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Comprehensive Clinical Evaluation Demonstrates Favorable Safety, Robust Neutralizing Antibody Responses, and Broad Population Immunogenicity to a Chikungunya Virus Virus-like Particle Vaccine (VIMKUNYA)

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Abstract

The chikungunya virus (CHIKV) virus-like particle (VLP) vaccine, VIMKUNYA™, has demonstrated favorable safety and immunogenicity throughout its clinical development program. Here, we present aggregated safety outcomes from 5 phase 2/3 trials and immunogenicity outcomes from 4 trials conducted at multiple US sites in healthy participants aged 12 to 95 years. Participants received a single intramuscular 40 μg dose of CHIKV VLP vaccine or placebo. Immunogenicity was assessed using serum neutralizing antibody (SNA) titers (NT_{80}), geometric mean titers (GMTs), and seroresponse rates at predefined timepoints. Preclinical nonhuman primate (NHP) data indicated that the regulatory clinical seroresponse threshold (NT_{80} ≥100) is more conservative, approximately 4-fold higher than titers associated with sterilizing immunity, prompting exploratory analyses at additional thresholds: NT_{80} ≥25.7 (associated with sterilizing immunity in NHPs) and NT_{80} ≥15 (assay lower level of quantitation). This exploration of other relevant thresholds may provide valuable context for healthcare professionals and policy makers when evaluating immunization strategies. The CHIKV VLP vaccine elicited rapid and robust neutralizing antibody responses: 47% of recipients achieved NT_{80} ≥100 at 7 days postvaccination (Day 8), rising to 96% at 2 weeks and 97% by 3 weeks postvaccination, with 85% maintaining seroresponse at 6 months (Day 183). At Day 8, 92% of participants achieved the NT_{80} ≥15 assay threshold and 86% achieved the NHP NT_{80} ≥25.7 biological threshold; at Day 183 these responses were maintained by 99% and 98%, respectively. Younger participants and females exhibited more rapid early responses and more sustained seroresponse at later timepoints, reflecting age- and sex- associated immunologic gradients. The vaccine was well-tolerated; most adverse events were mild or moderate, predominantly injection site pain, headache, fatigue, and myalgia. No vaccine-related safety signals or cases of CHIKV-like illness were identified. Older adults reported fewer solicited and unsolicited adverse events than younger age groups, and no treatment-related serious adverse events observed, supporting a favorable safety profile across all age groups. Together, these findings demonstrate that a single dose of CHIKV VLP vaccine induces rapid, high-magnitude, and durable neutralizing immunity with a favorable safety profile, supporting its use in individuals aged ≥ 12 years and its suitability for broad public health implementation.

Introduction

Chikungunya virus (CHIKV) is a mosquito-borne virus that continues to pose a significant and growing global health threat, with outbreaks increasingly reported in new regions due to climate change and expanding mosquito habitats. In July 2025, the World Health Organization issued an alert warning that rapidly expanding CHIKV outbreaks, first detected in the Indian Ocean islands, were spreading to Africa, South Asia, and Europe, placing 5.6 billion people in 119 countries at risk and prompting calls for urgent strengthening of surveillance and vector control to prevent widespread epidemics[1,2]. Furthermore, in February 2026, the Pan American Health Organization issued an epidemiological alert warning of a sustained rise in CHIKV cases across multiple countries in the Americas, including the reemergence of local transmission in areas previously free of the virus, and called on countries to intensify surveillance,

clinical preparedness, risk communication, and integrated vector control to mitigate further spread[3]. The acute phase of CHIKV infection is characterized by symptoms such as fever, arthralgia, myalgia, fatigue, and headache, with the potential for debilitating joint pain to persist for months or even years after initial infection in over 40% of patients[4–6]. This enduring morbidity underscores the urgent need for effective preventive measures, especially vaccines that can confer rapid and durable immunity across diverse populations.

The CHIKV virus-like particle (VLP) vaccine, VIMKUNYA™ (Bavarian Nordic A/S), licensed in the US, EU/EEA, UK, Switzerland, and Canada for the prevention of chikungunya disease in individuals aged 12 years and older, is an important tool for CHIKV prevention. Virus-like particle vaccines mimic the native structure of the virus without containing replicable genetic material, enabling robust immune responses while maintaining a favorable safety profile[7,8]. The CHIKV VLP vaccine development program included three phase 2[9,10,11] and 2 phase 3 trials[12,13], conducted across multiple sites in the United States. These trials enrolled healthy participants aged 12 to 95 years, providing a broad evaluation of the vaccine's safety and immunogenicity in adolescent, adult, and older adult populations. Early postauthorization data also support the favorable safety profile of CHIKV VLP vaccine in a real-world setting, including in ≥ 65-year-olds[14].

Immunogenicity was assessed by measuring serum neutralizing antibody (SNA) titers, with NT_{80} ≥100 selected by regulators as a conservative surrogate marker for protection. Because CHIKV outbreaks are unpredictable and often geographically limited, large-scale efficacy trials are not feasible, leading regulators to base vaccine licensure on immunogenicity endpoints. This threshold is notably higher than levels associated with sterilizing immunity in nonhuman primate (NHP) studies, where a titer of 25.7 was sufficient to protect against CHIKV challenge[15], making the NT_{80} ≥100 cutoff approximately 4-fold more stringent. In the absence of established clinical correlates of protection for neutralizing antibody titers in humans, the analysis using a conservative threshold of 100 reflects a cautious approach. Exploration of additional thresholds, including a biological threshold of NT_{80} ≥25.7 associated with sterilizing immunity in NHPs and an assay threshold of NT_{80} ≥15 representing the lower level of quantitation, may offer additional context for interpreting and assessing the magnitude of the immunological response elicited by the vaccine.

This analysis of aggregated safety and immunogenicity data from the CHIKV VLP vaccine clinical development program underscores its potential as a VLP-based vaccine for protection against CHIKV disease. The findings demonstrate rapid onset and durable immune responses, supporting CHIKV VLP vaccine as a viable option for immunizing individuals aged 12 years and older.

Results

1.1. Trial Populations

A total of 3436 participants from 4 clinical trials were included in the immunogenicity evaluable population (IEP), of whom 2829 received a single dose of aluminum hydroxide adjuvanted 40 μg CHIKV VLP vaccine and 607 received placebo. The safety population comprised 3816 participants, 3141 vaccinated and 675 placebo recipients, from the same 4 clinical trials as well as an additional dose and schedule finding trial. Across treatment groups, demographic characteristics including sex, race, and ethnicity were well balanced (Table 1). Adolescents aged 12 to 17 years were enrolled exclusively in the phase 3 adolescent and adult trial (vaccine-to-placebo ratio of 6:1)[12]. Older adults aged ≥ 65 years were enrolled in the phase 3 older adult trial (vaccine-to-placebo ratio of 1:1)[13]; as a result, the placebo group had a higher mean age than the vaccine group due to the inclusion of the dedicated older adult trial.

Table 1
Demographic and other baseline characteristics in the immunogenicity evaluable population and safety population.

	Immunogenicity Evaluable Population		Safety Population	
	CHIKV VLP (n = 2829)	Placebo (n = 607)	CHIKV VLP (n = 3141)	Placebo (n = 675)
Age (years)				
Mean (SD)	41 (16.0)	49 (19.1)	41 (15.9)	49 (19.3)
Median (Min, Max)	40 (12, 95)	50 (12, 84)	39 (12, 95)	50 (12, 84)
Age Stratum (years), n (%)				
12 to < 18	201 (7.1)	33 (5.4)	217 (6.9)	37 (5.5)
18 to < 46	1528 (54.0)	245 (40.4)	1746 (55.6)	274 (40.6)
46 to < 65	911 (32.2)	146 (24.1)	972 (30.9)	157 (23.3)
65 to < 75	149 (5.3)	143 (23.6)	159 (5.1)	159 (23.6)
≥75	40 (1.4)	40 (6.6)	47 (1.5)	48 (7.1)
Sex, n (%)				
Male	1362 (48.1)	287 (47.3)	1520 (48.4)	324 (48.0)
Female	1467 (51.9)	320 (52.7)	1621 (51.6)	351 (52.0)
Race, n (%)				
White	2097 (74.1)	460 (75.8)	2315 (73.7)	511 (75.7)
American Indian or Alaska Native	28 (1.0)	3 (0.5)	31 (1.0)	3 (0.4)
Asian	79 (2.8)	15 (2.5)	90 (2.9)	17 (2.5)
Black or African American	515 (18.2)	107 (17.6)	588 (18.7)	119 (17.6)
Native Hawaiian	6 (0.2)	2 (0.3)	6 (0.2)	4 (0.6)
Multiracial	83 (2.9)	13 (2.1)	86 (2.7)	14 (2.1)
Unknown/Not Reported	21 (0.7)	7 (1.2)	25 (0.8)	7 (1.0)
Ethnicity, n (%)				

BMI = Body Mass Index, CHIKV VLP = Chikungunya Virus Virus-Like Particle, kg = kilogram, m = meter, Max = Maximum, Min = Minimum, n = Number of participants, SD = Standard Deviation

	Immunogenicity Evaluable Population		Safety Population	
	CHIKV VLP (n = 2829)	Placebo (n = 607)	CHIKV VLP (n = 3141)	Placebo (n = 675)
Age (years)				
Not Hispanic or Latino	2233 (78.9)	451 (74.3)	2472 (78.7)	497 (73.6)
Hispanic or Latino	542 (19.2)	143 (23.6)	606 (19.3)	163 (24.1)
Unknown/Not Reported	54 (1.9)	13 (2.1)	63 (2.0)	15 (2.2)
BMI (kg/m^2)				
Mean (SD)	26.9 (4.55)	26.8 (4.43)	26.92 (4.59)	26.79 (4.44)
Median (Min, Max)	27.0 (13.1, 47.3)	26.8 (15.7, 34.9)	26.90 (13.1, 48.2)	26.70 (15.7, 42.4)

BMI = Body Mass Index, CHIKV VLP = Chikungunya Virus Virus-Like Particle, kg = kilogram, m = meter, Max = Maximum, Min = Minimum, n = Number of participants, SD = Standard Deviation

1.2. Immunogenicity

Immunogenicity was assessed at baseline on Day 1, prior to vaccination, and on Days 8 (with the exception of the older adult ≥ 65 years trial), 15, 22, and 183. At Day 8, 47% (1217/2591) of vaccine recipients had achieved a seroresponse (anti-CHIKV SNA NT_{80} ≥100), which increased to 96% (2526/2637) at Day 15, 97% (2749/2829) at Day 22, the primary endpoint, and was 85% (2157/2542) at Day 183. While the CHIKV VLP vaccine group seroresponse rate peaked in all age subgroups at Day 15 and Day 22, seroresponse rate by age subgroup showed that the younger age groups elicited a more rapid and longer lasting response (Fig. 1). In the vaccinated adolescent 12 to 17-year-old subgroup, seroresponse rate was 71% at Day 8, 98% at Day 15, 97% at Day 22, and 95% at Day 183. In the vaccinated adult 18 to 65-year-old subgroup, the seroresponse rate was 45% at Day 8, 97% at Day 15, 98% at Day 22, and 85% at Day 183. In the vaccinated older adult > 65-year-old subgroup the seroresponse rate was 82% at Day 15, 87% at Day 22, and 75% at Day 183 (Day 8 was not measured in this age group). Females and younger participants showed more rapid (Day 8) and sustained (Day 183) immune responses (Table S1, Table S2). The difference between vaccine and placebo was statistically significant at all timepoints across all subgroups (Table S1).

Geometric mean titers were assessed at all time points. In the CHIKV VLP vaccine group, GMTs increased from 96 at Day 8 to 1019 at Day 15 and peaked at 1556 at Day 22, followed by a decline to 327 at Day 183 (Table S2). Across age groups, a clear gradient was observed, with adolescents showing the highest GMTs and progressively lower responses seen with increasing age (Table S2). Females consistently demonstrated higher GMTs than males across all time points (Table S3). By race, GMTs at Day 8 were comparable across subgroups; however, by Days 15 and 22, Asian participants exhibited the

highest GMTs, followed by Black/African American participants, White participants, and other racial groups (Table S3). At Day 183, White participants showed the highest GMTs, whereas Black/African American participants had the lowest. GMTs were similar between Not Hispanic/Latino and Hispanic/Latino participants.

Seroresponse rates evaluated at NT_{80} thresholds of ≥ 15 (assay lower limit of quantitation) and ≥ 25.7 (sterilizing immunity observed in NHP passive transfer and challenge study[15]) are shown in Fig. 1 and Table 2. In the CHIKV VLP vaccine group, 92% of participants had seroconverted (NT_{80} ≥15) by Day 8, increasing to 99% at all subsequent timepoints. Using the NT_{80} ≥25.7 threshold, seroresponse rates were 86% at Day 8, 99% at Days 15 and 22, and 98% at Day 183, compared to the ~ 4-fold higher NT_{80} ≥100 threshold seroresponse rates of 47% at Day 8, 96% at Day 15, 97% at Day 22, and 85% at Day 183. Age-stratified analyses showed the greatest divergence between the NT_{80} ≥100 and ≥ 25.7 thresholds at Day 8 and Day 183. At Day 8, adolescents (12 to 17 years) demonstrated a 26-percentage-point increase (71% vs 97%) and adults (18 to 65 years) a 40-percentage-point increase (45% vs 85%) when using the lower NT_{80} ≥25.7 threshold; Day 8 was not assessed in older adults. At Day 183, differences between thresholds were: 3-percentage-points in adolescents (95% vs 98%), 13 points in adults (85% vs 98%), and 14 points in older adults (75% vs 89%) (Table 2).

Table 2
Participants with anti-CHIKV SNA at or above selected titers by age group and visit (immunogenicity evaluable population – CHIKV VLP vaccinated participants)

Trial Day	Threshold Titer	Adolescents Age 12 to 17 n/N (%) [95% CI]	Adults Age 18 to 65 n/N (%) [95% CI]	Older Adults Age > 65 n/N (%) [95% CI]	All CHIKV VLP n/N (%) [95% CI]
Day 8	≥ 15	194/199 (97.5) [94.3, 98.9]	2188/2392 (91.5) [90.3, 92.5]	N/A	2382/2591 (91.9) [90.8, 92.9]
	≥ 25.7	193/199 (97.0) [93.6, 98.6]	2041/2392 (85.3) [83.9, 86.7]	N/A	2234/2591 (86.2) [84.8, 87.5]
	≥ 100	141/199 (70.9) [64.2, 76.7]	1076/2392 (45.0) [43.0, 47.0]	N/A	1217/2591 (47.0) [45.1, 48.9]
Day 15	≥ 15	187/191 (97.9) [94.7, 99.2]	2275/2284 (99.6) [99.3, 99.8]	152/162 (93.8) [89.0, 96.6]	2614/2637 (99.1) [98.7, 99.4]
	≥ 25.7	187/191 (97.9) [94.7, 99.2]	2270/2284 (99.4) [99.0, 99.6]	149/162 (92.0) [86.8, 95.3]	2606/2637 (98.8) [98.3, 99.2]
	≥ 100	187/191 (97.9) [94.7, 99.2]	2207/2284 (96.6) [95.8, 97.3]	132/162 (81.5) [74.8, 86.7]	2526/2637 (95.8) [95.0, 96.5]
Day 22	≥ 15	195/201 (97.0) [93.6, 98.6]	2444/2458 (99.4) [99.0, 99.7]	161/170 (94.7) [90.2, 97.2]	2800/2829 (99.0) [98.5, 99.3]
	≥ 25.7	195/201 (97.0) [93.6, 98.6]	2441/2458 (99.3) [98.9, 99.6]	158/170 (92.9) [88.1, 95.9]	2794/2829 (98.8) [98.3, 99.1]
	≥ 100	195/201 (97.0) [93.6, 98.6]	2406/2458 (97.9) [97.2, 98.4]	148/170 (87.1) [81.2, 91.3]	2749/2829 (97.2) [96.5, 97.7]
Day 183	≥ 15	189/192 (98.4) [95.5, 99.5]	2166/2185 (99.1)	152/165 (92.1) [87.0, 95.3]	2507/2542 (98.6)

Trial Day	Threshold Titer	Adolescents Age 12 to 17 n/N (%) [95% CI]	Adults Age 18 to 65 n/N (%) [95% CI]	Older Adults Age > 65 n/N (%) [95% CI]	All CHIKV VLP n/N (%) [95% CI]
			[98.6, 99.4]		[98.1, 99.0]
	≥ 25.7	189/192 (98.4) [95.5, 99.5]	2142/2185 (98.0) [97.4, 98.5]	147/165 (89.1) [83.4, 93.0]	2478/2542 (97.5) [96.8, 98.0]
	≥ 100	182/192 (94.8) [90.7, 97.1]	1851/2185 (84.7) [83.1, 86.2]	124/165 (75.2) [68.0, 81.1]	2157/2542 (84.9) [83.4, 86.2]

CI = Confidence Interval, n = number of participants with a sample result available at the indicated visit, N = total number of participants in the group, N/A = not assessed. 95% CIs of seroresponse rates are based on the Wilson method. Day 8 immunogenicity was not measured in the > 65-year age group.

Because all IEP analyses required participants to be seronegative at baseline, outcomes for baseline seropositive participants were evaluated using the modified intent-to-treat (mITT) population. Of the 3714 participants in the mITT set, 3628 were baseline seronegative and 86 were baseline seropositive (71 in the CHIKV VLP vaccine group and 15 in the placebo group). Although the number of baseline seropositive vaccine recipients was small, this subgroup consistently demonstrated higher immune responses than baseline seronegative vaccine recipients and all placebo participants at subsequent timepoints (Table S4, Table S5).

1.3. Safety

Solicited adverse events (AEs) were reported more frequently among CHIKV VLP vaccine recipients (37%) than placebo recipients (23%) (Table 3). Most solicited AEs in both groups were grade 1 (mild) or grade 2 (moderate) in severity. Among vaccine recipients who experienced a solicited AE, 49% reported symptoms lasting 1 day and 26% reported symptoms lasting 2 days, with a mean duration of 2 days. The most common local solicited AE was injection site pain (vaccine group 23%, placebo group 8%), while injection site redness or swelling were uncommon. The most frequently reported systemic solicited AEs were fatigue (vaccine group 19%, placebo group 14%), headache (vaccine group 17%, placebo group 14%), and myalgia (vaccine group 17%, placebo group 9%). Grade ≥ 3 solicited AEs occurred in 1.6% of vaccine recipients and 0.5% of placebo recipients; all were grade 3 except for a single grade 4 fever (40.6°C) reported in an electronic diary by a vaccine recipient, which was later deemed to be an erroneous entry by the trial site.

Table 3
Solicited reactogenicity within 7 days postvaccination (safety population)

Parameter	**CHIKV VLP Vaccine (N = 3141)**	**Placebo (N = 675)**
Any Solicited Reaction n/N (%)	**1156/3115 (37.11)**	**154/661 (23.30)**
≥Grade 3, n/N (%)	50/3115 (1.61)	3/661 (0.45)
Mean duration in days (SD)	2.0 (1.43)	1.8 (1.35)
Solicited Local Reaction n/N (%)	**730/3114 (23.44)**	**53/661 (8.02)**
≥Grade 3, n/N (%)	6/3114 (0.19)	0
Mean duration in days (SD)	1.6 (1.03)	1.1 (0.44)
Injection Site Pain n/N (%)	725/3114 (23.28)	52/661 (7.87)
≥Grade 3, n/N (%)	5/3114 (0.16)	0
Mean duration in days (SD)	1.6 (1.02)	1.1 (0.44)
Injection Site Redness n/N (%)	11/3114 (0.35)	1/661 (0.15)
≥Grade 3, n/N (%)	1/3114 (0.03)	0
Mean duration in days (SD)	1.4 (0.92)	1.0 (NE)
Injection Site Swelling n/N (%)	10/3114 (0.32)	0
≥Grade 3, n/N (%)	0	0
Mean duration in days (SD)	1.4 (0.97)	--
Solicited Systemic Reaction n/N (%)	**956/3115 (30.69)**	**143/661 (21.63)**
≥Grade 3, n/N (%)	48/3115 (1.54)	3/661 (0.45)
Mean duration in days (SD)	2.0 (1.47)	1.8 (1.37)
Fever n/N (%)	26/3109 (0.84)	3/660 (0.45)
≥Grade 3, n/N (%)	7/3109 (0.23)	0
Mean duration in days (SD)	1.3 (0.94)	1.0 (0.00)
Chills n/N (%)	246/3114 (7.90)	21/661 (3.18)
≥Grade 3, n/N (%)	5/3114 (0.16)	0
Mean duration in days (SD)	1.4 (0.97)	1.4 (0.81)
Fatigue n/N (%)	582/3114 (18.69)	90/661 (13.62)
≥Grade 3, n/N (%)	23/3114 (0.74)	1/661 (0.15)

Parameter	CHIKV VLP Vaccine (N = 3141)	Placebo (N = 675)
Mean duration in days (SD)	1.9 (1.37)	1.6 (1.13)
Headache n/N (%)	530/3115 (17.01)	92/661 (13.92)
≥Grade 3, n/N (%)	12/3115 (0.39)	2/661 (0.30)
Mean duration in days (SD)	1.7 (1.27)	1.4 (0.88)
Myalgia n/N (%)	523/3114 (16.80)	58/661 (8.77)
≥Grade 3, n/N (%)	13/3114 (0.42)	3/661 (0.45)
Mean duration in days (SD)	1.7 (1.22)	1.8 (1.46)
Arthralgia/Joint Pain n/N (%)	230/3114 (7.39)	41/661 (6.20)
≥Grade 3, n/N (%)	7/3114 (0.22)	1/661 (0.15)
Mean duration in days (SD)	1.9 (1.45)	2.0 (1.38)
Nausea n/N (%)	219/3114 (7.03)	34/661 (5.14)
≥Grade 3, n/N (%)	12/3114 (0.39)	0
Mean duration in days (SD)	1.7 (1.27)	1.4 (0.85)

N = number of participants per group; n = number of participants per parameter; NE = not evaluable; SD = standard deviation. Percentages are based on the number of safety population participants in each treatment group who have completed any diary anytime. Participants are counted at most once per sign or symptom at the highest severity reported within 7 days (Days 1–8) following vaccination. Grade 3 (severe) redness or swelling is > 100 mm diameter; grade 3 (severe) fever is ≥ 39.0°C. Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = potentially life-threatening.

Unsolicited AEs occurred at similar rates in the CHIKV VLP vaccine and placebo groups and were mostly mild or moderate and unrelated to trial treatment. Unsolicited AEs were reported by 16% of CHIKV VLP vaccine recipients and 14% of placebo recipients; the most common unsolicited AEs were COVID-19, upper respiratory tract infection, and headache (Table S6). Grade 3 or higher unsolicited AEs were reported by 1.3% of vaccine recipients and by 0.6% of placebo recipients. Grade 3 or higher unsolicited AEs that were considered treatment-related included a grade 3 dehydration (probably related) and a grade 3 fatigue (possibly related), both in the vaccine group. Treatment-related unsolicited AEs were reported by 2.4% of vaccine and 1.9% of placebo recipients. No cases of CHIKV-like illness including neurological or cardiac safety signals were observed. There were 4 unrelated grade ≥ 3 neurological AEs in participants that all had relevant prior medical history; there were no grade ≥ 3 cardiac AEs.

Eight participants experienced an adverse event of special interest (AESI), defined as new or worsening arthralgia that was medically attended, (vaccine: n = 6, placebo: n = 2), all of which were nonserious and grade 1 or grade 2 in severity (Table S7). Four participants had an AESI that was assessed as related to trial treatment (3 arthralgia in the vaccine group and 1 arthralgia in the placebo group). The incidence of SAEs was low and balanced between groups; SAEs were uncommon, reported in 1.0% of vaccine recipients and 0.6% of placebo recipients. One SAE (retinal detachment) that was considered as possibly related by the trial investigator but was assessed by the sponsor and independent safety monitoring committee chair as unrelated due to prior medical history of seeing 'black spots' in the eye 1 month before the trial vaccine was administered to the participant. Three nonrelated deaths were reported: a placebo participant aged 70 to 74 years (malignant lung neoplasm), a vaccine participant aged 75 to 79 years (respiratory failure due to worsened community-acquired pneumonia), and a vaccine participant aged 30 to 39 years (road traffic accident).

Five pregnancies occurred among participants in the safety population, including 1 in the placebo group for whom the date of the last menstrual period was 5 days prior to placebo administration, and 4 in CHIKV VLP vaccine recipients. The pregnancies in vaccine recipients occurred between 55 days and > 1 year after vaccination. One pregnancy was associated with an SAE (fronto-ethmoid encephalocele in the infant), which was assessed as unrelated to trial treatment. An additional 6 pregnancies occurred among participants who received alternative dose regimens of CHIKV VLP vaccine in the phase 2 trial NCT03483961; 3 were associated with SAEs, all of which were assessed as unrelated to vaccination. No apparent vaccine pregnancy-related safety signals were identified. The limited number of pregnancies and the interval between vaccination and conception preclude conclusions regarding the safety of CHIKV VLP vaccine during pregnancy or lactation.

Adolescents (12 to 17 years) who received the CHIKV VLP vaccine were more likely to report solicited AEs (44%) and unsolicited AEs (19%) compared to adults (solicited 38%; unsolicited 16%) and older adults (solicited 11%; unsolicited 14%) (Table 4). Whether this reflects true differences in reactogenicity or differences in reporting behavior is uncertain. The same trend was not seen among those who received the placebo dose. Although the number of adolescents who reported grade ≥ 3 severity solicited (vaccine: 1.9%) or unsolicited (vaccine: 1.4%) AEs was low, the proportion was similar to adults and older adults. A single adolescent participant experienced an unrelated SAE (diabetic ketoacidosis). No adolescents experienced an AESI and no deaths occurred.

Older adults (> 65 years) who received the CHIKV VLP vaccine were less likely to report solicited AEs and unsolicited AEs compared to adolescents and younger adults (Table 4). Notably, within the older adult group, placebo recipients reported a higher proportion of both solicited and unsolicited AEs than vaccine recipients. Although grade ≥ 3 AEs were uncommon across all age groups, older adults reported more grade ≥ 3 unsolicited AEs but fewer grade ≥ 3 solicited AEs. Proportion of treatment-related unsolicited AEs was comparable to the 18 to 65 year-old subgroup. Older adults were more likely to experience an SAE in both the vaccine and placebo groups; none of which were treatment-related. The only AESI in an older adult participant occurred in the placebo group and was not treatment-related.

Table 4
Summary of adverse events for adolescents, adults, and older adults (safety population)

Parameter	Age 12 to 17 (N = 254) n (%)		Age 18 to 65 (N = 3187) n (%)		Age > 65 (N = 375) n (%)	
	CHIKV VLP (N = 217)	Placebo (N = 37)	CHIKV VLP (N = 2738)	Placebo (N = 449)	CHIKV VLP (N = 186)	Placebo (N = 189)
Any Solicited AE	94/213 (44.13)	8/37 (21.62)	1042/2717 (38.35)	120/441 (27.21)	20/185 (10.81)	26/183 (14.21)
≥Grade 3	4/213 (1.88)	1/37 (2.70)	45/2717 (1.66)	2/441 (0.45)	1/185 (0.54)	0
Mean duration in days (SD)	2.2 (1.73)	1.6 (1.19)	2.0 (1.40)	1.7 (1.27)	2.5 (1.40)	2.3 (1.62)
Any Unsolicited AE	41 (18.89)	3 (8.11)	425 (15.52)	61 (13.59)	26 (13.98)	33 (17.46)
≥Grade 3	3 (1.38)	0	34 (1.24)	1 (0.22)	4 (2.15)	3 (1.59)
Treatment-Related	2 (0.92)	0	68 (2.48)	8 (1.78)	4 (2.15)	5 (2.65)
Any Serious AE	1 (0.46)	0	26 (0.95)	1 (0.22)	4 (2.15)	3 (1.59)
Any AESI	0	0	6 (0.23)	1 (0.22)	0	1 (0.53)
Any MAAE	24 (11.06)	2 (5.41)	229 (8.75)	40 (8.99)	19 (10.22)	23 (12.17)
Deaths	0	0	1	0	1	1

AE = adverse event; AESI = adverse event of special interest; MAAE = medically attended adverse event; N= number of participants per group; n = number of participants per parameter; SAE = serious adverse event; SD = standard deviation. Percentages are based on the number of safety population participants in each treatment group.

Female participants were more likely than male participants to report AEs in both the vaccine and placebo groups, including solicited AEs, grade ≥ 3 solicited AEs, unsolicited AEs, and SAEs (Table S8). By race subgroup, African American participants reported the lowest frequency of both solicited and unsolicited AEs.

By baseline serostatus, baseline seronegative participants exhibited similar rates of solicited AEs (vaccine 37%, placebo 23%) as baseline seropositive participants (vaccine 34%, placebo 27%) (Table S9). However, unsolicited AEs were more frequently reported by baseline seronegative participants (vaccine 16%, placebo 15%) compared with baseline seropositive participants (vaccine 10%, placebo 6%).

Discussion

This analysis integrates data across phase 2 and phase 3 trials to provide a comprehensive assessment of the immunogenicity and safety of a single-dose CHIKV VLP vaccine in adolescents and adults aged ≥ 12 years. The vaccine elicited a robust, rapid, and durable neutralizing antibody response with a safety profile broadly comparable to placebo, underscoring its translational potential for prevention of chikungunya disease in a broad range of individuals. Across the pooled trials, 96% of vaccine recipients achieved the prespecified seroresponse threshold (NT_{80} ≥100) at 2 weeks postvaccination (Day 15), with 85% maintaining seroresponse at 6 months (Day 183), highlighting both the magnitude and durability of the response. Nearly half of vaccine recipients reached the seroresponse threshold at 1 week postvaccination (Day 8), indicating a rapid onset of immunity.

Immunogenicity patterns aligned with expected biological gradients. Geometric mean titers were > 180-fold higher in vaccine recipients than placebo and showed an age-related gradient; adolescents mounted the highest responses, and progressively lower responses were observed with increasing age. This pattern of successively lower immune responses from younger to older age subgroups is consistent with the known decline in immune function with age. In a systematic review of infectious disease outcomes, peak immune function was suggested to occur between 5 to 14 years of age, followed by a rise in infectious disease severity (decreasing immunity) by age 20 for many infections, and a steeper rise of infections (further decreasing immunity) into old age, although the pattern varies by disease[16]. Females consistently exhibited higher GMTs than males across time points, consistent with broader vaccine literature showing stronger humoral immune responses in females, likely driven by hormonal, genetic, and immunoregulatory differences[17]. Baseline serostatus also influenced response: baseline seropositive participants demonstrated higher postvaccination GMTs at all time points, suggesting that pre-existing CHIKV immunity may boost the GMT response following CHIKV VLP vaccination. Although interpretation of these subgroup differences is limited by the substantially larger number of baseline seronegative versus seropositive participants, the findings are consistent with a prior phase 2 post hoc analysis evaluating safety and long-term immunogenicity of an unadjuvanted version of CHIKV VLP vaccine in baseline seropositive individuals during a 2015 CHIKV outbreak in the Caribbean[18].

Vaccination against CHIKV is based on surrogate endpoints for protection. In addition to inducing neutralizing antibodies, CHIKV VLP vaccine has also been shown to elicit CHIKV-specific $CD4^+$ T cell responses with early onset and sustained durability, contributing to the overall immune profile of the vaccine[19]. The primary seroresponse definition (NT_{80} ≥100) was intentionally conservative reflecting regulatory guidance and offers a margin of safety in the absence of a well-defined correlate of protection for humans. However, evidence from preclinical studies[15] and studies on immunoresponse after natural infection[20] demonstrates that protection is achieved at lower titers in both NHPs and humans. In NHP challenge studies, sterilizing immunity occurred at an NT_{80} titer of 25.7, which is almost 4-fold lower than the NT_{80} ≥100 threshold applied in this program. Even with the conservative benchmark, 96% of vaccine recipients achieved seroresponse by Day 15, and most maintained these titers through 6

months. Analyses using the lower assay threshold (NT_{80} ≥15; lower limit of quantitation of the assay) and the NHP-derived biological threshold (NT_{80} ≥25.7), demonstrated higher seroresponse rates at the assessed timepoints. At NT_{80} ≥15, seroresponse rates were 92% at Day 8 and 99% at subsequent timepoints. At NT_{80} ≥25.7, seroresponse rates were 86% at Day 8, 99% at Days 15 and 22, and 98% at Day 183. At 1 week postvaccination (Day 8), NT_{80} ≥25.7 was achieved by 97% of adolescents and 85% of adults (data from earliest timepoint in older adults was 92% at Day 15), and at Day 183 was maintained in 98% of adolescents, 98% of adults, and 89% of older adults.

The safety profile of CHIKV VLP vaccine was favorable and is consistent with expectations for aluminum-adjuvanted VLP vaccines[21,22]. Solicited local and systemic AEs were predominantly mild to moderate, transient, and resolved without intervention; the most common were injection site pain, headache, fatigue, and myalgia. Rates of unsolicited AEs, SAEs, and AESIs were low and comparable between vaccine and placebo groups, and no vaccine-related SAEs, deaths, or cases of vaccine-associated enhanced disease were observed. Notably, older adults (> 65 years) demonstrated lower overall reactogenicity than younger age groups, with fewer solicited AEs and no apparent increase in treatment-related serious safety. Adolescents reported more solicited and unsolicited AEs overall, however, grade ≥ 3 events were uncommon across all ages, and no adolescents experienced an AESI or death.

Sex and race subgroup analyses of safety suggested reporting differences. Female participants were more likely than males to report solicited AEs, grade ≥ 3 solicited AEs, unsolicited AEs, and SAEs, and African American participants reported the lowest frequency of both solicited and unsolicited AEs. However no clinically meaningful differences in safety outcomes were detected across sex, race, or ethnicity. These observations may reflect biological and/or reporting factors, although the trial was not designed to determine whether cultural or societal influences affected AE perception or reporting.

Current recommendations and guidance for the use of CHIKV VLP vaccine in travelers are risk-based, considering factors such as travel destination, duration of travel, and age and underlying medical conditions. In the absence of data from the use of CHIKV VLP in pregnancy, recommendations on the use of the vaccine vary by country; in the US[23], for instance, pregnant women are advised to avoid CHIKV exposure if possible and pregnancy is a precaution for vaccination, with administration generally deferred until after the first trimester unless infection risk is high. If vaccination during pregnancy is necessary, CHIKV VLP vaccine is preferred over live vaccines, but safety data are limited and a careful risk-benefit discussion is essential. For breastfeeding, there are no restrictions on CHIKV VLP vaccine use according to US guidance[23].

Future trials will further investigate the clinical benefit of the vaccine and provide more clarity on the interpretation of different levels of antibody titers and if the lower titers, as seen in the NHP challenge study[15], correspond to meaningful protection in humans. The complementary threshold of 25.7 equips clinicians with additional understanding of the breadth, timing, and durability of vaccine-induced

immunological response, supporting informed counseling for both last minute travelers and individuals at prolonged risk of CHIKV infection.

Limitations include the use of immunological surrogates (seroresponse and GMT) rather than clinical efficacy endpoints; a field trial will evaluate efficacy, immunogenicity, and safety (NCT07467707), and try to establish a correlate of protection. Follow-up in the present study was limited to 6 months, and rare safety events and longer term durability will be better characterized in an ongoing extension trial (NCT06007183). Evidence in pregnant and lactating individuals was limited, precluding firm safety conclusions in these populations.

Collectively, the rapid onset, high peak, and durability of neutralizing antibody responses support use of the CHIKV VLP vaccine across diverse age groups and geographic settings, including both endemic and nonendemic regions. Routine CHIKV immunization in endemic regions, reactive vaccine campaigns from stockpile doses in regions at risk for CHIKV outbreaks, or a combination of both strategies could considerably reduce the burden of CHIKV disease[24]. The CHIKV VLP vaccine showed no safety signals in clinical trials or in early postmarketing surveillance[14]. Overall, the VLP platform was well tolerated and may offer advantages over live-attenuated approaches, with fewer severe adverse events and no reported CHIKV-like illness, including neurologic or cardiac safety signals, which are of particular concern in older adults[25].

In summary, a single dose of CHIKV VLP vaccine induced rapid, robust, and durable neutralizing antibody responses with broad immunogenicity across demographic subgroups. As the geographic range of CHIKV continues to expand, these findings provide important evidence to inform public health strategies aimed at reducing the burden of chikungunya disease.

Methods

1.4. Trial Design and Oversight

This aggregated analysis combines data from multiple clinical trials evaluating the immunogenicity and safety of CHIKV VLP vaccine (40 µg VLP with aluminum hydroxide adjuvant) in healthy adolescents and adults. The trials were comprised of a phase 2 open-label trial of prior alphavirus naïve and non-naïve participants[10], a phase 2 open-label trial to assess safety and immunogenicity[11], and 2 pivotal phase 3 randomized placebo-controlled trials: an adolescent and adult trial[12], and an older adult trial[13]. Safety analysis also included participants who received the 40 µg VLP dose from a phase 2 dose and schedule finding trial[9]; however, this trial was not included in the immunogenicity evaluable population because it did not generate sufficient data at the Day 22 primary immunogenicity endpoint, per regulatory guidance. All trials were conducted in accordance with Good Clinical Practice (GCP), the Declaration of Helsinki, and applicable regulatory requirements. Protocols and amendments were approved by institutional review boards (IRBs) or ethics committees at each participating site and written informed consent (and assent for adolescents) was obtained from all participants prior to enrollment.

1.5. Trial Populations

1.5.1. Immunogenicity Evaluable Population

The primary analysis population for immunogenicity was the immunogenicity evaluable population (IEP), defined as participants who: received CHIKV VLP vaccine or placebo, had no measurable anti-CHIKV SNA titer at baseline (Day 1), provided an evaluable Day 22 SNA sample (primary endpoint) within the analysis window (Day 19 to 27), and had no exclusionary protocol deviations as defined prior to unblinding. The modified intent-to-treat (mITT) population included all randomized and vaccinated participants with at least 1 postvaccination SNA result; immunogenicity analyses were repeated in the mITT population as a measure of robustness.

1.5.2. Safety Population

The safety population included all participants who received CHIKV VLP vaccine or placebo. Safety analyses were conducted for the overall population and stratified by age, sex, race, and other relevant subgroups as appropriate.

1.6. Intervention

Participants received a single intramuscular dose of CHIKV VLP vaccine or placebo (same excipient composition without CHIKV VLP or aluminium hydroxide components) administered in the deltoid muscle. Trial visits for immunogenicity and safety assessments were scheduled at Day 1 prevaccination (baseline), and follow-up visits at Day 8, Day 15, Day 22 (primary endpoint), and Day 183 (end of trial), with minor variations in visit schedules between trials. The Day 8 visit was not included in the phase 3 Tindale *et al* trial, the Day 15 visit was not included in the phase 2 Hamer *et al*, the Day 183 visit was not included in the phase 2 NCT05065983 trial.

1.7. Immunogenicity Assessments

Immunogenicity was assessed by measuring anti-CHIKV SNA titers using a validated luciferase-based neutralization assay (NT_{80})[26]. Titers were expressed as the reciprocal of the serum dilution achieving 80% neutralization. Immunogenicity analyses included the proportion of participants achieving an anti-CHIKV SNA NT_{80} ≥100 (seroresponse rate, considered the presumptive seroprotection rate) and GMTs at Days 8, 15, 22 (primary endpoint), and 183, as available, as well as the proportion of participants achieving an anti-CHIKV SNA titer ≥ 15 (assay lower limit of quantitation and SNA NT_{80} ≥27.5 (sterilizing immunity in NHPs[15]) at each timepoint.

1.8. Safety Assessments

Safety was evaluated through the collection of solicited and unsolicited adverse events (AEs, serious adverse events (SAEs), and adverse events of special interest (AESIs). AESI were defined as the occurrence of new onset or worsening arthralgia that was medically attended. Solicited local and systemic reactions were recorded for 7 days postvaccination, unsolicited AEs were collected for 28 days postvaccination, and SAEs and AESIs were monitored throughout the trial duration. Laboratory assessments, vital signs, and physical examinations were performed at scheduled visits. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and graded according to standardized toxicity grading scales.

1.9. Statistical Analysis

1.9.1. Immunogenicity

For each timepoint, seroresponse rates and GMTs were calculated, with associated 95% confidence intervals (CIs). Seroresponse rates and CIs were determined using the Wilson score method, while differences and CIs were calculated using the Newcombe hybrid score method. Group comparisons were performed using 2-sided chi-square tests for proportions and analysis of variance (ANOVA) on $\log_{10}$-transformed titers for GMTs. Subgroup analyses were performed by age, sex, race, ethnicity, and baseline CHIKV serostatus. Regression analysis assessed the effect of age on SNA titers. All immunogenicity analyses were repeated in the mITT population to evaluate robustness.

1.9.2. Safety

The incidence of solicited local reactions (injection site pain, redness, and swelling) and solicited systemic reactions (fever, chills, fatigue, headache, myalgia, arthralgia, and nausea) that were grade ≥ 3 and overall, unsolicited AEs, SAEs, and AESIs were summarized by treatment group, severity, and relationship to the trial vaccine. Solicited and unsolicited AEs were summarized by system organ class and preferred term. Solicited and unsolicited AEs were graded by the investigator according to severity grading scales (grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = potentially life-threatening). Causality of AEs was assessed as unrelated, possibly related, or probably related. Laboratory abnormalities were summarized descriptively. Safety data were analyzed by age, sex, race, and other relevant subgroups.

Declarations

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Bavarian Nordic A/S.

Contributions

DMA, PA, LB, JSR contributed to trial concept and design. SM contributed to the acquisition of data. VAJ, PA supervised the trial. DMA, LB analysed and verified data presented in the manuscript. LCT, JSR, TL interpreted the data. LCT drafted the manuscript. All authors contributed to and reviewed the final version of the paper.

Competing interests

Authors LCT, DMA, SM, TL, VAJ, PA, LB, JSR are current or previous employees of Bavarian Nordic A/S and/or Emergent BioSolutions Inc.

Data availability

Aggregated data generated or analyzed during this trial are included in this published article and its supplementary information files. 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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Figures

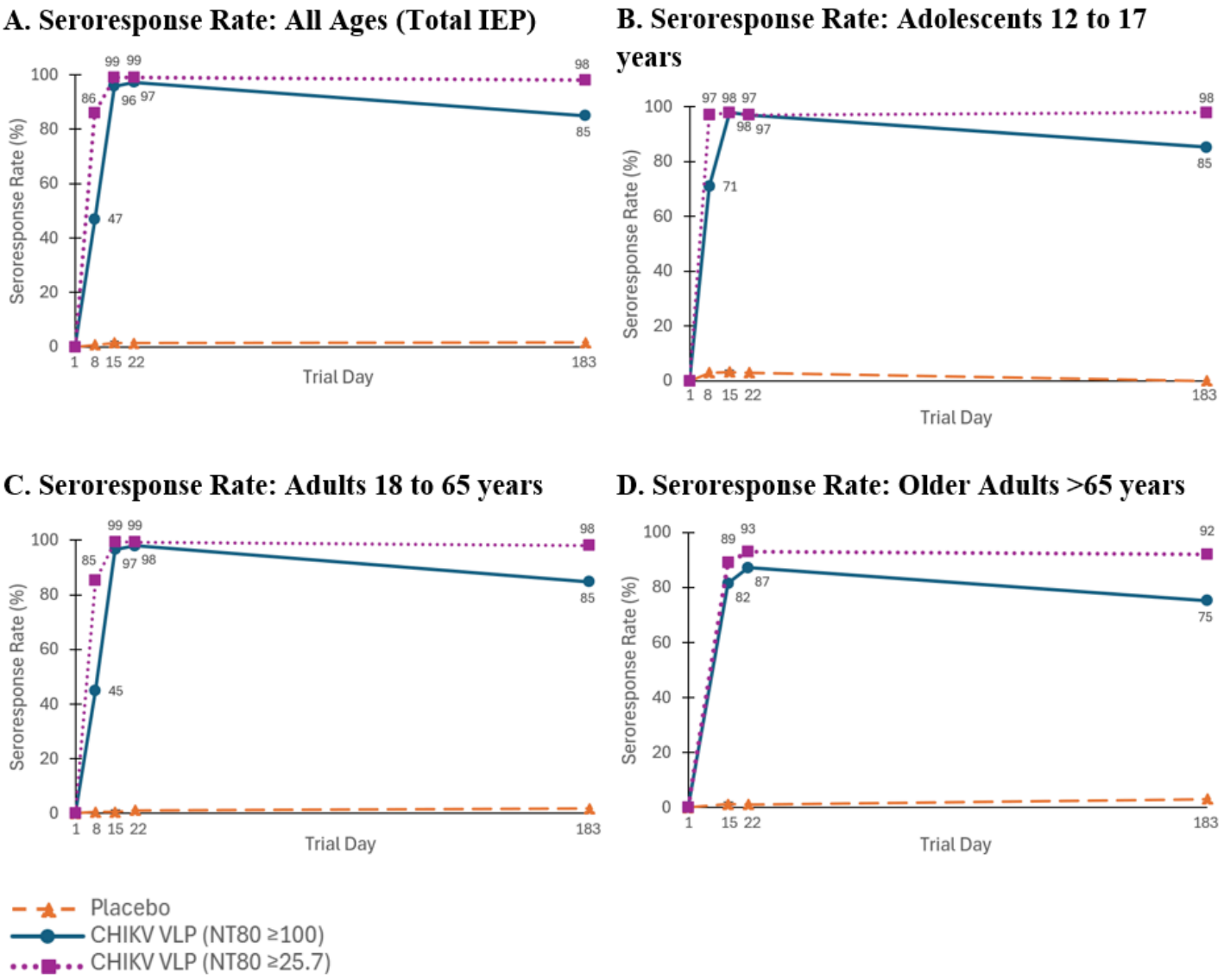

Figure 1

Seroresponse rate at serum neutralizing antibody NT80 ≥100 and ≥25.7 by trial day and age subgroup. IEP = immunogenicity evaluable population

Supplementary Files

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