Overview of the Valneva's single-shot chikungunya vaccine – IXCHIQ®/ VLA1553, planned phase IV post-licensure studies and updates on potential for outbreak response

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The World’s First Chikungunya Vaccine

IXCHIQ® / VLA1553

IXCHIQ® is currently approved by the U.S. Food & Drug Administration (FDA), European Medicines Agency (EMA), The UK’s Medicines and Healthcare products Regulatory Agency (MHRA) and Health Canada for the prevention of disease caused by chikungunya virus in individuals 18 years of age and older. It is approved as well for adolescents age 12+ years by EMA.

Continued approval of IXCHIQ® in the U.S. is contingent upon verification of clinical benefit in confirmatory studies.

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IXCHIQ® is approved for use only in the United States, Canada, Europe, and the United Kingdom. VLA1553 is an investigational vaccine candidate that has not been approved for use in other jurisdictions and has not been determined by any regulatory authorities in such jurisdictions to be safe or effective.

Partnerships in Brazil & India

Ensuring the vaccine is available where needed most

- In May 2020, Valneva partnered with **Instituto Butantan**, Brazil, and in December 2024 with **Serum Institute of India** for the development, manufacturing (following a tech transfer) and marketing of Valneva's chikungunya vaccine in Low and Middle Income Countries.

- Collaboration with Instituto Butantan also includes joint VLA1553 clinical trials (e.g., Ph3 trial in adolescents in Brazil) and observational Ph4 studies in Brazil (post-marketing commitments/ requirements).

IXCHIQ®/VLA1553 vaccine candidate is a live-attenuated, single-dose vaccine[1,2]

- Designed to target all globally circulating chikungunya virus (CHIKV) strains[2]
- Intended to trigger the rapid development of a protective antibody titer[2]
- Based on the La Réunion strain (LR2006-OPY1) of the East/Central/South African (ECSA) genotype[1,2]
- Attenuation of the LR2006-OPY1 strain was achieved by reverse genetics resulting in a large deletion of amino acids within the C-terminal part of the non-structural protein 3 (nsP3) of the replicase complex[1]

IXCHIQ®/VLA1553 vaccine candidate construct:

61 amino acid deletion in nsP3 protein of La Réunion CHIKV strain[1]

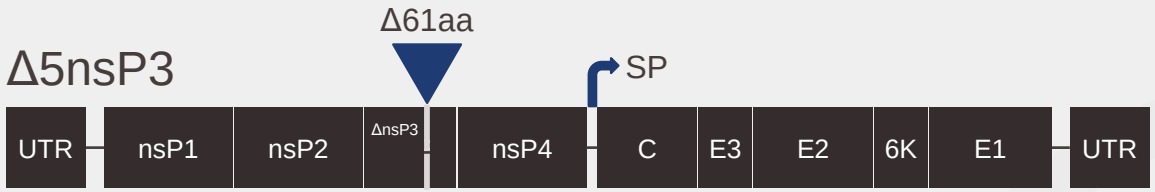

Image adapted from Hallengard D, et al., 2014.

- No change of deletion detectable after serial passages on Vero cells[1]
- Smaller plaque size as compared to CHIKV clone LR2006-OPY1[1]
- Reduced replication capacity as compared to CHIKV parent clone LR2006-OPY1 in vitro and in vivo[1]

1. Hallengärd D, et al. J Virol. 2014;88(5):2858-2866. 2. Schneider M, et al. Lancet 2023;401(10394):2138-2147.

IXCHIQ® - Valneva's Chikungunya Vaccine

IXCHIQ®
(CHIKUNGUNYA VACCINE, LIVE)

The 1st vaccine against chikungunya providing a strong and persistent immune response with only one dose

- 98.9% seroresponse rate at Day 29 - Sustained seroresponse rate at 96% after three years[1]
- Strong and persistent immune response in adults 18-64 yrs and 65+[2], as well as adolescents
- Generally well tolerated among the >3,600 adults, 754 adolescents and 304 children evaluated for safety[3]
- Convenient single dose administration

1. Two-year antibody persistence (97%) included in current EU label; submitted for inclusion in U.S. and Canadian labels; 2. Included in current U.S., EU, UK, and Canadian labels; 3. No adverse drug reaction reported since approval of IXCHIQ® indicate any changes compared to knowledge from clinical trials.

Licensure Pathway for Chikungunya Vaccines

Accelerated approval pathway agreed with regulators for chikungunya vaccines

Regulators agreed licensure based on serological endpoint: surrogate endpoint "Seroresponse Rate"

A non-human primate (NHP) model was used to determine a surrogate of protection

- The NHP model mimics many aspects of human disease

Experimental Set-Up[1]:

- Sera from human vaccinees at varying titer levels were transferred to NHP's
- Animals challenged with wild-type chikungunya virus, monitored for fever and viremia

Results[1]:

- **No fever** in any of the NHP's who received human post-vaccination serum
- **No live, replicating virus** detected
- All animals had **strongly reduced, some undetectable, viral RNA** load, depending on titer
  - Determined **pre-challenge titer** resulting in **sterilizing immunity** in NHPs – very conservative approach: **seroresponse defined as $\mu PRNT_{50} \geq 150$**

Further evidence[1]:

Protective titer determined in a **prospective seroepidemiological trial** in the Philippines translated into a **$\mu PRNT_{50}$ of ~49**

1 Roques P, et al. *JCI Insight.* 2022;7(14):e160173. doi: 10.1172/jci.insight.160173.

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VLA1553-301 & -303: Pivotal Phase 3 and Long-term Follow-up Clinical Trial

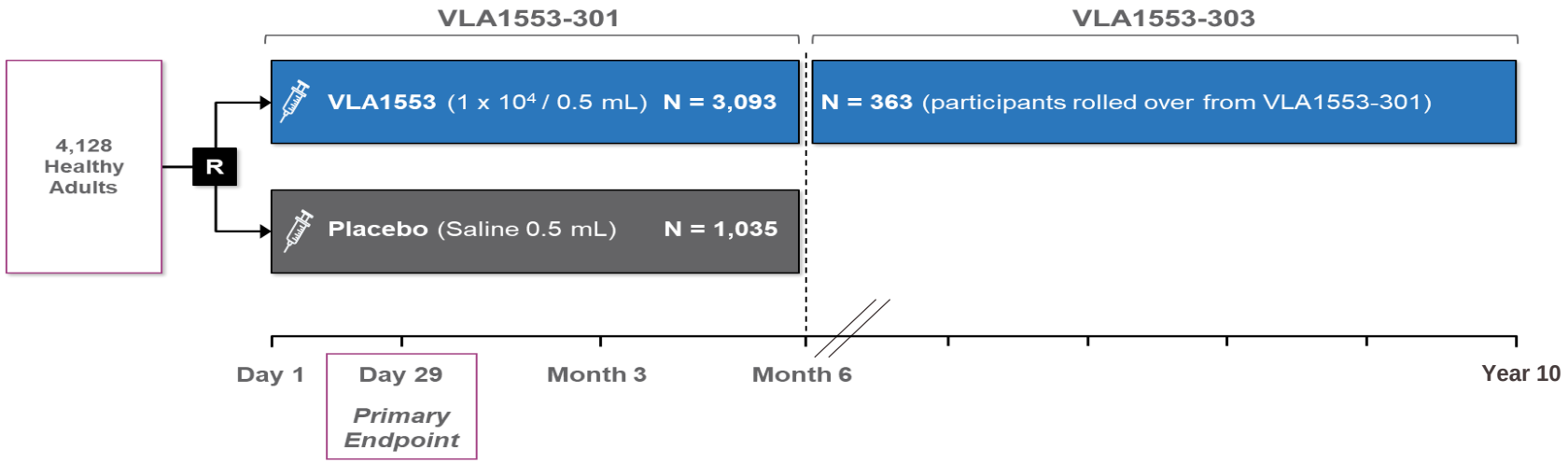
Designed to provide safety and immunogenicity data as the basis for licensure and to evaluate antibody persistence and long-term safety of VLA1553

VLA1553-301: Multicenter, randomized, placebo-controlled double-blind Phase 3 clinical trial in adults conducted in US

- 4,128 healthy adults, ≥ 18 years old, randomized 3:1 to receive a single vaccination of VLA1553 or placebo
- **Primary endpoint: rate of participants achieving seroresponse** (or CHIKV-specific neutralizing antibody titers ≥ 150) after single vaccination of VLA1553

VLA1553-303 is an open-label phase 3b, single-arm study

- 363 participants rolled over from VLA1553-301, after completing the 6-month follow-up
  - **Primary objective**: Evaluate **persistence of antibodies** annually for up to 10 years after the single immunization with VLA1553
  - Secondary objective: Evaluate long-term **safety** through 2 years
- Includes new-onset SAEs and any ongoing AESIs from VLA1553-301



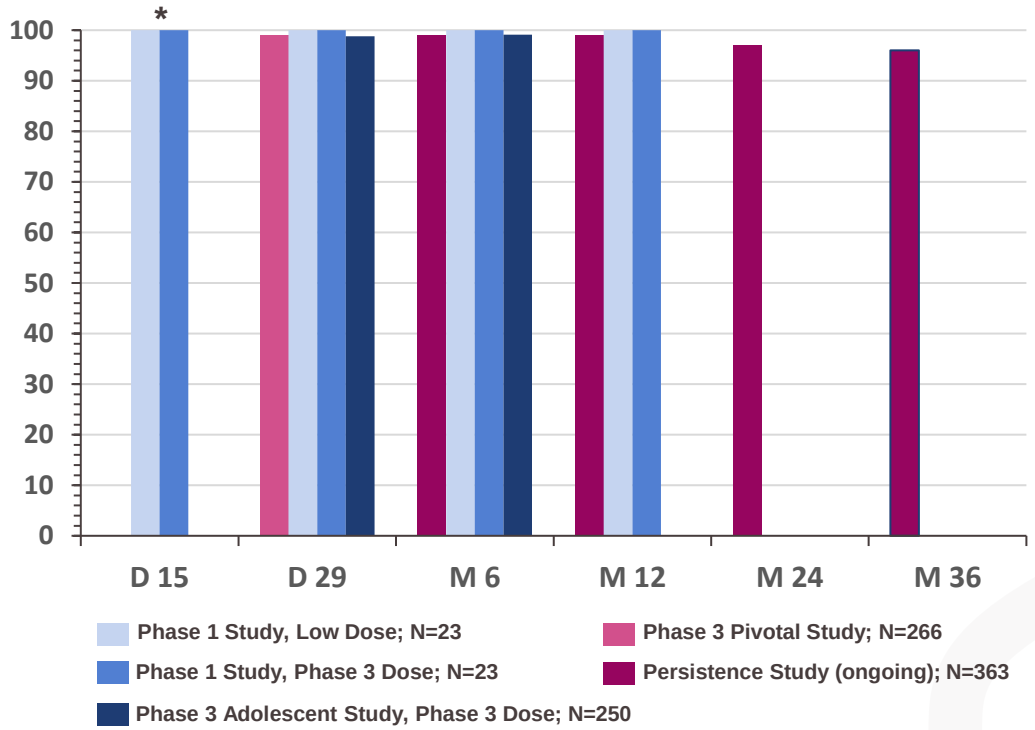
N = number of participants in the intention-to-treat population

WHO consultation on CHIKV outbreak – 08-Apr-2025

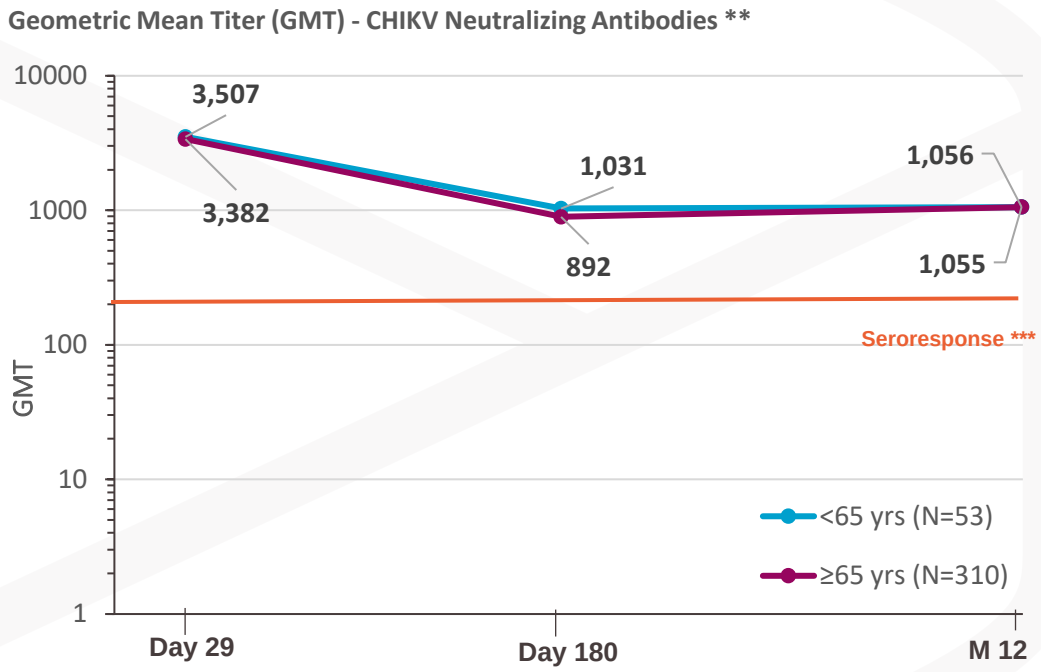
VLA1553 Induces Early and Sustained Response Regardless Of Age

High seroresponse rates across studies

Seroresponse sustained at highest levels up to Month 36



Comparable titers in younger and older adults



** Persistence Study, Whole Sample Population
*** Seroresponse : µPRNT50 ≥ 150, titer reasonably likely to predict protection

***** Wressnigg et al, Lancet ID: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30238-3/fulltext; Re-testing of Phase 1 sera (vaccinated with liquid formulation of VLA1553) using the final assay/threshold used for the pivotal endpoint; data presented at CISTM18, May 2023

Proven in Clinical Trials To Maintain Long-Lasting Immunity For No Less Than 3 Years

Differentiated vaccine shows rapid, long-lasting immunity across all age groups tested[1,2,5]

Immunogenicity Data

- 99% Seroresponse[3] Rate (SRR) after single vaccination → maintained at 96% after 36 months[4,5,6]
- Similar SRR and antibody titers in age 65+ adults as younger adults[1,4]
- 100% SRR after 14 days and sustained for 12 months[2]
- Adolescent trial met primary endpoint[7]: highly immunogenic in baseline-negative individuals; 99% SRR sustained at 98% after 12 months[8]

Safety Data

- Generally well tolerated by >3,600 adults and 754 adolescents
- Pivotal Safety (solicited systemic AEs):
  - ~50% of participants, most commonly headache, fatigue, myalgia
  - Majority mild or moderate; 2.0% reported as severe, most commonly fever
- Adolescent[9] and pediatric[10] trials demonstrated favorable safety profile regardless of previous CHIKV infection

1. Valneva Successfully Completes Pivotal Phase 3 Trial of Single-Shot Chikungunya Vaccine Candidate; 2. Re-testing of Phase 1 sera (vaccinated with liquid formulation of VLA1553) using the final assay/threshold used for the pivotal endpoint; data presented at CISTM18, May 2023; 3. CHIKV neutralizing antibody titer of ≥150 by $\mu PRNT_{50}$ (Micro Plaque Reduction Neutralization Test), agreed with regulators to be used as a surrogate endpoint in Phase 3; 4. Valneva Reports Positive 12-Month Antibody Persistence Data for Single-Shot Chikungunya Vaccine Candidate; 5. Valneva Reports Positive 24-Month Antibody Persistence Data for its Single-Shot Chikungunya Vaccine IXCHIQ®; 6. Valneva Reports Positive Three-Year Antibody Persistence Data for its Single-Shot Chikungunya Vaccine IXCHIQ®; 7. Valneva Reports Positive Pivotal Phase 3 Immunogenicity Data in Adolescents for its Single-Shot Chikungunya Vaccine Candidate; 8. Valneva Reports High Sustained Immune Response in Adolescents One Year After Single Vaccination with its Chikungunya Vaccine; 9. Valneva Reports Positive Initial Phase 3 Safety Data in Adolescents for its Single-Shot Chikungunya Vaccine Candidate; 10. Valneva Reports Positive Phase 2 Results in Children for its Chikungunya Vaccine and Announces Phase 3 Dose Decision

IXCHIQ® is Approved under the Accelerated Licensure Pathway[1]

Phase 3b/4 aim to verify the clinical benefit in two[2] key post-marketing effectiveness studies - Supported by a CEPI grant[3]

VLA1553-402

Observational effectiveness study in endemic areas of Brazil

- To evaluate the effectiveness of IXCHIQ® (VLA1553) in the prevention of symptomatic, virologically confirmed chikungunya infection ≥14 days after vaccination
- Test-negative case control study (RT-PCR case confirmation), ~400 cases / ~800 controls
- Municipality selection based on CHIKV risk, immunization, surveillance and test infrastructure
- Prerequisite: roll-out of pilot vaccination strategy
- Adjacent protocols:
  - Prospective safety cohort (n ~ 5000)
  - Safety in pregnant women (n ~ 100)
  - Serosurvey (Pre-exposure assessment on n ~ 5000)
- Close collaboration with Instituto Butantan, the Brazilian MoH and municipalities is key

2025 – 2028 (including pilot vaccination)

VLA1553-404

Pragmatic randomized controlled trial on effectiveness and safety in adolescents and adults (n ~ 20.000)

- To assess the effectiveness of IXCHIQ® (VLA1553) in preventing acute symptomatic virologically confirmed CHIKV infection with onset ≥14 days after vaccination
- 1:1 randomization to VLA1553 or Placebo
- Safety evaluation (n ≥10.000 VLA1553 vaccinees) for potential chikungunya-like adverse reactions and prolonged arthralgia
- Statutory requirement[4] for well-controlled clinical investigation to address potential biases associated with an observational design

2025 - 2029

1. https://www.fda.gov/vaccines-blood-biologics/ixchiq; 2. https://www.fda.gov/media/173759/download; 3. https://valneva.com/press-release/cepi-expands-partnership-with-valneva-with-a-41-3-million-grant-to-support-broader-access-to-the-worlds-first-chikungunya-vaccine/; 4. https://www.fda.gov/media/172166/download

Thank you
Merci
Danke
Tack

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