



Chikungunya virus virus-like particle vaccine safety and immunogenicity in adults older than 65 years: a phase 3, randomised, double-blind, placebo-controlled trial

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Summary

Background Adults older than 65 years are at increased risk for atypical presentations of chikungunya disease, as well as for severe outcomes including death.

Methods In this phase 3, randomised, double-blind, placebo-controlled, parallel-group trial, adults aged 65 years and older received a single intramuscular dose of Vimkunya (previously chikungunya virus virus-like particle vaccine) or placebo at ten sites in the USA. Participants, clinical site personnel, and the sponsor were masked to individual treatment assignments until all participants had completed their involvement in the trial and the database was cleaned and locked. Baseline and postvaccination chikungunya virus serum neutralising antibody (SNA) titres (NT₈₀) were assessed at selected timepoints. Safety was assessed up to 183 days after dose administration in all participants from the exposed population who provided safety assessment data. This trial is registered with ClinicalTrials.gov, NCT05349617, and is completed.

Findings Between May 12 and Dec 2, 2022, 413 participants were recruited and randomly assigned (1:1) to receive the Vimkunya vaccine (n=206) or placebo (n=207). The coprimary endpoints of immunologic superiority of chikungunya virus SNA titres compared with placebo and geometric mean titre at day 22 were met. Vimkunya induced a protective seroresponse (SNA NT₈₀≥100, considered the presumptive seroprotective antibody response) in 149 (82%) of 181 participants (95% CI 76·1–87·2) at day 15, in 165 (87%) of 189 participants (81·8–91·3) at day 22, and in 139 (76%) of 184 participants (68·9–81·2) at day 183. Although there was a slightly higher early immune response in the 65–74 years age group at day 15 compared with the 75 years and older age group, the seroresponse rates at day 22 and day 183 were similar. There were no notable differences in adverse event rates between groups, and most adverse events were grade 1 or 2 in severity and of short duration. No vaccine-related serious adverse events or deaths occurred.

Interpretation We provide robust data from adults aged 65 years and older showing that Vimkunya is well tolerated and can provide a high rate of protection within 2 weeks postvaccination and during 6 months of follow-up.

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Introduction

Chikungunya virus is transmitted to humans through the bite of infected mosquitoes.¹ In the human host, the virus incubates for 1–12 days before reaching high viraemia levels and inducing initial symptoms of fever and influenza-like syndrome.² There is no specific antiviral treatment for chikungunya and clinical management is supportive.³ Individuals with acute febrile chikungunya commonly present with fever and joint pain; other symptoms can include joint stiffness or swelling, muscle pain, low appetite, fatigue, headache, and rash.⁴ In nearly half of chikungunya virus cases, chronic symptoms such as continual or recurrent arthralgias, depression, and mood and sleep disorders persist for months or years,^{5–7} with a severe effect on quality of life and daily productivity. Advanced age and severe acute symptoms are associated with worse arthritic sequelae.⁸ Additionally, advanced age

has been associated with atypical (ie, neurological, cardiovascular, dermatological, ophthalmological, hepatic, renal, respiratory, or haematological) and severe disease presentations when compared with younger individuals, potentially due to the increased presence of comorbidities and age-related immune system decline in older adults.^{9,10} Although the overall mortality rate from chikungunya disease is low, the risk of death increases with age. A retrospective study of 127 deaths from chikungunya over a 4-year period in Brazil found that, whereas the overall fatality rate was 0·35%, the risk of death from chikungunya progressively increased from age 40 years, with a 14 times greater risk among individuals aged 40–49 years (95% CI 2–106), a 28 times greater risk among those aged 50–59 years (4–206), and a 79 times greater risk among those aged 60 years and older (11–567), compared with the reference age group of 20–29 years.¹¹

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See Online for appendix

Research in context

Evidence before this study

Before this trial, there were no licensed vaccines to prevent chikungunya virus infection or disease and this was cited as an unmet need by WHO, the Coalition for Epidemic Preparedness Innovations, and the US Centers for Disease Control and Prevention. Vimkunya received US Food and Drug Administration and European Commission approval in February, 2025, for active immunisation to prevent disease caused by chikungunya virus infection in individuals aged 12 years and older. Additionally, one live-attenuated vaccine delivered as a single dose after reconstitution, IXCHIQ, received regulatory approval by the US Food and Drug Administration (November, 2023), Health Canada (June, 2024), and the European Commission (July, 2024) for the prevention of disease caused by chikungunya virus in individuals aged 18 years and older who are at increased risk of exposure to chikungunya virus. Immune function is known to decline with age, so it is important to assess older adult age groups during vaccine development.

Added value of this study

Two pivotal phase 3 trials in individuals aged 12 years and older have been completed with the Bavarian Nordic (Hellerup, Denmark) virus-like particle-based chikungunya virus vaccine (NCT05072080 and NCT05349617). The present trial provides data specifically for older adults aged 65 years and older

(206 receiving Vimkunya and 207 receiving placebo), with immunogenicity results for 149 participants aged 65–74 years and 40 participants aged 75 years and older. The results show that Vimkunya induced a presumptive seroprotective antibody response in 82% of participants 14 days postvaccination, 86% at 21 days postvaccination, and 76% at 182 days. Vimkunya was also seen to have a favourable safety profile; most adverse events were self-limited and grade 1 or 2 in severity.

Implications of all the available evidence

Vimkunya has the potential to offer safe and rapid onset of protection for a wide range of travellers. The US Advisory Committee on Immunization Practices recommends chikungunya vaccination for people aged 18 years and older travelling to a country or territory where there is a chikungunya virus outbreak. There are additional recommendations for people older than 65 years travelling to a country or territory without an outbreak but with evidence of chikungunya virus transmission among humans within the last 5 years, particularly for individuals with underlying medical conditions or a prolonged duration of travel. Here we provide data from a robust chikungunya virus vaccine trial of individuals aged 65 years and older, showing that Vimkunya is well tolerated and can provide a high rate of protection within 2 weeks postvaccination and through 6 months of trial follow-up.

Chikungunya virus vaccination is of particular importance for international travellers, both for personal disease prevention and to prevent seeding of outbreaks in non-endemic countries upon return.¹² In a study of 1202 travellers with chikungunya in 2005–20, individuals older than 65 years accounted for 8·5% of cases (median age 43 years [IQR 31–55]),¹³ and this proportion is expected to increase with the growing population of older adults worldwide.^{14,15} With overall larger numbers of older adults and older international travellers, there is a higher incidence of infectious diseases and a greater need for vaccine programmes that target this group.¹⁵ Infection due to international travel can have substantial cost impacts, including the cost of hospitalisation abroad, non-refundable travel costs incurred due to illness, and loss of income due to missing work.¹⁶ Although the safety and efficacy of Vimkunya have not been assessed in special populations, other virus-like particle (VLP) vaccines have been shown to be generally safe, particularly in populations for whom live-attenuated vaccines have been contraindicated (eg, pregnant or immunocompromised individuals), owing to the inability of VLPs to replicate.^{17,18}

The immunogenicity threshold used in this trial was defined based on a non-human primate passive antibody transfer and challenge study in which human sera from chikungunya virus VLP-vaccinated individuals was used

to prevent viraemia following wild-type chikungunya virus challenge in cynomolgus macaques. In non-human primates, a serum neutralising antibody (SNA) titre of 23·6 was estimated to be associated with an 80% probability of protection from chikungunya virus. On the basis of these results, a conservative threshold of SNA titre (NT₈₀) of 100 was selected as the protective threshold in humans (US Food and Drug Administration and European Medicines Agency agreed threshold) and was the basis of the seroresponse threshold for phase 3 trial endpoints.

Vimkunya (previously chikungunya virus VLP vaccine and PXVX0317)¹⁹ is a formulation of 40 µg chikungunya virus VLP adjuvanted with aluminium hydroxide adjuvant and supplied as a prefilled syringe for ease of use, improved dosing accuracy, reduced risk of administrative errors, and faster preparation and administration time.^{20,21} Findings from studies in adults are not necessarily applicable to older adults, and it is important to assess immunogenicity and efficacy of vaccines in older age groups as these can be greatly reduced compared with younger individuals.¹⁵ Due to immunosenescence and the associated reduction in T-cell responses that occur with ageing, direct evaluation of the safety and effectiveness of Vimkunya in older adults provides essential information on the benefits and risks in this population. Here we report safety, tolerability,

and immunogenicity for Vimkunya in a robust population of adults aged 65 years and older for up to 6 months postvaccination.

Methods

Study design

In this phase 3, randomised, placebo-controlled, double-blind, parallel-group, multicentre trial, generally healthy participants aged 65 years and older were recruited at ten clinical trial sites in the USA. The trial was conducted 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 Western-Copernicus Group (Princeton, NJ, USA) Institutional Review Board (20220872). This trial is registered with ClinicalTrials.gov, NCT05349617.

Participants

We recruited 413 participants through contracted clinical site databases, advertising, and recruitment agencies. Sex (both birth and self-identified), race (self-identified), and ethnicity (self-identified) data were collected. 242 (59%) participants were female and 171 (41%) were male. Eligible participants were healthy adults aged 65 years and older. Key exclusion criteria were participation in another investigational clinical trial 30 days before day 1 or during the trial, previous receipt of any chikungunya virus vaccine, current HIV or hepatitis B or C infection, BMI of 35 kg/m² or higher, history of allergy to a component of the trial drug, history of any known immunodeficiency that could affect response to vaccination, moderate or severe acute disease, 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 appendix 1 (pp 3–4). Written informed consent was obtained before any trial procedure.

Randomisation and masking

Participants were stratified into two age strata (65–74 years and ≥75 years) and randomly assigned (1:1) to receive either Vimkunya or placebo (the same excipient composition without chikungunya virus VLP or aluminium hydroxide components). A randomisation module generated a randomisation number that matched a masked vaccine or placebo kit available at the site. 400 participants were planned for enrolment. Participants, clinical site personnel, and the sponsor were all masked to 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 sponsor testing laboratory had access to any data pertaining to trial participants and results, the sample testing operators did not have access, and

sponsor sample testing staff only had access to a randomly assigned barcode. The assay titre results were not delivered to the sponsor data management and analysis team until after database lock.

Procedures

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

Participants were monitored for signs of an acute adverse reaction to vaccination for 30 min. Solicited adverse events were collected from injection administration on day 1 up to day 8 using 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 of 38·0°C (100·4°F) or higher, chills, fatigue, headache, myalgia, arthralgia, and nausea. Unsolicited adverse events were collected from day 1 up to day 29. 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 postvaccination up to day 183. The investigator assessed all adverse events for severity as grade 1 (mild), grade 2 (moderate), grade 3 (severe), or grade 4 (potentially life-threatening). The investigator assessed adverse event causality. If the relationship between the adverse event and the trial drug was determined to be possible or probable, the event was considered related.

An independent safety monitoring committee reviewed aggregated, masked safety data after the first 50 participants completed 7 days of safety follow-up. The remaining participants were enrolled following the safety review.

A luciferase-based chikungunya virus human SNA assay was used to measure SNA NT₈₀ against chikungunya virus in human serum samples (appendix 1 p 5). Seroprotection rate was defined as the proportion of participants with SNA NT₈₀ of 100 or higher (presumptive seroprotection rate agreed with the US Food and Drug Administration and European Medicines Agency).

Protocol deviations were reviewed on an ongoing basis during the trial. 95 (23%) participants had at least one important protocol deviation, including 83 (20%) out-of-window or missed visits, four (1%) non-compliance, and three (1%) eligibility. No participants received the wrong treatment.

Outcomes

The objective of this trial was to evaluate the safety and immunogenicity of Vimkunya. The coprimary endpoints were difference in chikungunya virus SNA seroprotection rate (vaccine minus placebo) at day 22, and chikungunya

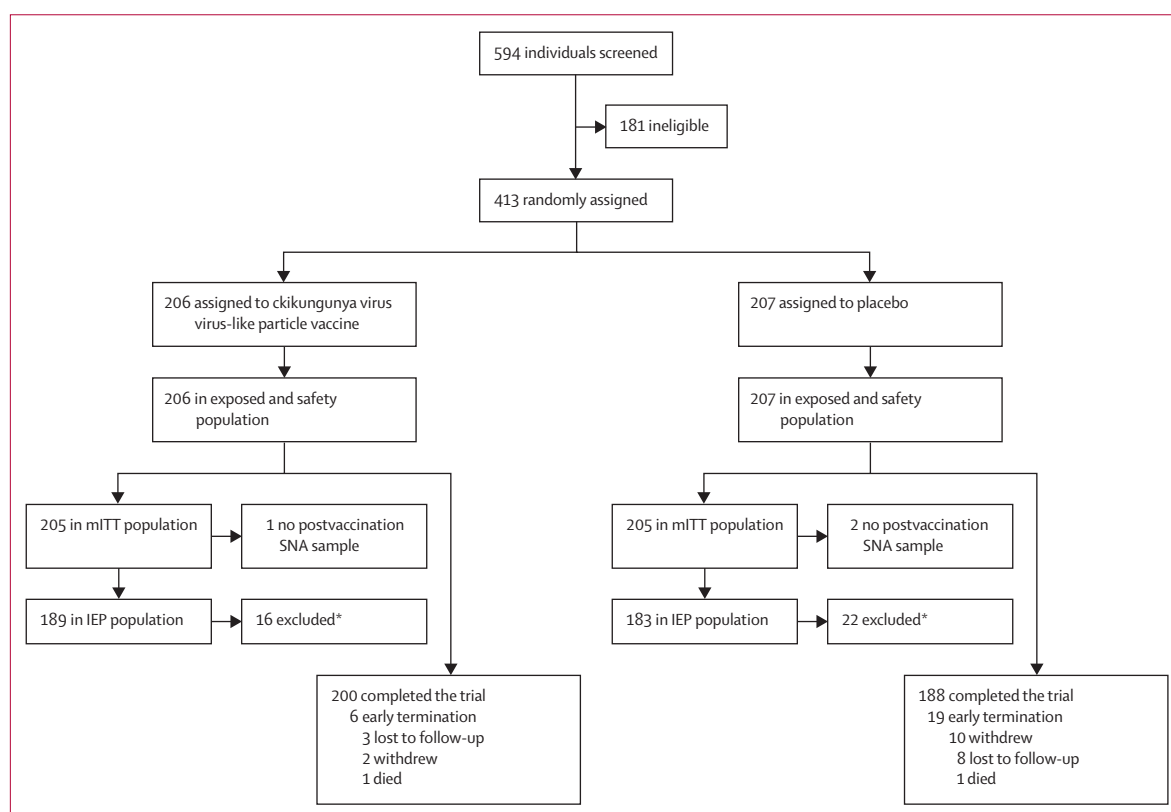


Figure 1: Trial profile

IEP=immunogenicity evaluable population. mITT=modified intention-to-treat. SNA=serum neutralising antibody. *Exclusions from IEP were due to no SNA result in 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.

virus SNA geometric mean titre (GMT) at day 22 for the vaccine and placebo.

The key secondary endpoints were the difference in chikungunya virus SNA seroresponse rates at day 15 and day 183, in that order. Other secondary endpoints were chikungunya virus SNA GMTs by trial arm at day 15 and day 183, geometric mean fold increase from day 1 to subsequent collection timepoints, and number and proportion of participants with SNA NT₈₀ of 15 or higher and a four-fold rise over baseline.

Safety endpoints were incidence of solicited adverse events from vaccination up to day 8; incidence of unsolicited adverse events up to day 29; and incidence of adverse events of special interest, medically attended adverse events, and serious adverse events up to day 183.

Statistical analysis

The sample size was chosen based on expected seroresponse rate to be approximately 90% versus less than 5% for participants assigned to placebo at day 22. With an assumed 10% rate of non-evaluable participants, the power to show superiority over placebo with 180 evaluable participants assigned to Vimkunya and 180 to placebo was greater than 99.9% for the combined age strata. The difference in seroresponse rate between vaccine and placebo groups that was considered clinically

relevant was 70% or higher. With 180 baseline seronegative vaccine-treated participants and a target seroresponse rate of 90% versus a rate of 5% for placebo, the width of a two-sided 95% CI would be 5.4%. If the target vaccine seroresponse were 77%, the width would be 6.9%. Therefore, the difference in seroresponse rate was required to be above 77% for the lower bound of the 95% CI for the difference to be 70% or higher.

The exposed population comprised all participants who received a Vimkunya or placebo injection. The safety population comprised all participants from the exposed population who provided safety assessment data. The modified intention-to-treat population comprised all participants who were vaccinated and had at least one post-injection chikungunya virus SNA result. The immunogenicity evaluable population (IEP) comprised participants in the modified intention-to-treat population who had no measurable chikungunya virus SNA at day 1 (below the lower limit of quantitation [LLOQ]), had evaluable SNA 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 SNA NT₈₀ calculated to determine the chikungunya virus neutralising antibody response. The difference between treatment groups in seroresponse rate (proportion of

participants with SNA NT₈₀≥100) was tested using a χ^2 test with a two-sided α of 0·05 in the IEP across both age strata combined, and the two-sided 95% CI for the difference was computed using the Newcombe hybrid score method. In the computation of the GMTs, values below the assay LLOQ of 15 were assigned the value 7·5. The GMTs were compared between the Vimkunya and placebo treatment groups and were analysed via a linear model based on a two-sided α of 0·05. The primary model was an ANOVA, with logarithmically transformed chikungunya virus SNA titres (log₁₀) as the dependent variable and treatment group and trial site as the fixed effects in the model. The adjusted least-squares means and their 95% CIs calculated based on the ANOVA were backtransformed and reported as the group GMT values. The proportion of participants with seropositivity (SNA NT₈₀≥15; ie, above the LLOQ) and those with a four-fold increase in titre over baseline were also summarised. 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, frequency, and proportion of participants with either solicited or unsolicited adverse events were summarised descriptively, including duration and investigator-assessed severity and causality of the events observed.

Role of the funding source

Employees of the funders were responsible for trial design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between May 12 and Dec 2, 2022, 594 volunteers were screened for this trial, of whom 413 were deemed eligible and randomly assigned (1:1) to receive either the vaccine or placebo. The IEP included 372 participants, of whom 189 (51%) received Vimkunya and 183 (49%) received placebo (figure 1).

There was no appreciable difference in demographic characteristics between the Vimkunya and placebo groups (table 1). In the randomly assigned population, 242 (59%) participants were female and 171 (41%) were male. 318 (77%) participants were aged 65–74 years (159 [77%] of 206 in the vaccine group and 159 [77%] of 207 in the placebo group) and 95 (23%) were aged 75 years and older (47 [23%] in the vaccine group and 48 [23%] in the placebo group). 344 (83%) participants in the randomly assigned population were White, 49 (12%) were Black or African American, and 20 (5%) were of other races or not reported. Notably, 183 (44%) participants had Hispanic or Latino ethnicity.

At day 22, 165 (87%) of 189 participants in the Vimkunya group had a seroresponse (SNA NT₈₀≥100) compared with two (1%) of 183 participants in the placebo group for the IEP (table 2). The difference in seroresponse rate was 86% (95% CI 80–90), which was statistically significant

($p<0\cdot0001$, χ^2 test) and clinically relevant (lower bound of 95% CI ≥70%; appendix 1 pp 9–10). The chikungunya virus SNA GMT at day 22 was 724 for the vaccine group and 8 for the placebo group, for a GMT ratio of 90 (69–117; $p<0\cdot0001$, ANOVA) for the IEP (appendix 1 pp 11–12). All coprimary endpoints were met.

At day 15, 149 (82%) of 181 participants in the Vimkunya group had a seroresponse, compared with five (3%) of

	Vimkunya (n=206)	Placebo (n=207)
Age, years		
Mean (SD)	71·5 (5·3)	70·8 (4·5)
Median (range)	70 (65–95)	70 (65–84)
Sex		
Female	125 (61%)	117 (57%)
Male	81 (39%)	90 (43%)
Age group		
65–74 years	159 (77%)	159 (77%)
≥75 years	47 (23%)	48 (23%)
Race		
White	176 (85%)	168 (81%)
American Indian or Alaska Native	1 (<1%)	1 (<1%)
Asian	4 (2%)	1 (<1%)
Black or African American	20 (10%)	29 (14%)
Multiracial	4 (2%)	5 (2%)
Not reported	1 (<1%)	3 (1%)
Ethnicity		
Hispanic or Latino	93 (45%)	90 (43%)
Not Hispanic or Latino	112 (54%)	116 (56%)
Not reported	1 (<1%)	1 (<1%)
BMI, kg/m ²		
Mean (SD)	27·3 (4·0)	27·6 (3·9)
Median (range)	27·5 (17·5–34·8)	27·5 (19·3–34·9)
Baseline chikungunya virus SNA serostatus		
Negative (<LLOQ)	201 (98%)	196 (95%)
Positive (≥LLOQ)	5 (2%)	10 (5%)
Missing	0	1 (<1%)

Data are n (%) unless otherwise specified. LLOQ=lower limit of quantitation (SNA 80 titre <15). SNA=serum neutralising antibody.

Table 1: Baseline characteristics of the randomly assigned population

	Seroresponse rate in Vimkunya group (n=189)	Seroresponse rate in placebo group (n=183)	Seroresponse rate difference	p value
Day 15	149/181 (82% [76–87])	5/176 (3% [1–7])	80% (72–85)	<0·0001
Day 22	165/189 (87% [82–91])	2/183 (1% [0–4])	86% (80–90)	<0·0001
Day 183	139/184 (76% [69–81])	2/173 (1% [0–4])	74% (67–80)	<0·0001

Data are n/N (% [95% CI]), rate difference (95% CI), or p. Seroresponse rate difference is defined as seroresponse rate in the vaccine group minus that in the placebo group (immunogenicity evaluable population). 95% CIs are based on the Newcombe hybrid score method. p value is from 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 serum neutralising antibody seroresponse rate and seroresponse rate difference by trial visit

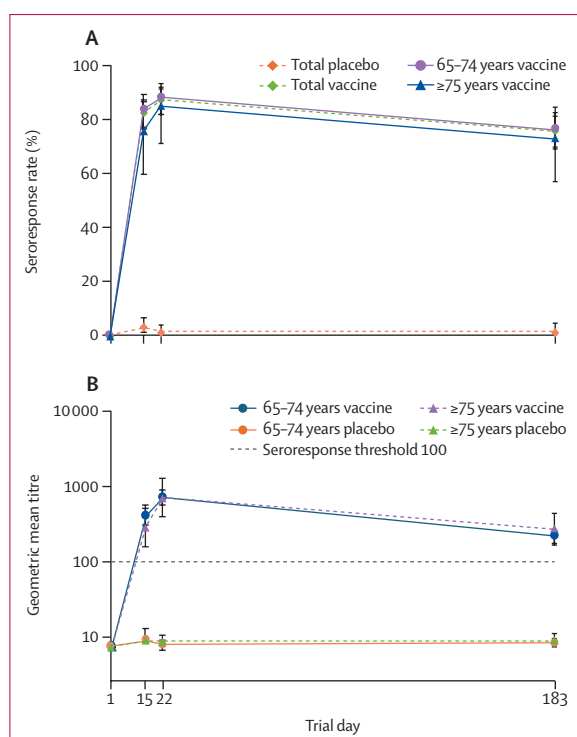


Figure 2: Seroreponse rate (A) and geometric mean titres (B) for chikungunya virus serum neutralising antibodies by visit and by age strata. Data are for the immunogenicity evaluable population. The y-axis in (B) is on a log₁₀ scale. Vertical bars denote 95% CIs. Values below the lower limit of quantitation (15) were assigned the value 7.5.

176 participants in the placebo group. The seroreponse rate difference at day 15 was 80% (95% CI 72–85), which was statistically significant ($p < 0.0001$, χ^2 test) and clinically relevant (lower bound of 95% CI $\geq 70\%$). At day 183, 139 (76%) of 184 participants in the vaccine group had a seroreponse, compared with two (1%) of 173 in the placebo group ($p < 0.0001$, χ^2 test).

Both SNA NT₈₀ GMT and geometric mean fold increase were significantly higher in the Vimkunya group than in the placebo group on all trial days after vaccination (appendix 1 pp 11–12). In the vaccine group, the SNA GMT increased from below the LLOQ at day 1 to a titre of 378 at day 15, followed by a rise to a peak titre of 724 at day 22, and then decreased to 233 at day 183. This change corresponded to a geometric mean fold increase of 49 at day 15, 94 at day 22, and 29 at day 183. Nearly all participants had a measurable SNA response to Vimkunya. Seroconversion (SNA NT₈₀ ≥ 15) was seen in 171 (95%) of 181 vaccine recipients at day 15, 180 (95%) of 189 at day 22, and 171 (93%) of 184 at day 183 (appendix 1 p 15). The nine participants in the placebo group who had a seroreponse were investigated and identified as potential sample handling errors, as each of these participants had an SNA NT₈₀ result of 100 or higher at a single timepoint only, with SNA NT₈₀ below 15 at all other sample collection times.

	Vimkunya (n=206)	Placebo (n=207)
Any adverse event (solicited and unsolicited)	47 (23%)	52 (25%)
$\geq$ Grade 3	4 (2%)	3 (1%)
Any unsolicited adverse event	26 (13%)	34 (16%)
$\geq$ Grade 3	4 (2%)	3 (1%)
Any related unsolicited adverse event	4 (2%)	6 (3%)
$\geq$ Grade 3	1 (<1%)	0
Any serious adverse event	4 (2%)	3 (1%)
Any related serious adverse event	0	0
Any adverse event of special interest	0	1 (<1%)
Any related adverse event of special interest	0	0
Any fatal adverse event	1 (<1%)	1 (<1%)
Any local solicited adverse event	11 (5%)	4 (2%)
$\geq$ Grade 3	0	0
Injection site pain	11 (5%)	3 (1%)
Injection site redness	0	1 (<1%)
Injection site swelling	0	0
Any systemic solicited adverse event	22 (11%)	27 (13%)
$\geq$ Grade 3	1 (<1%)	0
Myalgia	13 (6%)	13 (6%)
Fatigue	13 (6%)	12 (6%)
Headache	9 (4%)	15 (7%)
Arthralgia	6 (3%)	8 (4%)
Chills	6 (3%)	6 (3%)
Nausea	6 (3%)	3 (1%)
Fever	0	2 (1%)

Data are n (%). Relationship is investigator's assessment. Percentages are based on the number of participants in the safety population in each treatment group. Participants are counted at most once in each category. Percentages for solicited events are based on the number of participants with at least one diary observation (excluding not done or unknown) for a given symptom or a given day.

Table 3: Summary of adverse events

By age strata, the seroreponse rate for day 15 showed a trend that the younger age group elicited a more rapid response (figure 2A, appendix 1 pp 13–14). In the 65–74 years age group, the seroreponse rate for the vaccine group was 84% at day 15, 88% at day 22, and 76% at day 183, compared with 76% at day 15, 85% at day 22, and 73% at day 183 in the 75 years and older age group. The GMT at day 15 was higher in the 65–74 years age group (407) compared with the 75 years and older age group (299), at day 22 the GMTs were similar (726 for 65–74 years vs 716 for ≥ 75 years), and at day 183 the GMT was slightly higher in the older age group (222 for 65–74 years vs 281 for ≥ 75 years; figure 2B).

47 (23%) of 206 participants who received the Vimkunya vaccine had an adverse event, compared with 52 (25%) of 207 participants in the placebo group (table 3). Four (2%) participants in the Vimkunya group and three (1%) in the placebo group had adverse events that

were grade 3 or higher. 25 (12%) participants in the vaccine group and 28 (14%) in the placebo group reported a solicited adverse event, and a single participant in the vaccine group had two grade 3 solicited adverse events (headache and fatigue). The most reported systemic solicited adverse events were myalgia (13 [6%] participants in the vaccine group and 13 [6%] in the placebo group) and fatigue (13 [6%] in the vaccine group and 12 [6%] in the placebo group). The most reported local solicited adverse event was injection site pain, reported by 11 (5%) participants in the vaccine group and three (1%) in the placebo group. 26 (13%) participants in the vaccine group and 34 (16%) in the placebo group had unsolicited adverse events, with four (2%) in the vaccine group and six (3%) in the placebo group having treatment-related unsolicited adverse events (appendix 1 p 16). There was one treatment-related unsolicited adverse event in the vaccine group that was grade 3 or higher (grade 3 fatigue).

Four (2%) participants in the vaccine group and three (1%) in the placebo group had a serious adverse event, none of which was treatment related. One participant in the placebo group had an adverse event of special interest, defined as new-onset or worsening arthralgia that was medically attended (grade 2 joint dislocation). Two participants in the vaccine group had treatment-related medically attended adverse events (grade 3 fatigue and grade 1 hypertension). There were two fatal serious adverse events, one in the vaccine group and one in the placebo group, neither of which was treatment related (respiratory failure and lung cancer).

Discussion

Immunosenescence, the progressive age-related decline of the immune system, is associated with increased susceptibility, severity, and mortality from infectious diseases as well as a diminished response to vaccination in older adults.²² In this phase 3 trial, we provide results from a robust population of individuals aged 65 years and older. The Vimkunya vaccine was immunogenic in this age group, as shown by 87% of participants reaching seroprotective levels of antibodies and vaccine superiority to placebo in GMTs at day 22 postvaccination. Vimkunya also produced early seroprotective antibody levels in 82% of participants at day 15 and persisted up to day 183 of follow-up in 76% of participants. The early seroresponse at day 15 is particularly beneficial to travellers who receive their travel vaccinations 2 weeks or less before departure,²³ as they can expect to have some protection from chikungunya.

We performed a subgroup analysis of immune responses to Vimkunya by age strata (65–74 years and ≥75 years). Although there appeared to be a slightly higher early immune response in the 65–74 years age group at day 15 (seroresponse rate 84%) compared with the 75 years and older age group (76%), the seroresponse rates at day 22 (88% for age 65–74 years and 85% for age ≥75 years) and at day 183 (76% for age 65–74 years and 73% for age ≥75 years)

were similar. An unpublished analysis looking at the relationship between age and SNA titres at day 22 in the treated population showed a plateau around age 65 years, which is consistent with the findings in this study.

Vimkunya was well tolerated, with most adverse events being self-limited and grade 1–2 in severity. There were no notable differences in solicited or unsolicited adverse event rates between treatment groups. The most frequently reported systemic solicited adverse events were myalgia and fatigue, each occurring in more than 5% of participants in both the vaccine and placebo groups. The most common local solicited adverse event was injection site pain. On average, the duration of symptoms for treatment-related solicited adverse events in the vaccine group was 2·1 days, with day 2 being the most common day of symptom onset. Serious adverse events were infrequent (<2%), with none considered related to the investigational product. The incidence of adverse events of special interest and medically attended adverse events did not differ between the vaccine group and the placebo group.

As the older adult population continues to increase worldwide, it is important that travel medicine targets these travellers for vaccination programmes as immunosenescence and comorbidities increase their risk of morbidity and mortality from infectious diseases.^{14,15} The US Advisory Committee on Immunization Practices recognises the increased need for chikungunya disease protection in older adults and, in addition to recommending chikungunya vaccination for persons aged 18 years and older travelling to a country or territory where there is a chikungunya virus outbreak, they provide further recommendations for persons aged 65 years and older—particularly those with underlying medical conditions—travelling to a country or territory without an outbreak but with evidence of chikungunya virus transmission among humans within the last 5 years. Risk factors for hospitalisation include very young age and older age as well as certain pre-existing comorbidities, including cardiovascular or respiratory conditions, hypertension, and diabetes.^{24,25} There is a growing global population of older adults and vaccination is an essential approach to protection against chikungunya disease.¹⁵

VLP structures closely mimic the structures of the native virus, and VLP vaccines tend to be immunogenic at lower doses. VLP vaccines have an advantage over conventional vaccines (live-attenuated and inactivated vaccines) as VLPs do not replicate, making them generally safe, particularly in populations for whom live-attenuated vaccines have been contraindicated (eg, pregnant or immunocompromised individuals).^{26,27} Although there is a live-attenuated chikungunya virus vaccine available,²⁸ Vimkunya provides a well tolerated and immunogenic VLP vaccine option.

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 to be conducted in chikungunya virus endemic regions. Another limitation is that the trial population included healthy individuals; further trials are needed to assess specific disease populations. Additional trials are currently underway to assess Vimkunya long-term safety and a booster dose (NCT06007183), which includes follow-up from the participants of the present trial.

Vimkunya is the only VLP-based vaccine option indicated for active immunisation to prevent disease caused by chikungunya virus infection in individuals aged 12–64 years (NCT05072080) and 65 years and older. Findings from this pivotal phase 3 trial provide robust data in older adults aged 65 years and older that show that the chikungunya virus VLP platform delivers a non-replicating, safe, and immunogenic chikungunya vaccine option for a wide range of travellers. Vimkunya induces a rapid and robust immune response in most individuals by 14 days postvaccination, with protection lasting throughout the 6 months of trial duration.

Contributors

JSR, DMA, JM, TL, SRT, RR, LB, and PA contributed to trial concept and design. JM supervised the serological analyses. JSR, DMA, SM, VAJ, LB, and PA supervised the trial. DMA and LB analysed and verified the data presented in the manuscript. LCT, JSR, DMA, and LB interpreted the data. LCT drafted the manuscript. All authors had full access to all the data in the study, reviewed the manuscript, approved the final version, and had final responsibility for the decision to submit for publication.

Declaration of interests

All authors performed work while employed or contracted by Bavarian Nordic or Emergent BioSolutions.

Data sharing

The statistical analysis plan is provided at https://cdn.clinicaltrials.gov/large-docs/17/NCT05349617/SAP_001.pdf and the trial protocol is in appendix 2 (pp 1–78). 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.

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