)
Not Hispanic or Latino	2226 (79.7%)	379 (81.7%)	2605 (80.0%)
Not reported	61 (2.2%)	14 (3.0%)	75 (2.3%)
Unknown	1 (<0.1%)	0	1 (<0.1%)
BMI, kg/m²			
Mean (SD)	26.8 (4.5)	26.4 (4.6)	26.7 (4.5)
Median (IQR)	26.8 (23.5–30.3)	26.3 (22.7–30.0)	27.6 (23.4–30.3)
Range	13.1–35.4	15.7–34.9	13.1–35.4
Baseline chikungunya virus virus-like particle serum neutralising antibody serostatus			
Negative (<LLOQ)	2725 (97.5%)	458 (98.7%)	3183 (97.7%)
Positive (≥LLOQ)	63 (2.3%)	6 (1.3%)	69 (2.1%)
Missing	6 (0.2%)	0	6 (0.2%)

Data are n (%), unless otherwise indicated. LLOQ=lower limit of quantitation.

Table 1: Baseline characteristics

	Seroresponse rate for Vimkungunya groups (n=2559)	Seroresponse rate for placebo groups (n=424)	Seroresponse rate difference (95% CI)	p value
Day 8	1169/2510 (46.6%; 44.6–48.5)	2/419 (0.5%; 0.1–1.7)	46.1% (43.8–48.1)	<0.0001
Day 15	2355/2434 (96.8%; 96.0–97.4)	3/395 (0.8%; 0.3–2.2)	96.0% (94.3–96.8)	<0.0001
Day 22	2503/2559 (97.8%; 97.2–98.3)	5/424 (1.2%; 0.5–2.7)	96.6% (95.0–97.5)	<0.0001
Day 183	1967/2301 (85.5%; 84.0–86.9)	6/401 (1.5%; 0.7–3.2)	84.0% (81.7–85.6)	<0.0001

Data are n/N (%; 95% CI), unless otherwise indicated. p values were calculated with a two-sided χ^2 test of equality of seroresponse percentages between groups. 95% CIs of seroresponse rates are based on the Wilson method.

Table 2: Chikungunya virus serum neutralising antibody seroresponse rate and seroresponse rate difference by trial visit (immunogenicity evaluable population)

the vaccine group GMT was significantly higher than the placebo group GMT ($p < 0.0001$). At day 22, equivalence of the vaccine lots was demonstrated via pairwise lot comparison of serum neutralising antibody GMT response to Vimkunya in adults aged 18–45 years. GMT responses for lots A, B, and C were 1857 (95% CI 1641–2100), 1887 (1672–2130), and 1950 (1724–2207), respectively. The GMT ratios for the pairs of lots (A:B, B:C, and A:C) were 0.98 (95% CI 0.85–1.14), 0.97 (0.84–1.12), and 0.95 (0.82–1.10), respectively. The success criterion for this coprimary endpoint required all three 95% CIs for the GMT ratios to be within the range 0.667–1.5, so this coprimary endpoint was also met. All three co-primary endpoints were met.

At day 15, 2355 (96.8%) of 2434 participants in the Vimkunya group had a seroresponse, compared with three (0.8%) of 395 participants in the placebo group (table 2). The seroresponse rate difference at day 15 was 96.0% (95% CI 94.3–96.8; $p < 0.0001$) and clinically relevant. At day 183, 1967 (85.5%) of 2301 participants in the vaccine group had a seroresponse compared with six (1.5%) of 401 participants in the placebo group ($p < 0.0001$). At day 8, 1169 (46.6%) of 2510 participants in the vaccine group had a seroresponse compared with two (0.5%) of 419 participants in the placebo group ($p < 0.0001$). The Vimkunya group GMT was also significantly higher than that for the placebo group at all investigated timepoints ($p < 0.0001$; appendix pp 12–13).

Analysis by age strata showed that the younger age group had a more rapid and prolonged response (figure 2A; appendix pp 14–15). Although the seroresponse rate was relatively similar, with a peak in all age strata at day 15 and day 22, the largest differences were seen at day 8 and day 183. This early response, however, was more pronounced in adolescents, who had a day 8 seroresponse rate of 70.9% (141 of 199), than in adults, for whom 51.2% (737 of 1440) aged 18–45 years and 33.4% (291 of 871) aged 46–64 years reached the seroresponse threshold. Durability of antibody response was demonstrated up to 6 months after vaccination (overall day 183 seroresponse rate of 85.5% [1967 of 2301]). The durability was higher in the adolescent group (182 [94.8%] of 192) than in the two adult subgroups (18–45 years, 1098 [85.0%] of 1292; and 46–64 years, 687 [84.1%] of 817). The GMT in the vaccine group was highest in those aged 12–17 years (164 at day 8, 1706 at day 15, 2502 at day 22, and 511 at day 183), followed by those aged 18–45 years (115 at day 8, 1369 at day 15, 1878 at day 22, and 323 at day 183), and then those aged 46–64 years (60 at day 8, 709 at day 15, 1175 at day 22, and 322 at day 183; figure 2B).

Participants in the Vimkunya groups had high seroconversion (defined as chikungunya virus serum neutralising antibody $\text{NT}_{80} \geq 15$) and a 4-fold rise over baseline titres at all investigated timepoints (appendix pp 16–17). Seroconversion was seen in 2306 (91.9%) of 2510 vaccine recipients at day 8, 2421 (99.5%) of 2434 at day 15, 2539 (99.2%) of 2559 at day 22, and 2279 (99.0%) of 2301

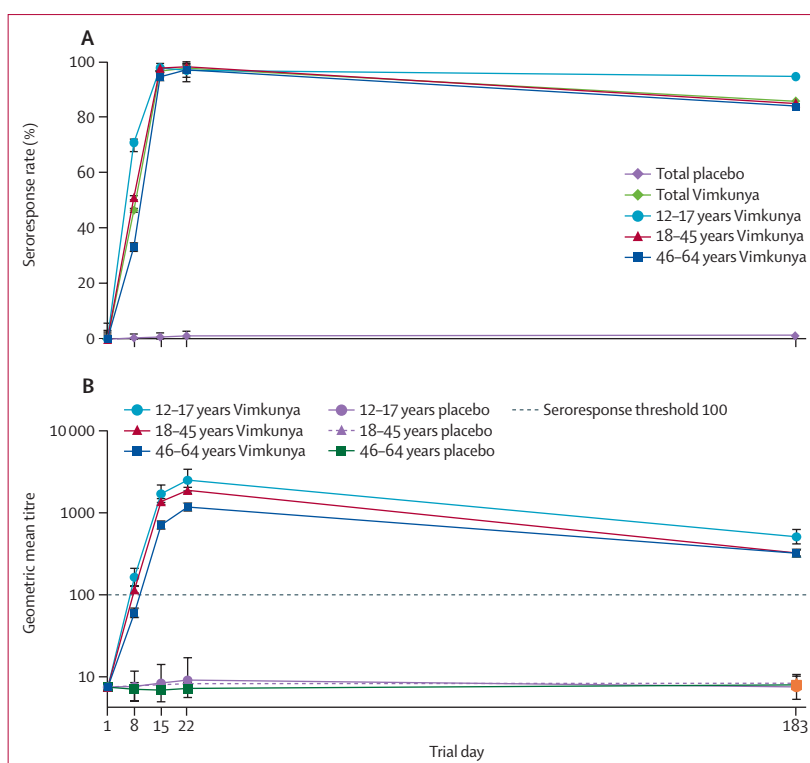


Figure 2: Seroresponse rate (A) and geometric mean titres (B) for chikungunya virus serum neutralising antibodies by visit and by age strata (immunogenicity evaluable population)

The y-axis is represented on a log₁₀ scale. Error bars denote 95% CIs around the geometric mean, calculated based on the Newcombe hybrid score method. Values below the LLOQ were assigned the value LLOQ/2=7.5. LLOQ=lower limit of quantitation.

at day 183. Placebo group participants who had a seroresponse at any timepoint ($n=16$) were investigated and identified as potential sample handling errors, as each of these participants had a serum neutralising antibody NT_{80} 100 or higher result at a single timepoint only, with serum neutralising antibody NT_{80} less than 15 at all other sample collection times.

A post-hoc analysis found that baseline seropositive (defined as day 1 pre-dose serum neutralising antibody $\text{NT}_{80} \geq 15$) Vimkunya group participants' ($n=63$) immune response could be boosted by Vimkunya and had higher serum neutralising antibody titres after vaccination than baseline seronegative vaccine group participants. Baseline seropositive vaccine recipients had a day 1 (baseline) GMT of 253, day 8 GMT of 944, day 15 GMT of 2878, day 22 GMT of 3645, and day 183 GMT of 862. Comparatively, baseline seronegative vaccine recipients (the immunogenicity evaluable population) had a day 1 GMT below the LLOQ, day 8 GMT of 93, day 15 GMT of 1096, day 22 GMT of 1618, and day 183 GMT of 338.

The most frequently reported treatment-related systemic solicited adverse events were fatigue, headache, and myalgia, each occurring in more than 15% of participants in the Vimkunya group (table 3). The most common treatment-related local solicited adverse event

	Vimkunya group (n=2790)	Placebo group (n=464)
Any adverse event	1257 (45.1%)	161 (34.7%)
≥Grade 3	73 (2.6%)	3 (0.6%)
Any unsolicited adverse event	440 (15.8%)	62 (13.4%)
≥Grade 3	31 (1.1%)	1 (0.2%)
Any related unsolicited adverse event	64 (2.3%)	7 (1.5%)
≥Grade 3	1 (<0.1%)	0
Any serious adverse event	23 (0.8%)	1 (0.2%)
Any related serious adverse event	1 (<0.1%)	0
Any adverse event of special interest	6 (0.2%)	1 (0.2%)
Any related adverse event of special interest	3 (0.1%)	1 (0.2%)
Any fatal adverse event	1 (<0.1%)	0
Any local solicited adverse event	661/2765 (23.9%)	49/458 (10.7%)
≥Grade 3	5 (0.2%)	0
Injection site pain	656/2764 (23.7%)	49/458 (10.7%)
Injection site redness	11/2764 (0.4%)	0/458
Injection site swelling	10/2764 (0.4%)	0/458
Any systemic solicited adverse event	891/2765 (32.2%)	114/458 (24.9%)
≥Grade 3	42 (1.5%)	2 (0.4%)
Fatigue	551/2764 (19.9%)	78/458 (17.0%)
Headache	498/2765 (18.0%)	76/458 (16.6%)
Myalgia	486/2764 (17.6%)	44/458 (9.6%)
Chills	238/2764 (8.6%)	15/458 (3.3%)
Arthralgia	214/2764 (7.7%)	33/458 (7.2%)
Nausea	208/2764 (7.5%)	30/458 (6.6%)
Fever	25/2760 (0.9%)	1/457 (0.2%)

Data are n (%) or n/N (%). Participants are counted at most once per sign or symptom by the total number of days for which they reported that event at any severity. Percentages for solicited events are based on the number of participants with at least one diary observation (excluding those not done or unknown) for a given symptom or a given day.

Table 3: Adverse events (safety population)

was injection site pain, reported by 656 (23.7%) of 2764 participants in the vaccine group. Mean duration of treatment-related solicited adverse events in the vaccine group was 2.0 days (SD 1.4), with onset for most on day 1 or day 2. Treatment-related unsolicited adverse events were reported by 64 (2.3%) of 2790 participants in the vaccine group and by seven (1.5%) of 464 participants in the placebo group, most of which were grade 1 or grade 2 in severity (appendix pp 18–20). The single grade 3 treatment-related unsolicited adverse event was a case of dehydration that resolved without medical intervention in the vaccine group. The most common treatment-related unsolicited adverse events that occurred beyond the 7-day solicited event collection window were headache (nine [0.3%] of 2790 participants in the vaccine group vs one [0.2%] of 464 participants in

the placebo group) and arthralgia (seven [0.3%] of 2790 participants vs two [0.4%] of 464 participants). More female participants reported solicited adverse events in both the vaccine group and placebo group (654 [45.8%] of 1429 participants in the vaccine group vs 70 [30.7%] of 228 participants in the placebo group) compared with male participants (404 [30.2%] of 1366 participants vs 54 [23.5%] of 230 participants).

Serious adverse events were reported by 23 (0.8%) of 2790 participants in the vaccine group and one (0.2%) of 464 participants in the placebo group. One serious adverse event, a retinal detachment in a 57-year-old female participant, was assessed as possibly related to trial treatment by the site investigator but was assessed by both the funders and the independent safety monitoring committee chair as unrelated due to previous medical history of seeing black spots in the affected right eye 1 month before enrolment of this participant in the trial.

Adverse events of special interest, defined as new-onset or worsening arthralgia that was medically attended, were reported by seven participants, six (0.2%) of 2790 participants in the vaccine group and one (0.2%) of 464 participants in the placebo group. All adverse events of special interest were grade 1 or 2 in severity. Four adverse events of special interest were assessed as related to trial treatment (three cases of arthralgia in the vaccine group and one case of arthralgia in the placebo group). Treatment-related medically attended adverse events were reported by 14 (0.5%) of 2790 participants in the vaccine group and two (0.4%) of 464 participants in the placebo group, all of which were grade 1 or 2 in severity.

There was one death in the vaccine group, which was unrelated to trial treatment—a 31–35-year-old male participant who was involved in a road traffic accident on trial day 124. Two participants in the vaccine group became pregnant during the trial despite precautionary measures taken to prevent pregnancy, as detailed in the inclusion criteria. One participant, a 26–30-year-old female participant, became pregnant 5.5 months after being vaccinated. Her prenatal care was complicated by gestational hypertension and diabetes and was managed by a high-risk maternal fetal medicine physician. The baby had frontoethmoidal encephalocele, which was assessed as unrelated to trial vaccine. The second pregnancy occurred in a 36–40-year-old female participant, 1 month and 27 days after vaccine administration, and resulted in the birth of a healthy infant.

Discussion

In this pivotal phase 3 trial, the virus-like particle-based chikungunya vaccine was immunogenic in healthy adolescents and adults aged 12–64 years, as shown by 96.8% of participants reaching seroprotective levels of neutralising antibodies at day 15, and 97.8% at day 22. The observed safety profile of Vimkunya is in line with what has been reported for other aluminium-adjuvanted

virus-like particle vaccines.^{21,22} A rapid immune response as early as 1 week after injection was observed, with almost half of participants showing a seroresponse at day 8. This early response was more pronounced in adolescents, who had a day 8 seroresponse rate of 70·9%, compared with adults, where 51·2% of those aged 18–45 years and 33·4% of those aged 46–64 years reached the seroresponse threshold. Durability of antibody response was shown up to 6 months after vaccination. Durability was higher in the adolescent group (94·8%) compared with the two adult subgroups (18–45 years 85·0% and 46–64 years 84·1%). Another phase 3 trial (NCT05349617) confirmed the immunogenicity and durability of Vimkunya in individuals aged 65 years and older. The trend of successively lower immune responses from younger to older age strata is expected, as immune function is known to decline with age. In a systematic review of infectious disease outcomes, it was suggested that peak immune function might occur at age 5–14 years, followed by a rise in infectious disease severity (decreasing immunity) by age 20 years for many infections, and a steeper rise of infections (further decreasing immunity) into older age, although the pattern varies by disease.²³

Post-hoc analysis of 63 participants who received Vimkunya but had detectable amounts of chikungunya virus neutralising antibodies at baseline found that baseline seropositive vaccine recipients appeared to have notably higher serum neutralising antibody titres compared with baseline seronegative vaccine recipients at all timepoints. Despite the small sample size of this analysis, these results provide promising evidence that Vimkunya will be well tolerated and elicit a strong boost response in individuals with previous chikungunya virus infection. Additionally, a phase 2 study of an unadjuvanted version of chikungunya virus virus-like particle vaccine found that the vaccine was well tolerated and immunogenic in individuals with pre-existing immunity.²⁴

Vimkunya was well tolerated, with most adverse events being grade 1 or 2 in severity and self-limiting, with resolution within 2 days. The most frequently reported treatment-related solicited adverse events were fatigue, headache, myalgia, and injection site pain. Serious adverse events were infrequent and the incidence of adverse events of special interest and medically attended adverse events did not differ between the vaccine and placebo groups.

A limitation of this trial is that the determination of Vimkunya effectiveness was based on an immunological surrogate marker. Efficacy against chikungunya virus disease will be investigated in a future clinical endpoint trial in chikungunya virus endemic regions. Another limitation is that the trial population included healthy individuals; further exploration might be useful to assess specific disease populations. Additionally, due to the small number of pregnant participants, the safety of Vimkunya in pregnant and lactating participants could not be established. There were no apparent vaccine pregnancy-related safety signals in the 11 pregnancies across the

Vimkunya clinical development programme nor in the two developmental and reproductive toxicology studies in rabbits and rats. Preliminary durability of protection up to 2 years was shown in phase 2 data (31 [82%] of 38 participants had a seroresponse ≥ 100 at day 760),¹⁷ and further long-term durability up to 5 years after vaccination is being assessed in an ongoing phase 3 trial (NCT06007183). Finally, our immunogenicity threshold is specific to the validated chikungunya virus human serum neutralising antibody assay used in this trial and, thus, cannot be directly compared with thresholds established using other assays.

Vimkunya is based on the virus-like particle platform. Virus-like particles are assembled from viral structural proteins that conformationally resemble wild-type virions but lack genetic material, preventing replication in the host, which reduces the risk of unexpected adverse effects or mutations versus live-attenuated virus vaccines.^{25–27} The virus-like particle platform is a technology with a decades-long track record of safety, as shown by the widespread use of licensed virus-like particle-based vaccines against human papillomavirus (HPV; Gardasil and Cervarix), hepatitis B virus (Engerix B), and hepatitis E virus (Hecolin, approved in China only). Virus-like particle vaccines are also generally not contraindicated for use in immunocompromised populations and pregnant people. Available data for hepatitis B and HPV vaccine showed no increased risk in pregnancy,^{28,29} which represents an advantage over other types of vaccine. A review comparing IXCHIQ with Vimkunya noted that the live-attenuated nature of IXCHIQ might limit its scope of use due to contraindication in immunocompromised individuals.³⁰

In conclusion, Vimkunya offers the first virus-like particle-based vaccine option for immunisation against chikungunya virus disease, providing a potential safe alternative to participants in whom live vaccines are contraindicated. Additionally, Vimkunya is the first chikungunya virus vaccine with safety and immunogenicity data in adolescents aged 12 years and older, providing critical access to chikungunya vaccines for this age stratum. Findings from this pivotal phase 3 trial show that Vimkunya induces a rapid and robust immune response as early as 7 days after vaccination and for at least 6 months, with a favourable safety profile.

Contributors

JSR, DMA, JM, TL, SRT, RR, KLW, PA, and LB contributed to the trial concept and design. JTC and the EBSI-CV-317-004 Study Group contributed to acquisition of data. JM supervised the serological analyses. JSR, DMA, SM, VAJ, PA, and LB supervised the trial. DMA and LB analysed and verified the data presented in the manuscript. JSR, DMA, LCT, and LB interpreted the data. LCT drafted the manuscript. All authors had full access to all the data in the trial, reviewed the manuscript, approved the final version, and had final responsibility for the decision to submit for publication.

Declaration of interests

All authors worked on this study while employed or contracted by Bavarian Nordic or Emergent BioSolutions.

Data sharing

The trial protocol (https://cdn.clinicaltrials.gov/large-docs/80/NCT05072080/Prot_000.pdf) and statistical analysis plan (https://cdn.clinicaltrials.gov/large-docs/80/NCT05072080/Stat_000.pdf) are available.

clinicaltrials.gov/large-docs/80/NCT05072080/SAP_001.pdf) are available on ClinicalTrials.gov. De-identified individual participant data will be made available after publication to researchers who provide a scientifically sound proposal by application to the corresponding author and sign a data sharing agreement.

Acknowledgments

We thank all participants, investigators, and trial site personnel who took part in this clinical trial. We also thank all employees of Bavarian Nordic and Emergent BioSolutions, past and present, and the members of the safety monitoring committee. Funding was provided by Emergent BioSolutions and Bavarian Nordic (as a successor in interest to Emergent BioSolutions).

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