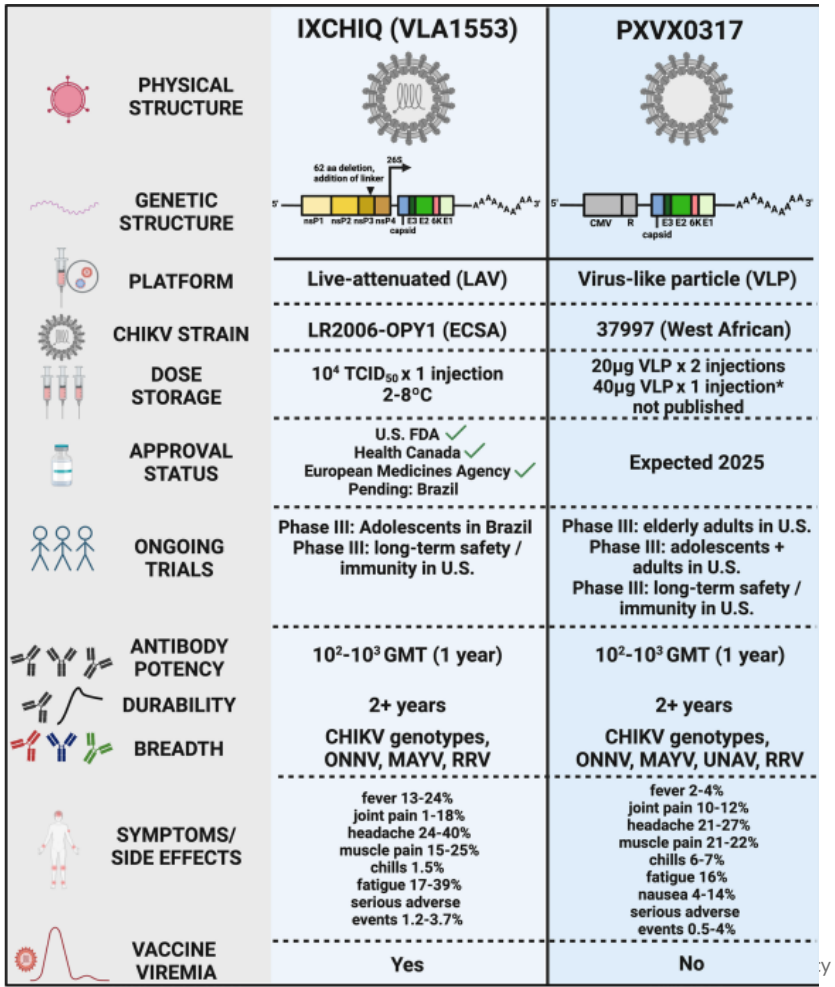
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Approved Chikungunya vaccines

GVIRF, Rio de Janeiro, 26 March 2025

- Dr. Marco Cavaleri
- Head of Health Threats and Vaccines Strategy
- Chair of EMA Emergency Task Force

Chikungunya vaccines approved at EMA



	IXCHIQ (VLA1553)	PXVX0317
PHYSICAL STRUCTURE		
GENETIC STRUCTURE	62 aa deletion, addition of linker; 26S; 5'; nsP1 nsP2 nsP3 nsP4; capsid; E3 E2 6K E1; 3'	5'; CMV R; capsid; E3 E2 6K E1; 3'
PLATFORM	Live-attenuated (LAV)	Virus-like particle (VLP)
CHIKV STRAIN	LR2006-OPY1 (ECSA)	37997 (West African)
DOSE STORAGE	10^4 $TCID_{50}$ x 1 injection 2-8°C	20µg VLP x 2 injections 40µg VLP x 1 injection* not published
APPROVAL STATUS	U.S. FDA ✓ Health Canada ✓ European Medicines Agency ✓ Pending: Brazil	Expected 2025
ONGOING TRIALS	Phase III: Adolescents in Brazil Phase III: long-term safety / immunity in U.S.	Phase III: elderly adults in U.S. Phase III: adolescents + adults in U.S. Phase III: long-term safety / immunity in U.S.
ANTIBODY POTENCY	10^2-10^3 GMT (1 year)	10^2-10^3 GMT (1 year)
DURABILITY	2+ years	2+ years
BREADTH	CHIKV genotypes, ONNV, MAYV, RRV	CHIKV genotypes, ONNV, MAYV, UNAV, RRV
SYMPTOMS/ SIDE EFFECTS	fever 13-24% joint pain 1-18% headache 24-40% muscle pain 15-25% chills 1.5% fatigue 17-39% serious adverse events 1.2-3.7%	fever 2-4% joint pain 10-12% headache 21-27% muscle pain 21-22% chills 6-7% fatigue 16% nausea 4-14% serious adverse events 0.5-4%
VACCINE VIREMIA	Yes	No

[Chikungunya Virus Vaccines: A Review of IXCHIQ and PXVX0317 from Pre-Clinical Evaluation to Licensure | BioDrugs]

Pre-existing chikungunya virus neutralizing antibodies correlate with risk of symptomatic infection and subclinical seroconversion in a Philippine cohort | Elsevier Enhanced Reader

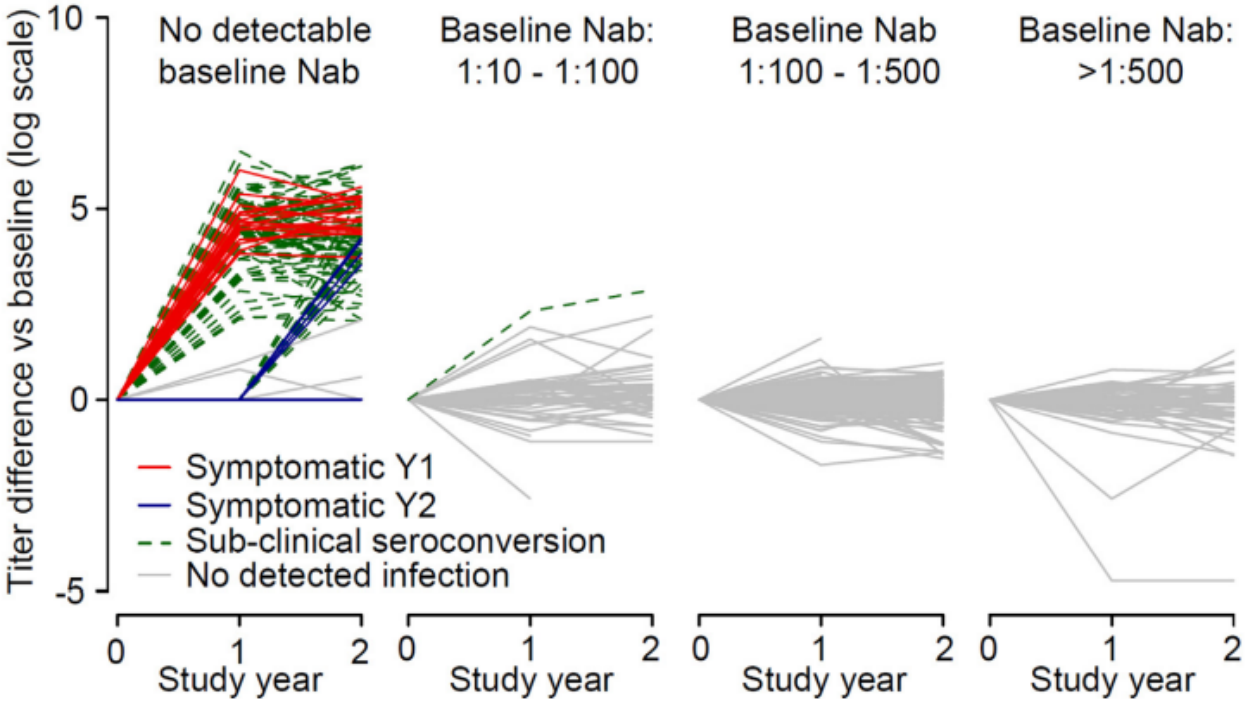


Figure 2. Changes in CHIKV PRNT80 titer (log scale) from baseline to 12 months (study year 1) and 24 months (study year 2) for each cohort participant according to baseline CHIKV PRNT80 titer group: no detectable NAb (<1:10), low titer (1:10 to <1:100), medium titer (1:100–1:500), high titer (>1:500). Red and blue solid lines indicate symptomatic infections, green dotted lines indicate subclinical seroconversions, and gray solid lines indicate no infections/seroconversions. CHIKV, chikungunya virus; PRNT80, 80% plaque reduction neutralization test; NAb, neutralizing antibody.

Clinical, Serological, and Virological Analysis of 572 Chikungunya Patients From 2010 to 2013 in India

Jaspreet Jain,[1] Kaustuv Nayak,[2] Neha Tanwar,[3] Rajni Gaind,[3] Bhupendra Gupta,[4] J. S. Shastri,[5] Raj K. Bhatnagar,[6] Murali Krishna Kaja,[2,7] Anmol Chandele,[2] and Sujatha Sunil[1]

[1]Vector Borne Diseases Group and [2]ICGEB-Emory Vaccine Center, International Center for Genetic Engineering and Biotechnology, Departments of [3]Microbiology and [4]Medicine, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, [5]Department of Microbiology, BYL Nair Ch. Hospital & T. N. Medical College, Mumbai, and [6]International Center for Genetic Engineering and Biotechnology, New Delhi, India; and [7]Emory Vaccine Center, Emory University School of Medicine, Atlanta, Georgia

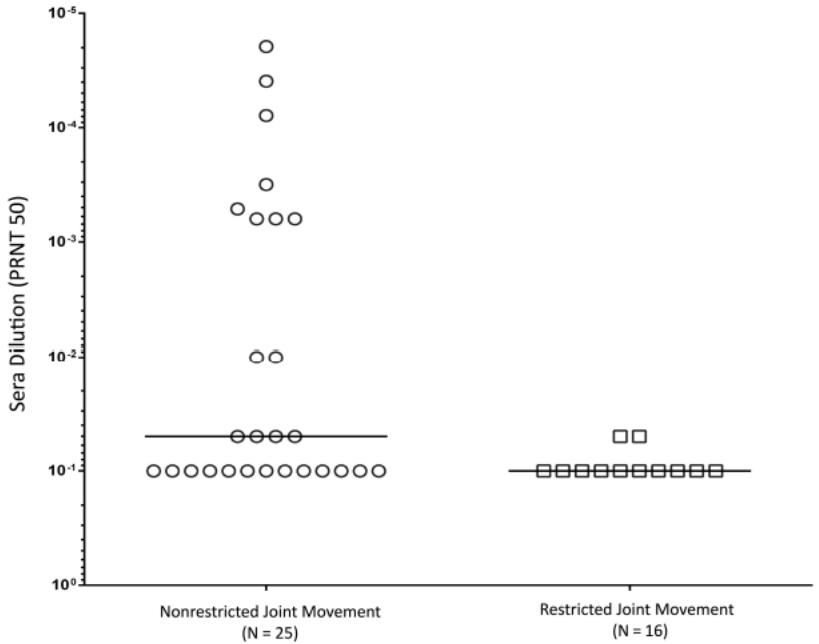
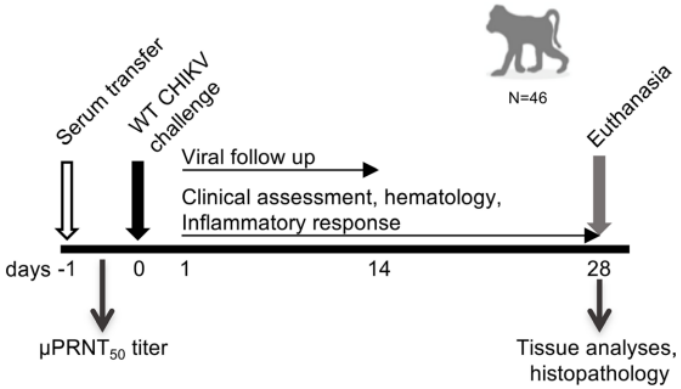


Figure 4. Neutralization status (plaque reduction neutralization test 50) of patient samples without and with joint movement restriction. Data points are plotted as open circles and open squares, respectively. n = 25 and 16 sample points, respectively. Abbreviation: PRNT, plaque reduction neutralization test.

cix283.pdf (silverchair.com)



Effectiveness of CHIKV vaccine VLA1553 demonstrated by passive transfer of human sera

Pierre Roques,[1] Andrea Fritzer,[2] Nathalie Dereuddre-Bosquet,[1] Nina Wressnigg,[2] Romana Hochreiter,[2] Laetitia Bossevot,[1] Quentin Pascal,[1] Fabienne Guehenneux,[3] Annegret Bitzer,[2] Irena Corbic Ramljak,[2] Roger Le Grand,[1] Urban Lundberg,[2] and Andreas Meinke[2]

[1]Université Paris-Saclay, INSERM, CEA, Center for Immunology of Viral, Auto-Immune, Hematological and Bacterial diseases (IMVA-HB/IDMIT), Fontenay-aux-Roses, France. [2]Valneva Austria GmbH, Campus Vienna Biocenter 3, Vienna, Austria. [3]Valneva SE, Saint Herblain, France.

Table 2. Peak viremia for animals with different µPRNT$_{50}$ titer thresholds.

		µPRNT$_{50}$ ≥ 50 (*n* = 13)	µPRNT$_{50}$ ≥ 100 (*n*=4)	µPRNT$_{50}$ ≥ 150 (*n* = 2)
Peak viremia (copies/mL) Day 2–6	Geometric mean	941.1	16.3	10
	[95% CI]	[100, 8846]	[4, 77]	[10, 10]
Number of NHPs with detected CHIKV RNA	Not detected	4 (30.8%)	3 (75.0%)	2 (100%)
	Detected	9 (69.2%)	1 (25.0%)	0 (0.0%)

The geometric mean for the peak viremia (copies/mL) is shown for each group of animals assigned to the 3 µPRNT$_{50}$ thresholds. Numbers of animals with or without detectable CHIKV RNA were calculated for the 3 µPRNT$_{50}$ thresholds. Therefore, animals with an µPRNT ≥ 150 are included in the µPRNT$_{50}$ ≥ 100 and µPRNT$_{50}$ ≥ 50 columns, and animals with an µPRNT ≥ 100 are included in the µPRNT$_{50}$ ≥ 50 column. Peak copies/mL values reported as 0 were set to 10 for this summary.

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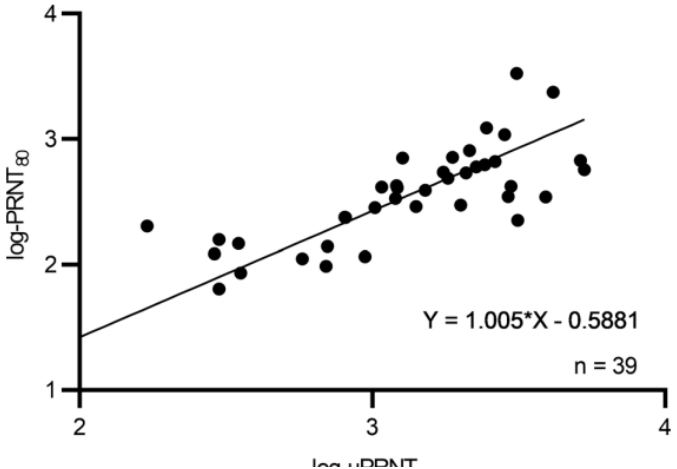

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Figure 5. Linear regression of neutralization antibody titer using Deming regression analysis. Log transformed data of $\mu PRNT_{50}$ versus $PRNT_{80}$ shown.

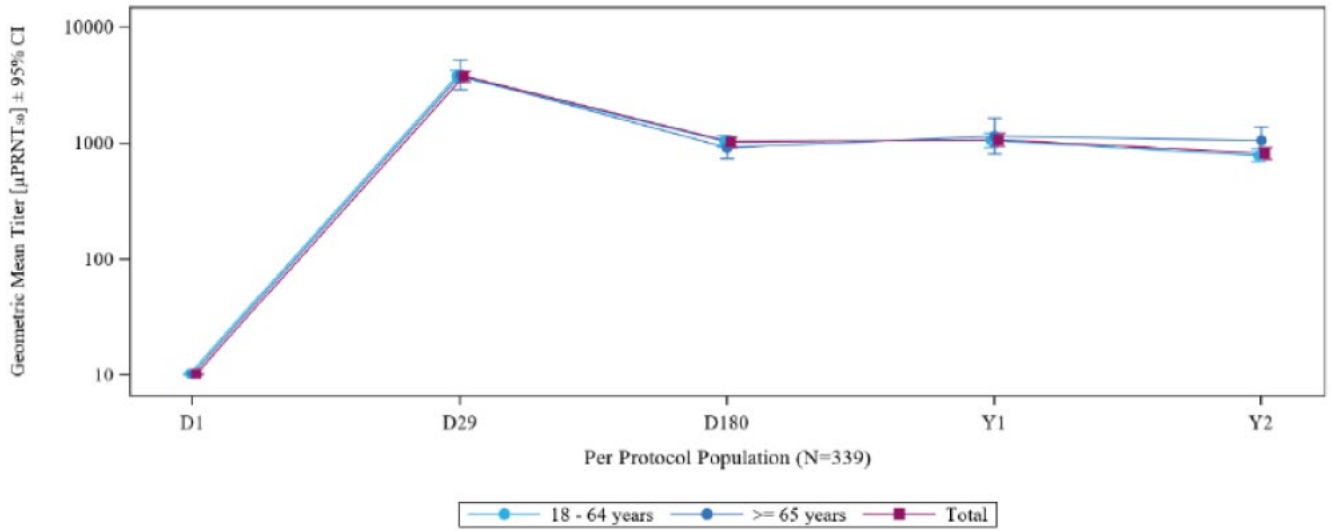
Table 3. Comparison of neutralization antibody titer results measured by the validated assay as $\mu PRNT_{50}$ titer or reported by AFRIMS ($PRNT_{80}$ titer).

	$\mu PRNT_{50}$	$PRNT_{80}$	Ratio $\mu PRNT_{50}/PRNT_{80}$
No. of nAb positive samples	39	39	39
Minimum	170	64	0.84
Maximum	5297	3347	13.93
Geometric mean	1341	360	3.73
Lower 99% CI of geometric mean	920	246	2.86
Upper 99% CI of geometric mean	1957	526	4.87

nAb, neutralizing antibodies; PRNT, plaque reduction neutralization test; $\mu PRNT_{50}$, neutralization titer determined in a microneutralization assay (96 well format) using a 50% plaque reduction; $PRNT_{80}$, neutralization titer using a 80% plaque reduction.

jciinsight-7-160173.pdf (nih.gov)

Persistence of antibodies over time- Ixchiq



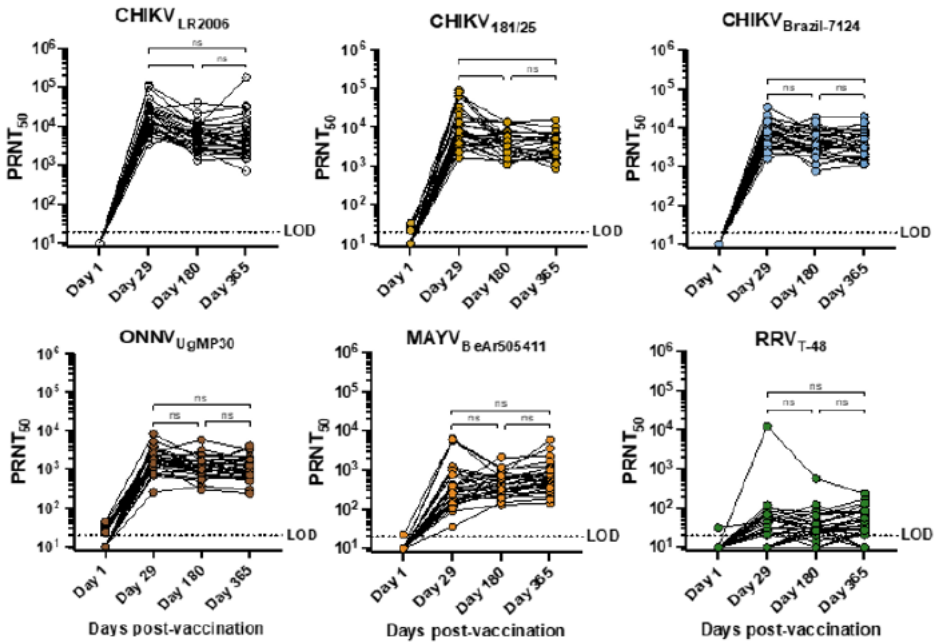
Age Strata	D1	D29	D180	Y1	Y2
18 - 64 years	290	240	279	157	234
>= 65 years	49	39	48	27	42
Total	339	279	327	184	276

CHIKV=chikungunya virus; CI=confidence interval; D1=VLA1553-301 Visit 1 - Day 1; D29=VLA1553-301 Visit 3 - Day 29; D180=VLA1553-301 Visit 5 - Day 180; GMT=geometric mean titers; SAP=statistical analysis plan; Y1=VLA1553-303 Visit 1 - Year 1; Y2=VLA1553-303 Visit 2 - Year 2.

Ixchiq; active substance: Chikungunya virus (CHIKV) Δ5nsP3 strain (live, attenuated)

Cross-immunity alphaviruses - Ixchiq

*Figure 19. : Antibodies in VLA1553 human immune sera cross-neutralize different CHIKV strains and related arthritogenic alphaviruses. Individual data per participant over time is displayed by virus strain. Neutralizing antibody titres are compared by one-way ANOVA with multiple comparisons (Friedman test) where * p < 0.05, ** p < 0.01. The LOD is shown with a dotted line and refers to the minimum dilution of 1:20 tested (source figure 26 of AtQ 150)*

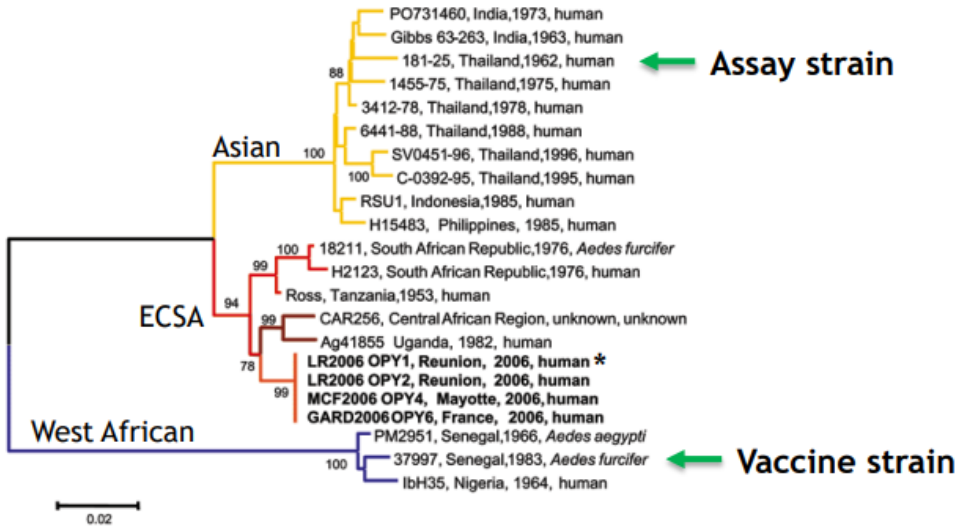


Ixchiq; active substance: Chikungunya virus (CHIKV) Δ5nsP3 strain (live, attenuated)

CHIKV-luciferase assay developed to evaluate vaccine efficacy measures cross-neutralization

- CHIK181/25 live-attenuated virus (Asian lineage AF15561) engineered to express luciferase transgene (CHIKV-luc assay reporter)
- Neutralization assay based on 80% (NT_{80}) reduction of luciferase activity following Vero cell infection with CHIKV-luc
- CHIKV-luc virus used in the assay is heterologous to the CHIKV VLP (Asian vs West African)

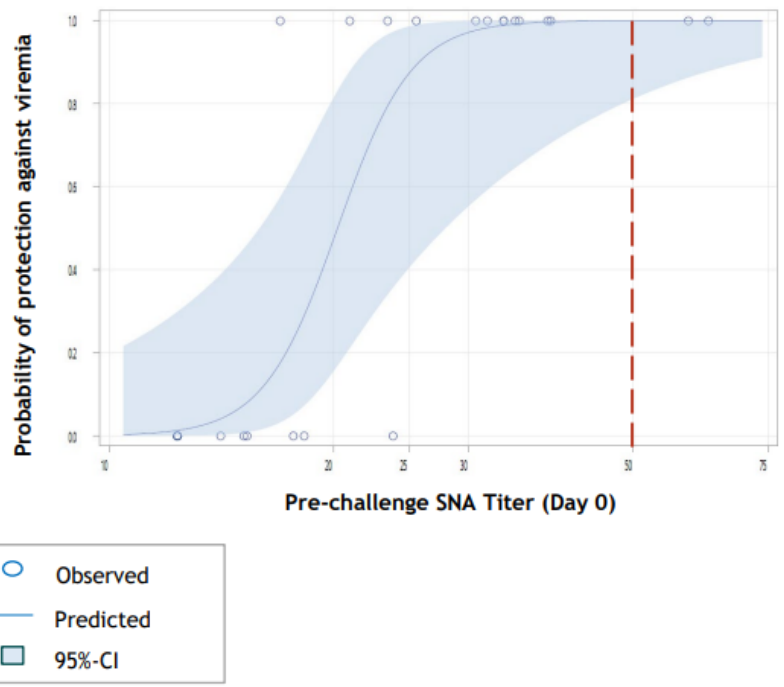
Phylogenetic analysis of CHIKV isolates based on a 1kb fragment in the E1 gene[1]



1. Parola P, de Lamballerie X, Jourdan J, Rovery C, Vaillant V, Minodier P, *et al*. Emerg Infect Dis. 2006;12(10):1493-1499.

ECSA, East-Central-South-African * CHIKV strain that was used as a challenge in nonhuman primate serum transfer study (next slide)

Conservative serum neutralizing antibody (SNA) threshold chosen for phase 3 study immunogenicity endpoints based on NHP data & regulatory agency recommendations

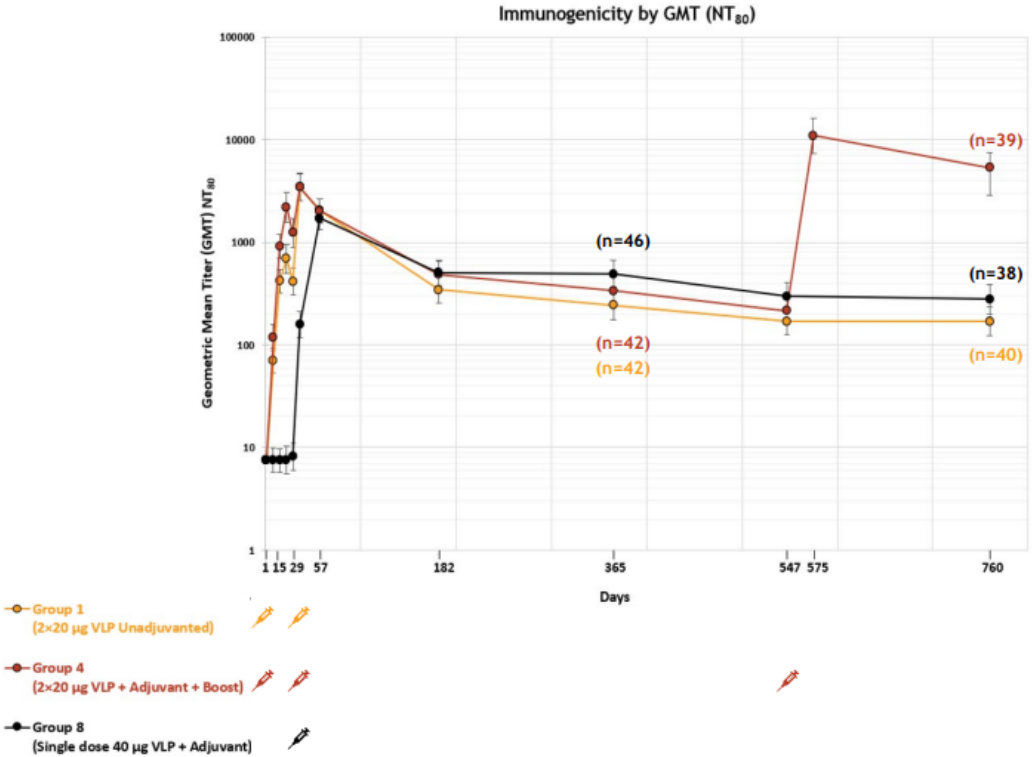


Serum passive transfer and challenge study in NHP

- NHPs received pooled sera from human participants vaccinated with CHIKV VLP at various dilutions intravenously and were challenged with CHIKV 24 hours later
- Logistic regression model:
  - SNA titer of 50 results in 99.97% [81-100] probability of protection against viremia
- Regulatory agencies* proposed and agreed a more conservative SNA titer threshold of 100 to be an acceptable surrogate endpoint

CHIKV, chikungunya virus; NHPs, nonhuman primate; SNA, serum neutralizing antibodies; CI, confidence interval
Data presented at ESCMID Global 2024 (not yet published in a peer-reviewed article)
*FDA and EMA

Single 40 µg CHIKV VLP adjuvanted dose had superior immunogenicity after first vaccination, showed a rapid and durable response, and was well-tolerated



- At year 1, Group 8 had significantly higher GMTs vs Group 1 (491.7 vs 243.4; p-value=0.0019); this was maintained at year 2 (279.7 vs 169.8; p-value=0.0369)
- AEs mostly mild to moderate; no serious treatment-related unsolicited AEs
- Local AEs more frequent in 40 ug adjuvanted CHIKV VLP group (40%) than in unadjuvanted group (23%)

Primary Endpoint: GMT of anti-CHIKV SNA level on Day 57 (28 days after last vaccination); adjuvant = aluminum hydroxide
Vertical bars denote 95% confidence interval. GMT = geometric mean titer; NT_{80} = Neutralization Titer showing 80% neutralization
Bennett *et al*. Lancet Infect Dis. 2022;22(9):1343-55.

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Vimkunya clinical immunogenicity - SmPC

Table 2: Anti-CHIKV SNA seroresponse rate (SRR) at visit days 8, 15, 22 and 183 for phase 3 Study 1 (12 to < 65 years of age) (immunogenicity evaluable population)

Study day	SRR VIMKUNYA (N=2 559) n/N (%)[a] [95% CI][b]	SRR placebo (N=424) n/N (%)[a] [95% CI][b]	SRR difference [95% CI][c]	p-value[d]
Day 8	1 169/2 510 (46.6%) [44.6%, 48.5%]	2/419 (0.5%) [0.1%, 1.7%]	46.1% [43.8%, 48.1%]	< 0.0001
Day 15	2 355/2 434 (96.8%) [96.0%, 97.4%]	3/395 (0.8%) [0.3%, 2.2%]	96.0% [94.3%, 96.8%]	< 0.0001
Day 22	2 503/2 559 (97.8%) [97.2%, 98.3%]	5/424 (1.2%) [0.5%, 2.7%]	96.6% [95.0%, 97.5%]	< 0.0001
Day 183	1 967/2 301 (85.5%) [84.0%, 86.9%]	6/401 (1.5%) [0.7%, 3.2%]	84.0% [81.7%, 85.6%]	< 0.0001

CI = confidence interval; SNA = serum neutralising antibody, SRR = seroresponse rate

[a] n is the number of participants with seroresponse ≥ titre 100, divided by N, the total number of participants in the group.

[b] 95% CIs of seroresponse rates are based on the Wilson method.

[c] Seroresponse rate difference is (VIMKUNYA minus placebo); 95% CIs are based on the Newcombe hybrid score method. Statistical superiority to placebo and lower bound of the 2-sided 95% CI on the difference in seroresponse rates between VIMKUNYA group and placebo group ≥ 70% (considered clinically significant).

[d] p-value is from a 2-sided chi-square test of equality of seroresponse percentages between groups.

Vimkunya Safety – EMA assessment report

Effect	Short Description	Unit	CHIKV VLP	Placebo	Uncertainties/ Strength of evidence	References
Solicited AEs (Reactogenicity)	Solicited administration site effects [a]	% of individuals	23.4	8.0	Transient effect, majority mild to moderate in severity	pooled data from ISS (mainly from study -004)
	Solicited systemic effects [b]	% of individuals	30.7	21.6		
Unsolicited AEs	all	% of individuals	15.7	14.4		
	related [c]	% of individuals	2.4	1.9		
SAEs	all	% of individuals	1.0	0.6		
	related	% of individuals	0	0		

a Solicited administration-site effects include injection-site pain, redness and swelling
b Solicited systemic effects include fever, chills, fatigue, headache, myalgia, arthralgia, nausea
c by PT most frequent: CHIKV VLP: headache (0.3%), arthralgia (0.3%), dizziness (0.2%), fatigue (0.2%), rash (0.2%) vs. Placebo: fatigue (0.4%), arthralgia (0.3%), myalgia (0.3%)

Ixchiq clinical immunogenicity - SmPC

Table 2. Seroresponse rates over time, as determined by µPRNT$_{50}$ assay, in study VLA1553-301 (PP population)

Study	**VLA1553-301**	
Treatment	Placebo	IXCHIQ
	N=96	N=266
	(n [95%CI])	(n (%) [95%CI])
28 days post-vaccination	0 [0.0, 3.8]	263 (98.9) [96.7, 99.8]
6 months post-vaccination	0 [0.0, 4.0]	233 (96.3) [93.1, 98.3]

Abbreviations: CI=confidence interval; µPRNT$_{50}$=50% micro plaque reduction neutralization test; PP=per-protocol (population)

Effect	Short Description	Unit	VLA1553	Placebo	Uncertainties / Strength of evidence	References
Liver function test increased	Alanine aminotransferase (ALT)	%	16.9 14.9 (15.5)*	9.9	301: 497 vac. part. 302: 273 vac. part.	301 T14.3.3.2.2 302 T14.3.3.2.2
	Aspartate aminotransferase (AST)	%	13.0 10.9 (11.7)*	7.4	301: 497 vac. part. 302: 273 vac. part.	301 T14.3.3.2.2 302 T14.3.3.2.2
Chikungunya-like adverse reactions (broad definition)	Combinations of fever with headache, fatigue, myalgia, arthralgia, or other symptoms also reported for acute-stage chikungunya illness	%	12.1	0.6	Total of 4,643 vaccinated participants	Post Hoc analysis
White blood cell count decreased	Neutropenia (neutrophile decreased)	%	42.3 42.7 (41.8)*	12.4	301: 497 vac. part. 302: 273 vac. part.	301 T14.3.3.1.2 302 T14.3.3.1.2
	Leukopenia (leukocyte decreased)	%	32.0 31.4 (31.2)*	5.8	301: 497 vac. part. 302: 408 vac. part.	301 T14.3.3.1.2 302 T14.3.3.1.2
	Lymphopenia (lymphocyte decreased)	%	23.5 22.0 (22.3)*	7.4	301: 497 vac. part. 302: 273 vac. part.	301 T14.3.3.1.2 302 T14.3.3.1.2

Ixchiq Safety –EMA assessment

4.3 Contraindications

Immunodeficient or immunosuppressed individuals due to disease or medical therapy (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised)

4.5 Concomitant administration with other vaccines

IXCHIQ is not recommended to be co-administered with other vaccines because there are no data on the safety and immunogenicity following concomitant administration of IXCHIQ with other vaccines.

Post-approval evidence for CHIKV vaccines

- Paediatric studies in PIPs: safety and immunogenicity from birth
- Pregnancy registries and for specific aspects also safety studies
- Efficacy: Individually randomised trials are requested, but ability to generate robust data on efficacy unclear
- Effectiveness studies are expected to be conducted in the context of emerging outbreaks and/or endemic areas and should be part of the portfolio of options
- Studies should measure efficacy/effectiveness against PCR confirmed symptomatic disease, e.g. per WHO case definition
- It would be relevant to collect evidence on post-acute sequalae to establish the impact of vaccination

Conclusions

- Neutralising antibodies titres have been used for inferring protection for CHIKV vaccines
- Threshold defined taking into account sero-epidemiological studies and NHP passive transfer data
- Seroresponse in seronegative subjects as primary outcome for immunogenicity shown for both vaccines (LB 95% CI above 70%)
- Limited data on seropositive individuals presented
- Post-approval commitments for clinical trials and studies for safety and efficacy/effectiveness