EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Approved Chikungunya vaccines and post-approval studies

WHO, 8 April 2025

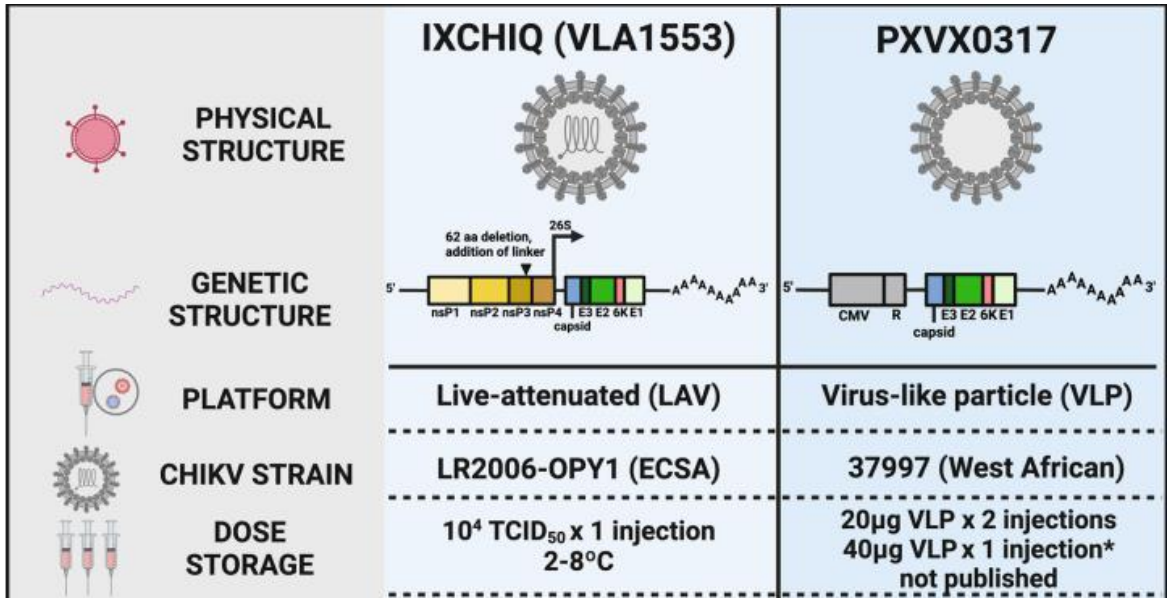

- Dr. Marco Cavaleri
- Head of Public Health Threats Department
- Chair of EMA Emergency Task Force

# Two vaccine products are currently licensed in various WHO Member States for use against chikungunya; neither have PQ / EUL status

| Product | Description | Dosing | Administration / presentation | Where licensed | Indicated age group | Contraindications |
|---|---|---|---|---|---|---|
| **IXCHIQ (Valneva)** | Live, attenuated vaccine | Single dose regimen | • Lyophilized powder, solvent<br>• Intramuscular administration (deltoid)<br>• 0.5 ml dose | • US (Nov 2023)<br>• Canada (Jun 2024)<br>• EU (Jul 2024)<br>• UK (Feb 2025) | • All countries: 18 and above<br>• EU: Pending label extension to 12 and above | • Immunocompromised individuals<br>• Caution in pregnant & breastfeeding women |
| **VIMKUNYA (Bavarian Nordic)** | Virus-like particle, aluminum adjuvant | Single dose regimen | • Pre-filled syringe<br>• Intramuscular administration<br>• 0.8 ml dose | • US (Feb 2025)<br>• EU (Feb 2025) | • All countries: 12 and above | • (Likely) Caution in pregnant & breastfeeding women |

☐ *Focus of today's discussion*

# *Chikungunya vaccines with full approval at EMA*




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

Vaccine is indicated for active immunisation for the prevention of disease caused by chikungunya virus (CHIKV) in individuals 12 years and older.

The use of this vaccine should be in accordance with official recommendations.

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

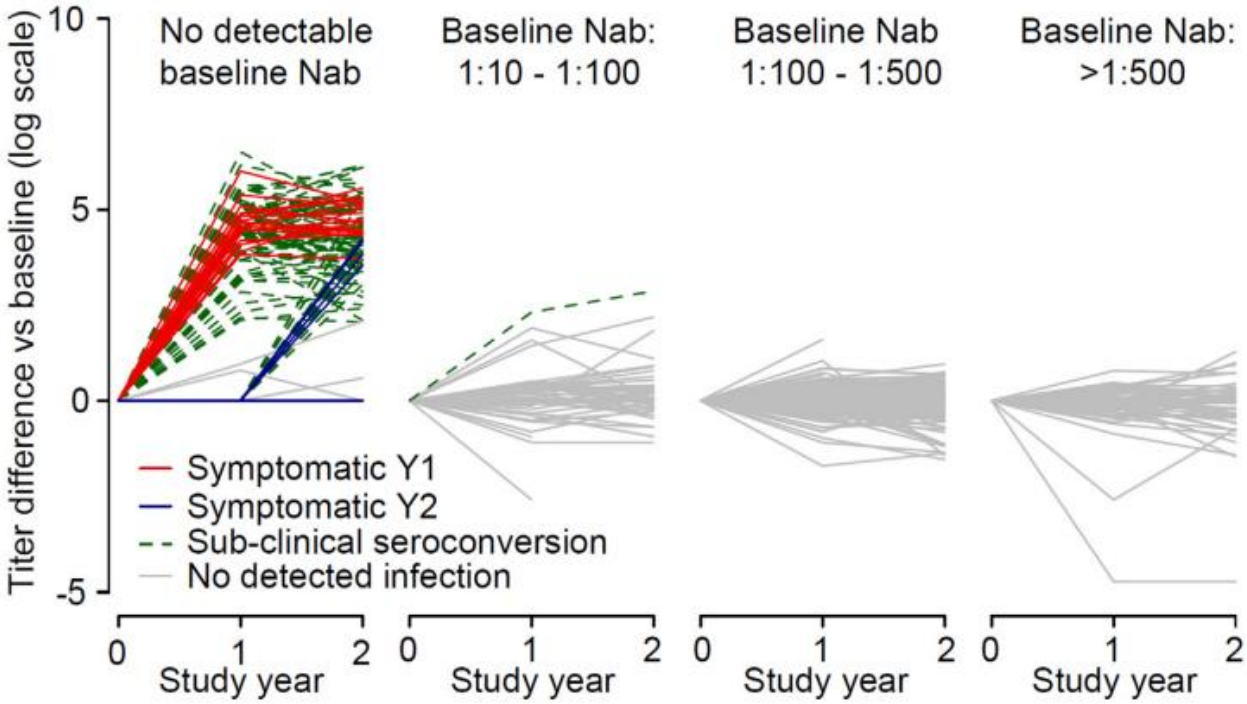
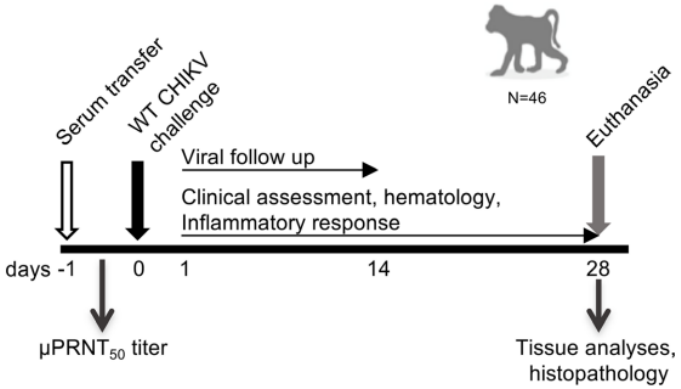



**Figure 2.** Changes in CHIKV PRNT80 titer (log scale) from baseline to 12 months (study year 1) and 24 months (study year 2) for each cohort participant according to baseline CHIKV PRNT80 titer group: no detectable NAb (<1:10), low titer (1:10 to <1:100), medium titer (1:100–1:500), high titer (>1:500). 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.




# 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.**

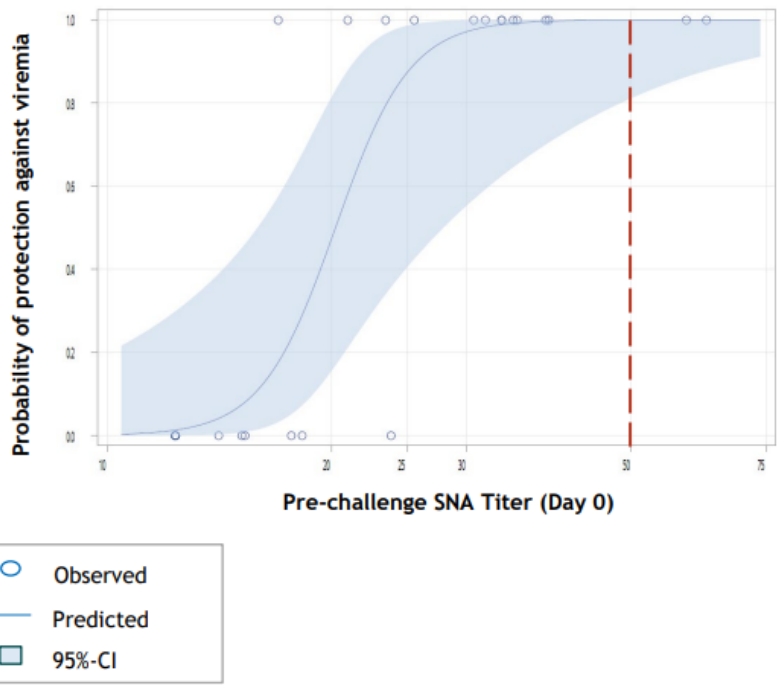
| | | µPRNT$_{50}$ ≥ 50 (*n* = 13) | µPRNT$_{50}$ ≥ 100 (*n*=4) | µPRNT$_{50}$ ≥ 150 (*n* = 2) |
|---|---|---|---|---|
| Peak viremia (copies/mL) Day 2–6 | Geometric mean | 941.1 | 16.3 | 10 |
| | [95% CI] | [100, 8846] | [4, 77] | [10, 10] |
| Number of NHPs with detected CHIKV RNA | Not detected | 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.



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

# 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

# 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.

# 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)

# 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%)

| Effect | Short Description | Unit | VLA1553 | Placebo | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| Liver function test increased | Alanine aminotransferase (ALT) | % | 16.9<br>14.9<br>(15.5)* | 9.9 | 301: 497 vac. part.<br>302: 273 vac. part. | 301<br>T14.3.3.2.2<br>302<br>T14.3.3.2.2 |
| | Aspartate aminotransferase (AST) | % | 13.0<br>10.9<br>(11.7)* | 7.4 | 301: 497 vac. part.<br>302: 273 vac. part. | 301<br>T14.3.3.2.2<br>302<br>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<br>42.7<br>(41.8)* | 12.4 | 301: 497 vac. part.<br>302: 273 vac. part. | 301<br>T14.3.3.1.2<br>302<br>T14.3.3.1.2 |
| | Leukopenia (leukocyte decreased) | % | 32.0<br>31.4<br>(31.2)* | 5.8 | 301: 497 vac. part.<br>302: 408 vac. part. | 301<br>T14.3.3.1.2<br>302<br>T14.3.3.1.2 |
| | Lymphopenia (lymphocyte decreased) | % | 23.5<br>22.0<br>(22.3)* | 7.4 | 301: 497 vac. part.<br>302: 273 vac. part. | 301<br>T14.3.3.1.2<br>302<br>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

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

| Description | Due date |
|---|---|
| Post-authorisation efficacy study (PAES): In order to confirm the efficacy of Ixchiq in individuals 18 years and older, the MAH should conduct, according to an agreed protocol, and submit the results of, a randomized, controlled trial with pragmatic elements to assess the effectiveness of Ixchiq vaccination in the prevention of symptomatic, laboratory confirmed chikungunya after a single vaccination with Ixchiq in adults in endemic areas. | Final report due date:<br>31 Dec 2029 |

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

| Description | Due date |
|---|---|
| Post authorisation efficacy study (PAES): In order to confirm the efficacy of VIMKUNYA in individuals 12 years and older, the MAH should conduct and submit the results of a randomized, placebo-controlled, double-blind, event-driven study to analyse efficacy, safety, and immunogenicity of VIMKUNYA in the prevention of chikungunya disease in healthy adults and adolescents in CHIKV-endemic areas, according to an agreed protocol. | Final report due date:<br>31st August 2030 |

# Post-approval evidence for CHIKV vaccines

- For RCTs, good understanding of the attack rate to define adequate sample size
- Impact of seropositivity at baseline
- Outbreaks tend to be fast-spreading and short-lived: timing of vaccination critical
- Acceptance by NRAs and RECs in Countries
- Case definition for PCR confirmed CHIKV disease: WHO? Others?
- Case ascertainment: active vs passive surveillance
- PCR testing: central lab vs local
- Evidence on post-acute sequalae besides symptomatic disease

# Post-approval evidence for CHIKV vaccines

- Vaccines are approved in the EU as full approval based on strong evidence on correlates of protection with commitments for post-approval clinical studies for confirmation
- Paediatric studies in PIPs: safety and immunogenicity from birth
- Pregnancy registries and for specific aspects also safety studies
- Efficacy: Individually randomised trials are requested, acknowledging the uncertainties on what can be achieved
- Effectiveness studies are expected to be conducted in addition and should be part of the portfolio of options