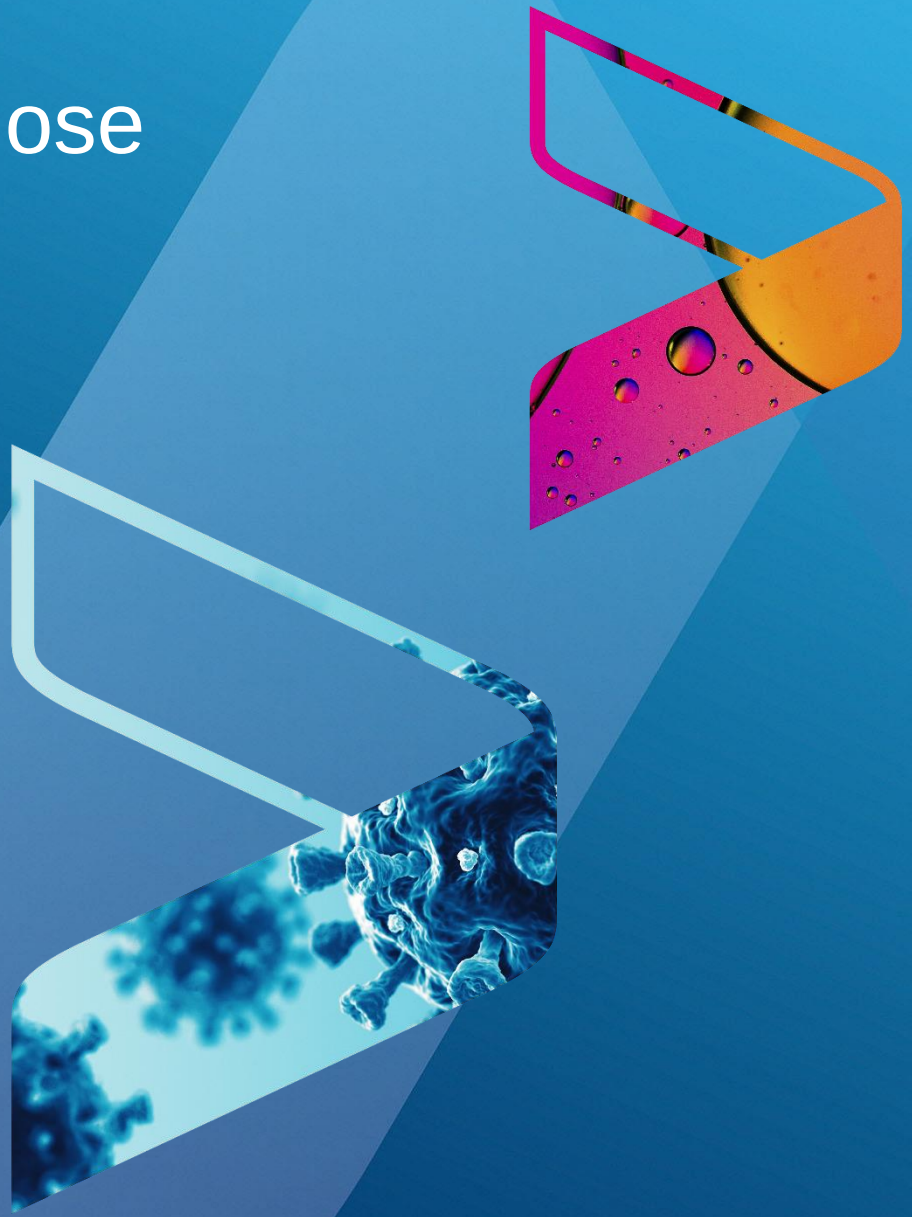
Antibody persistence of a single-dose live-attenuated chikungunya virus vaccine (VLA1553) in adults.



World Vaccine Congress, Washington
03-Apr-2024

Susanne Eder-Lingelbach
VP Clinical Development

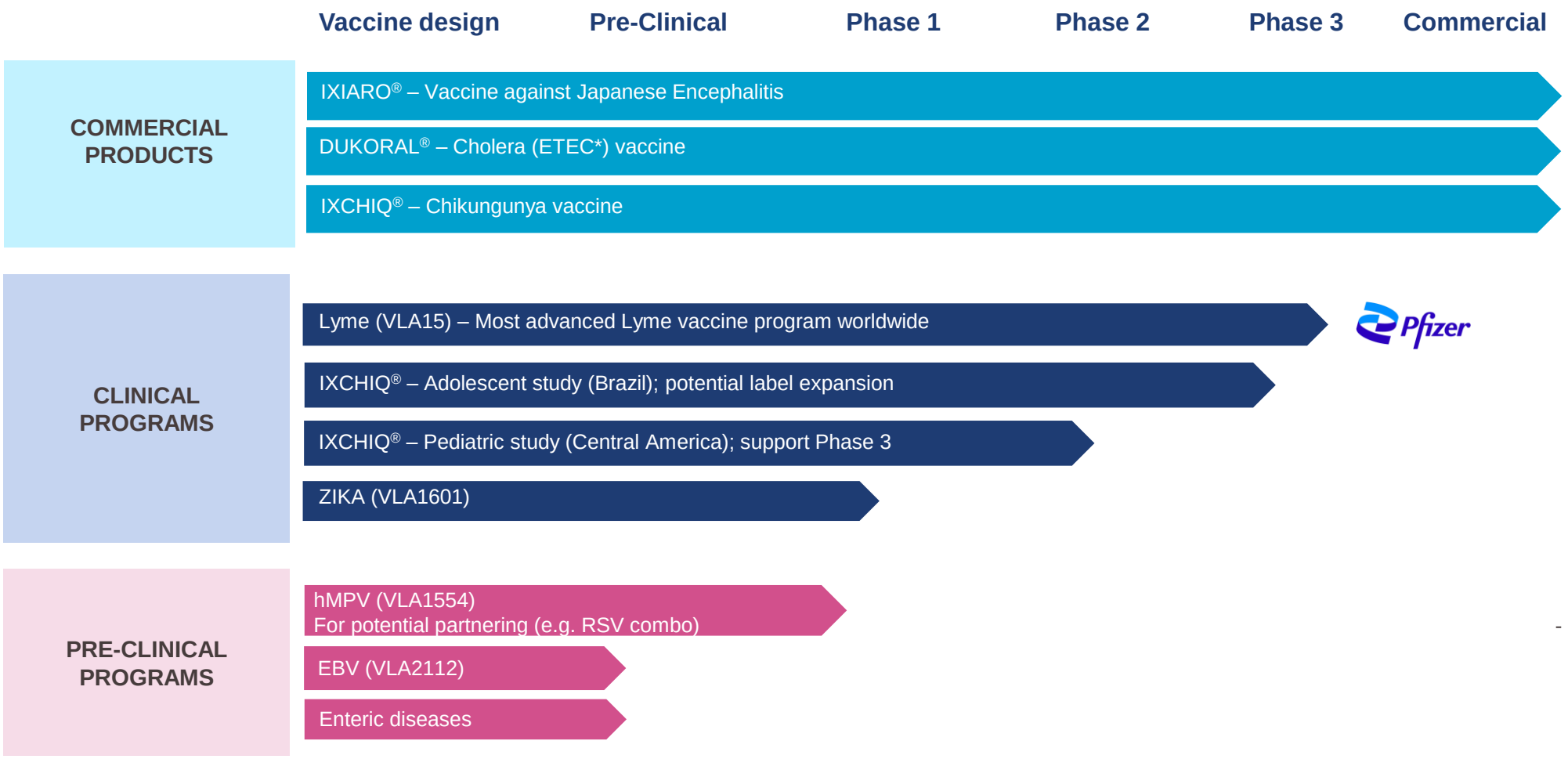
valneva

Valneva
A leading specialty vaccine company
Focused on vaccines that make a difference

- **Proven, Integrated Expertise:** Three in-house vaccine approvals; three proprietary commercialized travel vaccines
- **Focused R&D:** Advancing first-, only- or best-in-class vaccine candidates; Experience across multiple vaccine platforms
- **Leading in chikungunya virus:** World's first and only approved vaccine
- **Leading in Lyme disease:** Lead Phase 3 vaccine candidate partnered with Pfizer
- **Experienced leadership:** Substantial R&D, manufacturing and commercial expertise

Valneva's Commercial and R&D Portfolio

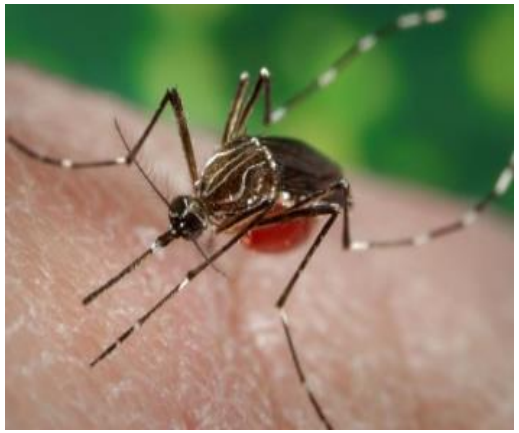
Further extending a unique, best-in class portfolio



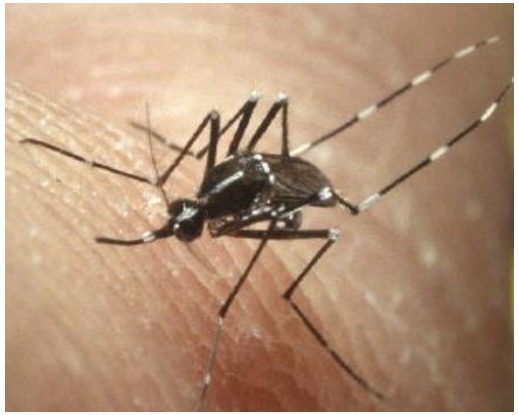
** Indications differ by country - Please refer to Product / Prescribing Information (PI) / Medication Guide approved in your respective countries for complete information, incl. dosing, safety and age groups in which this vaccine is licensed, ETEC = Enterotoxigenic Escherichia coli (E. Coli) bacterium*

Chikungunya: A Major Public Health Threat

Mosquito-transmitted disease with potentially debilitating consequences



Aedes aegypti



Aedes albopictus

- Chikungunya virus (CHIKV) is transmitted by ***Aedes*** mosquitoes[1]
- Acute chikungunya, seen in up to 97% of those infected, typically presents with sudden onset of **high fever and joint pain**.[1]
- Often causes **large, explosive outbreaks**, affecting one-third to three-quarters of the population[1]; difficult to predict next outbreaks[2]
- High burden of disease: outbreaks can have substantial health-economic impact; infection can progress to **severe chronic symptoms** in many patients[4]
- **Outbreaks** have occurred in Asia, Africa and across Latin America[1] with the potential for it to happen in the U.S. and Europe[2,4]; recent outbreak in Paraguay[5] with PAHO issuing an epidemiological alert for the Americas[6]
- **Returning infected travelers** can trigger local transmission in areas where relevant mosquitoes are established (e.g. Southern U.S./Europe)[2]

1. Staples et al. CDC Yellow Book 2020, Chapter 4 . 2. Bettis et al, PLOS Neglected Tropical Diseases 16(1): e0010069. 3. Lindsey et al *Am J Trop Med Hyg*. 2018;98(1):192-197. doi:10.4269/ajtmh.17-0668 4. Silva LA et al. J Clin Invest. 2017 Mar 1;127(3):737-749; 5 PAHO provides guidance to countries in response to increased chikungunya cases ; 6 Epidemiological Alert: Chikungunya increase in the Region of the Americas

High Acute Morbidity: Can Lead to Chronic Incapacitation

Lasting months to years in a high proportion of patients

Acute Phase
(up to 97%)[1]

- Symptoms typically begin 3-7 days after being bitten by an infected mosquito[1]
  - Fever and joint pain / joint inflammation, other systemic manifestations[1-4]
  - Joint symptoms are typically severe and can be debilitating[1]
- Viremia for 5-10 days[2,3]
- Acute symptoms typically resolve in 7-10 days[1]
- Sub-acute post-viremic state (6-21 days) can occur[3,4]
  - Persistent articular symptoms
  - Tenosynovitis and bursitis

Chronic Phase
(~43% of cases)[5]

- Long-term suffering differs per study:[6-8]
  - A study showed that 57% of patients are still somewhat affected by the disease after 2.5 years[6]
  - However, up to 78.6% of cases may have persistent muscle and joint symptoms at 27.5 months[7]
  - The CDC Yellow Book reports a range from 5 to 80% of patients with persistent joint pains, as well as prolonged tiredness, for months or years after their illness[8]

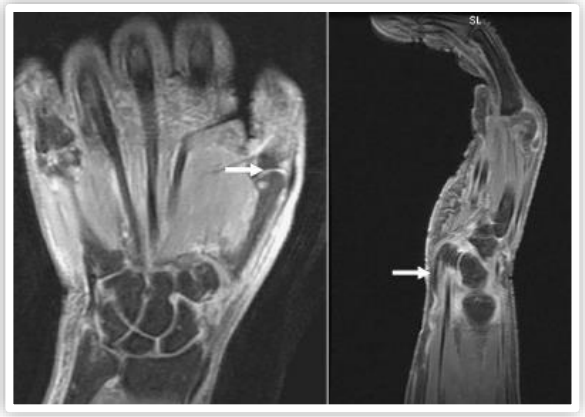
Chikungunya means “to become contorted” in Kimakonde, describing sufferers’ stooped appearance

1. Staples et al. CDC Yellow Book 2020, Chapter 4. 2. Rudolph KE et al. Am J Trop Med Hyg. 2014;90:882-891. 3 Suhrbier A et al. Nat Rev Rheumatol. 2012;8:420-429. 4. Stalkowsky F et al. PLoS one 2009;4:e7603-e7603. 5 Paixao ES, et al. Trans R Soc Trop Med Hyg. 2018;112(7):301-316. 6 Doran C, et al. PLoS Negl Trop Dis. 2022;16(3):e0010142. 7 Essackjee K, et al. Postgrad Med J. 2013;89(1054):440-447. 8 Centers for Disease Control and Prevention (CDC). Chikungunya CDC Yellow Book 2024. Available at: https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/chikungunya. Accessed: October 2023.

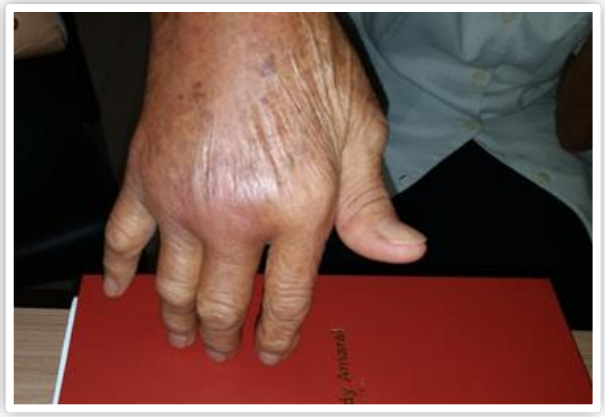
Chronic Chikungunya Negatively Impacts Quality of Life

Persistent rheumatologic disease

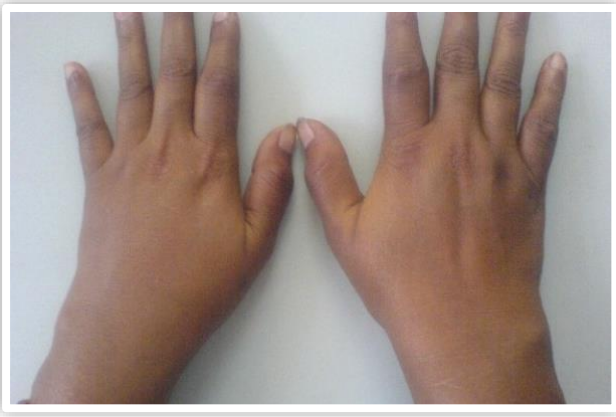
Post-CHIKV rheumatism 2 forms	**Effect of arthritis/ polyarthritis**	**Joints typically involved by polyarthritis[5]**	**Impact on life activities[1-4]**
Mechanical musculoskeletal disorders	Long-term joint pain[1-3]	• Hands • Knees • Wrists • Ankles • Shoulders	• Standing up • Walking/mobility • Using hands • Self-care • Daily/leisure activities
	Stiffness after immobility[1-3]		
Chronic inflammatory arthritis	Can be triggered by change in temperature and physical effort[4]		



Carpitis and thumb arthritis (left) – Multiple tenosynovitis of fingers and wrist (right)[1]



Two years after CHIKV infection: Intense arthritis of metacarpophalangeal joints and wrist[5]



Symmetrical inflammatory polyarthritis[3]

CHIKV = chikungunya virus.

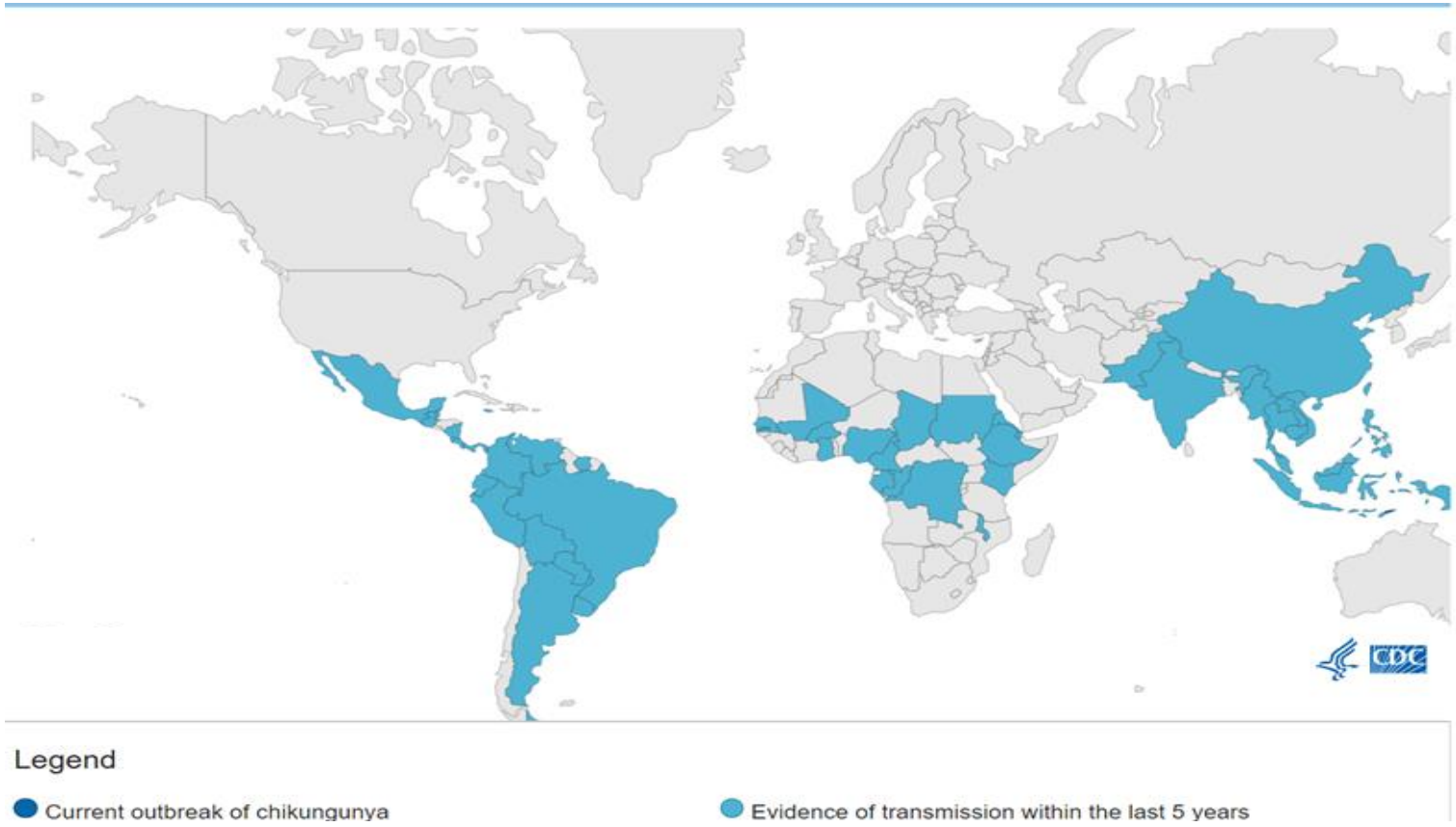
1. Simon F, et al. Medicine. 2007;86:123-137. 2. Tritsch S, et al. J Rheum. 2020;47:1267-1274. 3. Mohan A, et al. Indian J Dermatol. 2010;55:54-63. 4. Schilte C, et al. PLOS Negl Trop Dis. 2013;7:e2137. 5. Amaral J, et al. Viruses. 2019;11:289.

Chikungunya: A Global Threat

Chikungunya virus has been identified in >110 countries on all continents except Antarctica[1]

- Chikungunya virus (CHIKV) was first identified in Tanzania in 1952[1]
- Over the following ~50 years CHIKV was geographically isolated and caused occasional outbreaks in Africa and Asia[1]
- CHIKV has since spread rapidly and been identified in over 110 countries throughout the world[1]
- It is estimated that over three quarters of the world's population live in areas at-risk of CHIKV transmission[3]

Countries with current outbreaks or evidence of chikungunya virus transmission among people within the last 5 years[2]



*Does not include countries or territories where only imported cases have been documented (see reference 3 for imported cases in Europe).

1. WHO CHIGV factsheet. Available at https://www.who.int/news-room/fact-sheets/detail/chikungunya. Accessed: March 2024. 2. CDC Chikungunya Virus Disease Information. Available at: https://www.cdc.gov/chikungunya/geo/index.html. Accessed: March 2024. 3. Puntasecca CJ, et al. PLoS Negl Trop Dis. 2021; 15(3): e0009055.

VLA1553 at a Glance

Live-attenuated CHIKV vaccine targeting long-lasting immunity with a single dose

CHIKV VLA1553

- **Live-attenuated**, **single dose**, i.m., **lyophilized**
- Based on **La Reunion strain** of East Central South African genotype
- **Attenuation by reverse genetics,** large deletion within the non-structural nsP3 protein

Development Status – FDA Approved, Preparing Phase 4

- **Pivotal** Phase 3 Trial: **Primary Endpoint (Seroresponse Rate) met**
- **Lot-to-Lot consistency** Trial: **Primary Endpoint met**
- Antibody persistence trial ongoing: positive 24 months data
- Adolescents trial in Brazil ongoing: positive Day 29 data

Regulatory Milestones

- Approved by the FDA (November 2023)
- Additional filings under review by EMA, Health Canada and Anvisa (Brazil)

Target Populations & Geographic Reach

- **Non-endemic** countries: Travelers / Military / Outbreak preparedness in U.S., EU, CAN[1]
- **Endemic** use: Partnered with CEPI and Instituto Butantan, technology transfer

1 https://www.cdc.gov/vaccines/acip/recommendations.html

Licensure Pathway for Chikungunya Vaccines

Accelerated approval pathway agreed with regulators for chikungunya vaccines

Classical efficacy studies for chikungunya vaccines are considered unfeasible in a pre-licensure setting[1]

- Unpredictable and short-lived outbreaks
- Logistical boundaries
- Acceptable timeframes and cost barriers

In the U.S., chikungunya vaccines can be licensed following the "accelerated approval" pathway

- Other regulators also agreed to licensure based on serological endpoints

FDA-agreed surrogate endpoint: "Seroresponse Rate"

1 VRBPAC Meeting, Nov 2019.

Evidence Supporting the Serological Endpoint

After transfer of human post-vaccination sera, neutralizing antibodies conferred sterilizing immunity in non-human primates

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 µPRNT$_{50}$≥150**

Further evidence[1]:

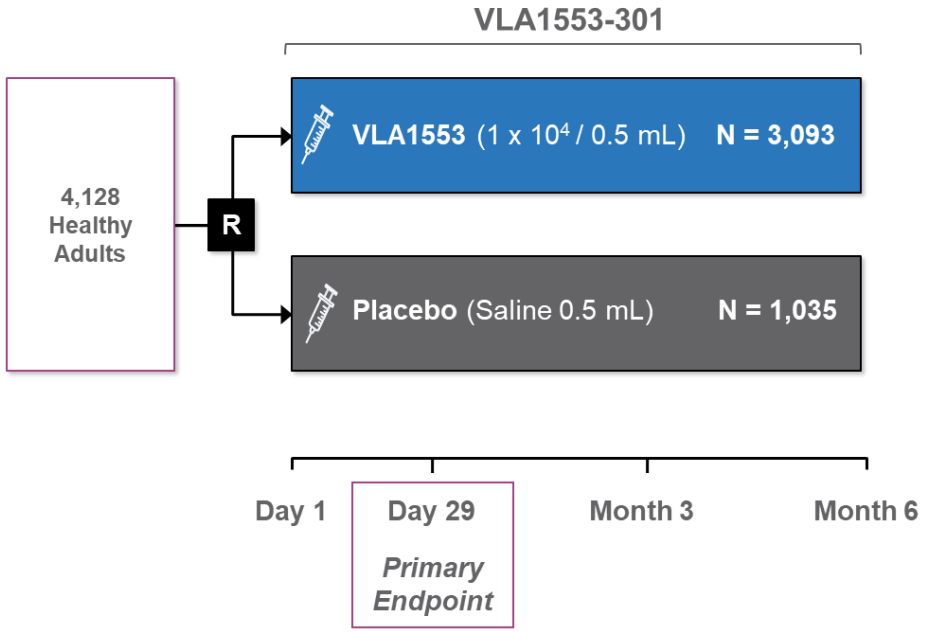
Protective titer determined in a **prospective seroepidemiological trial** in the Philippines translated into a **µPRNT$_{50}$ of ~49**

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

Pivotal Clinical Trial VLA1553-301[1]

Provides safety and immunogenicity data as the basis for licensure

- Multicenter, randomized, placebo-controlled double-blind Phase 3 clinical trial in adults conducted in US
- 4,128 healthy adults, ≥ 18 years old, were randomized 3:1 to receive a single vaccination of VLA1553 or a saline control
- **Primary endpoint: rate of participants achieving seroresponse** (or CHIKV-specific neutralizing antibody titers ≥ 150) after single vaccination of VLA1553



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

1 Schneider et al.2023; Lancet 401: 2138–47;

Demographic Data

Similar baseline characteristics between VLA1553 group and Placebo

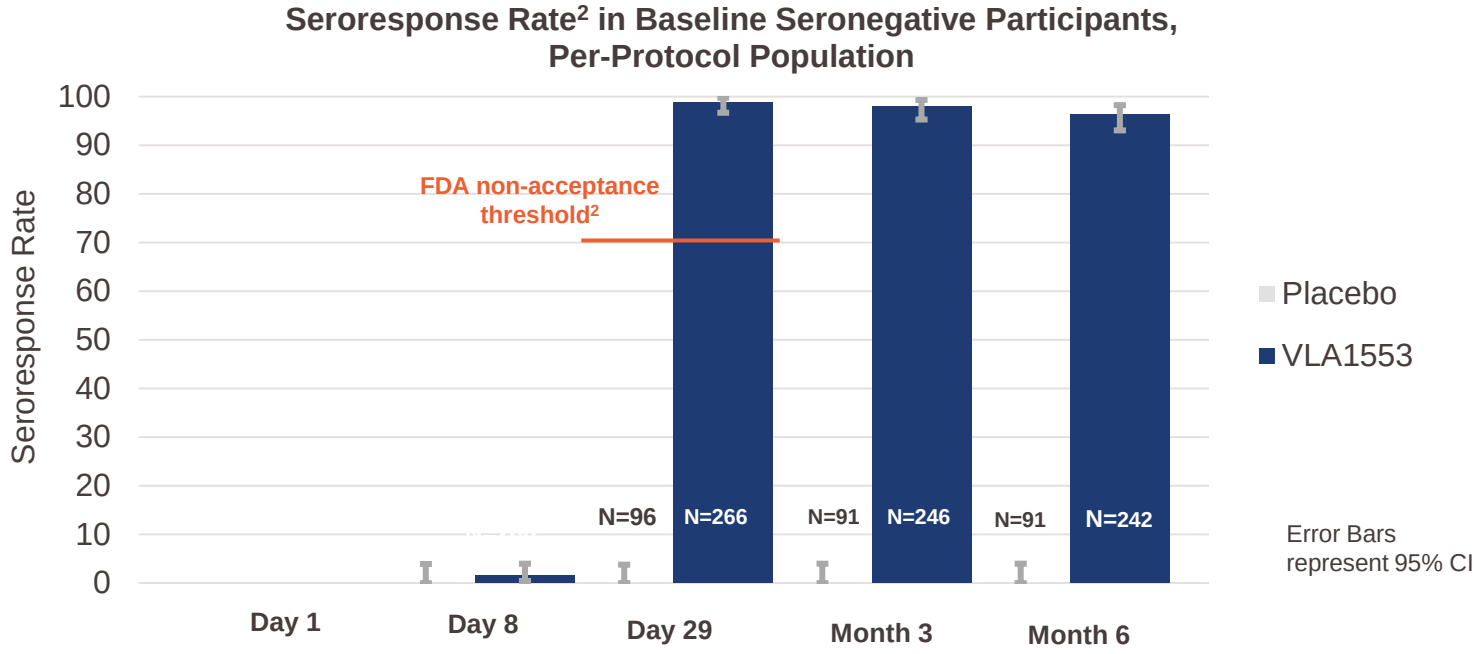
	VLA1553 N=3082	**Placebo** N=1033
Gender n (%)		
Female	1682 (54.6)	569 (55.1)
Male	1400 (45.4)	464 (44.9)
Race n (%)		
American Indian or Alaskan Native	27 (0.9)	5 (0.5)
Asian	51 (1.7)	17 (1.6)
Black or African American	451 (14.6)	122 (11.8)
Native Hawaiian or Other Pacific Islander	13 (0.4)	5 (0.5)
White	2456 (79.7)	853 (82.6)
Other	84 (2.7)	31 (3.0)
Age at screening (years)		
Mean	45.1	45.0
(Min/Max)	18, 88	18, 94
Age Group n (%)		
≥ 18 years - 64 years	2736 (88.8)	916 (88.7)
≥ 65 years	346 (11.2)	117 (11.3)

Safety Population

ACIP Presentation Slides: October 19-20, 2022 Meeting. Chikungunya Vaccines: Vaccine immunogenicity and safety (Dr. K Dubischar). Available at https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-10-19-20/03-Chikungunya-Dubischar-508.pdf Accessed: 21 March 2023;

VLA1553-301 Primary Endpoint met

Seroresponse[1] in 99% of Participants

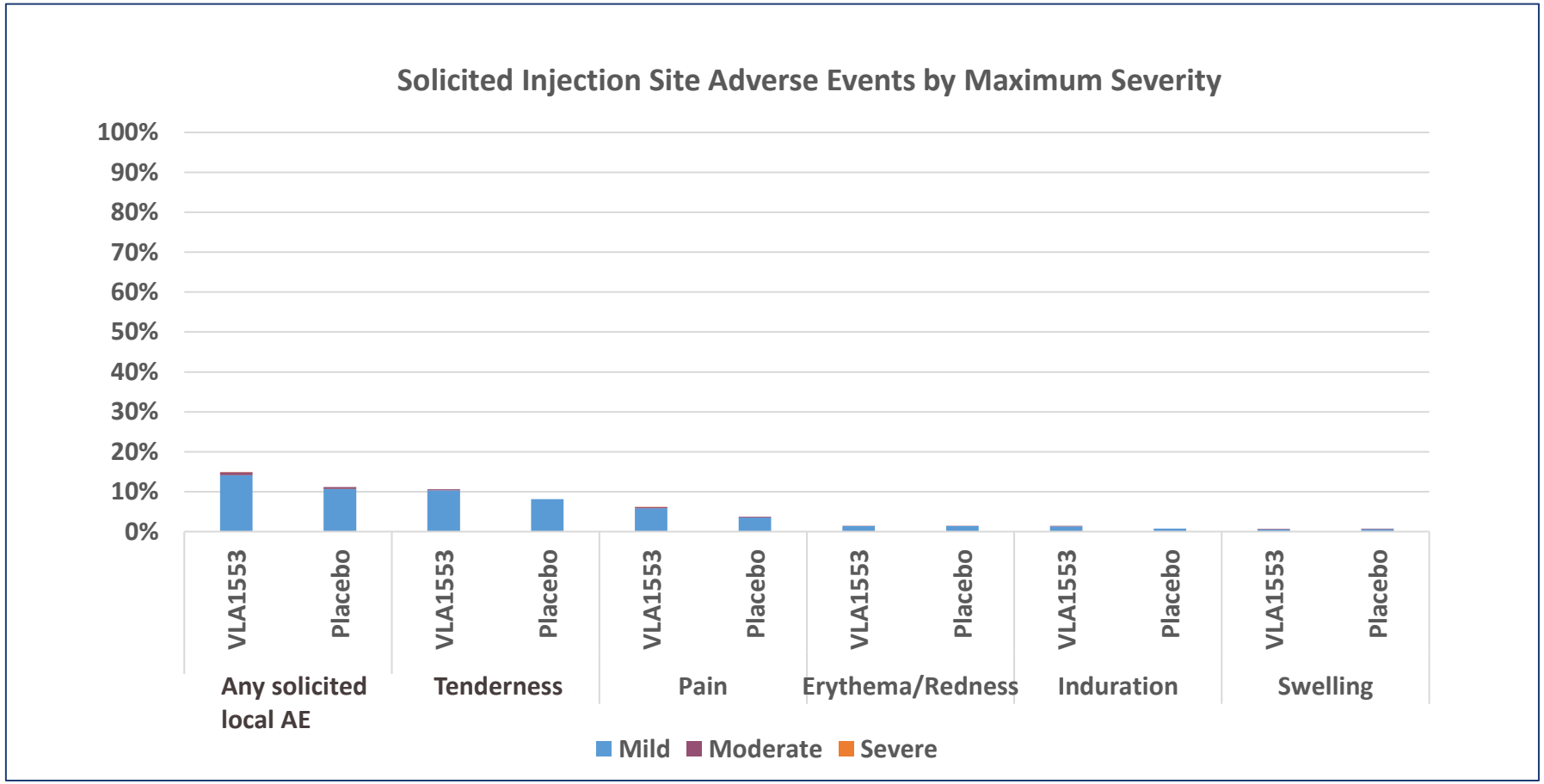


- **Per-Protocol population: 362 / 462 participants from immunogenicity set**
- **Day 29 Seroresponse rate (SRR):**
  - **98.9% (263/266, 95% CI: 96.7- 99.8) vs placebo 0% (0/96, 95%CI 0.0 - 3.8)**
- **High SRR was maintained after six months at 96.3% (233/242, 95% CI: 93.1 - 98.3)**

1 CHIKV neutralizing antibody titer ≥150 by μPRNT$_{50}$; 2 Schneider et al.2023; Lancet 401: 2138–47;

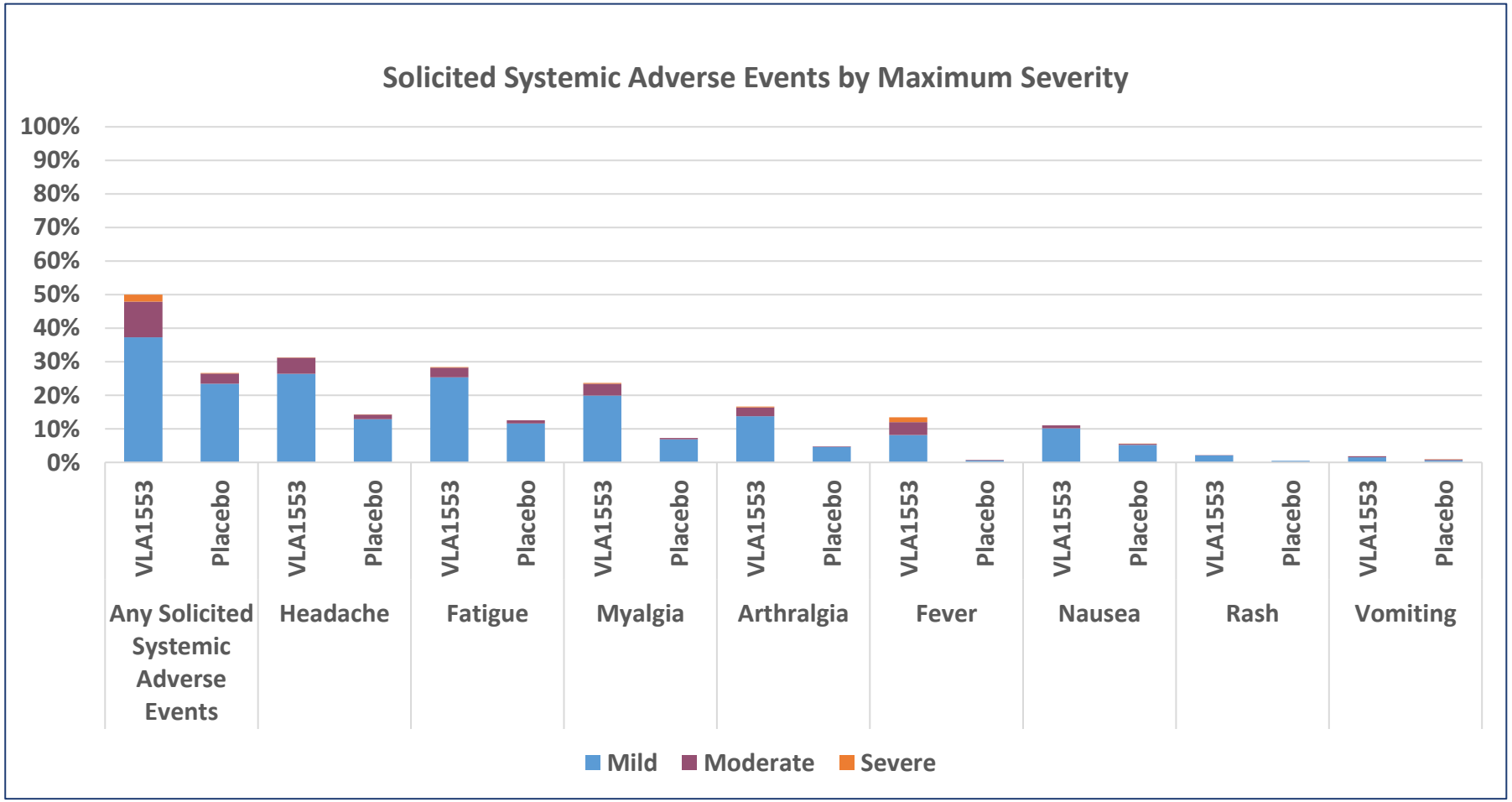
Pivotal Phase 3 Solicited Local AE Within 10 Days After Vaccination (VLA1553-301)

Local AEs in 15% of participants, majority of AEs mild-moderate



Pivotal Phase 3 Solicited Systemic AE Within 10 Days After Vaccination (VLA1553-301)

Generally well tolerated, majority of AEs mild-moderate



Safety Summary

- VLA1553 was generally well tolerated among the 3,082 subjects evaluated for safety
- Approximately 50% of study participants experienced solicited systemic adverse events, most commonly headache, fatigue and myalgia - solicited AE rates comparable with other licensed vaccines[1]
  - Majority of solicited adverse events mild or moderate. 2.0% of study participants reported severe solicited adverse events, most commonly fever.
- Two SAEs considered related to immunization were reported, both participants fully recovered
- FDA Prescribing Information contains chikungunya-like adverse reactions*; defined as individuals with fever and any other symptom also seen with chikungunya, within 30 days after vaccination, 11.7%
- An independent DSMB continuously monitored safety and did not identify a safety concern.

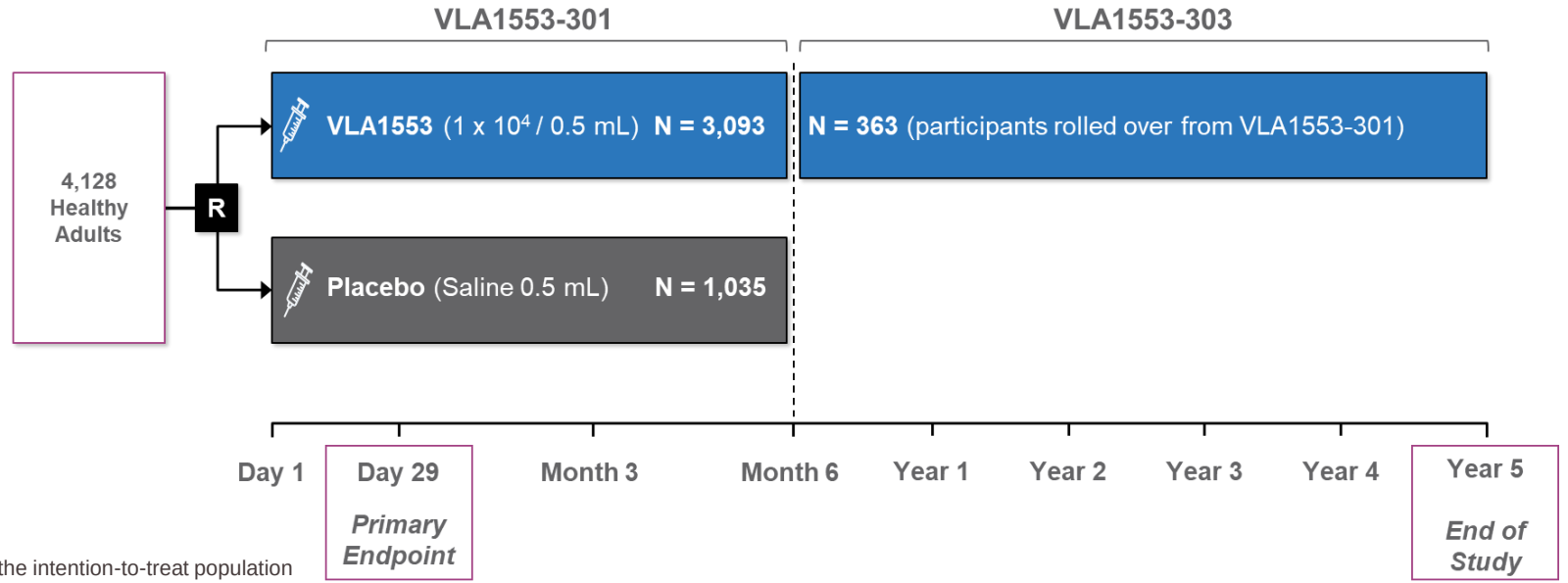
Link to PI https://www.fda.gov/media/173758/download?attachment

1 E.g. compare FDA prescribing information Comirnaty, Bexsero, Shingrix, YF-VAX, all accessiable at https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states
*Fever + at least one other ChikV symptom, within 30 days post vaccination

VLA1553-303: long-term follow-up clinical trial

Designed to evaluate antibody persistence and long-term safety 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 5 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



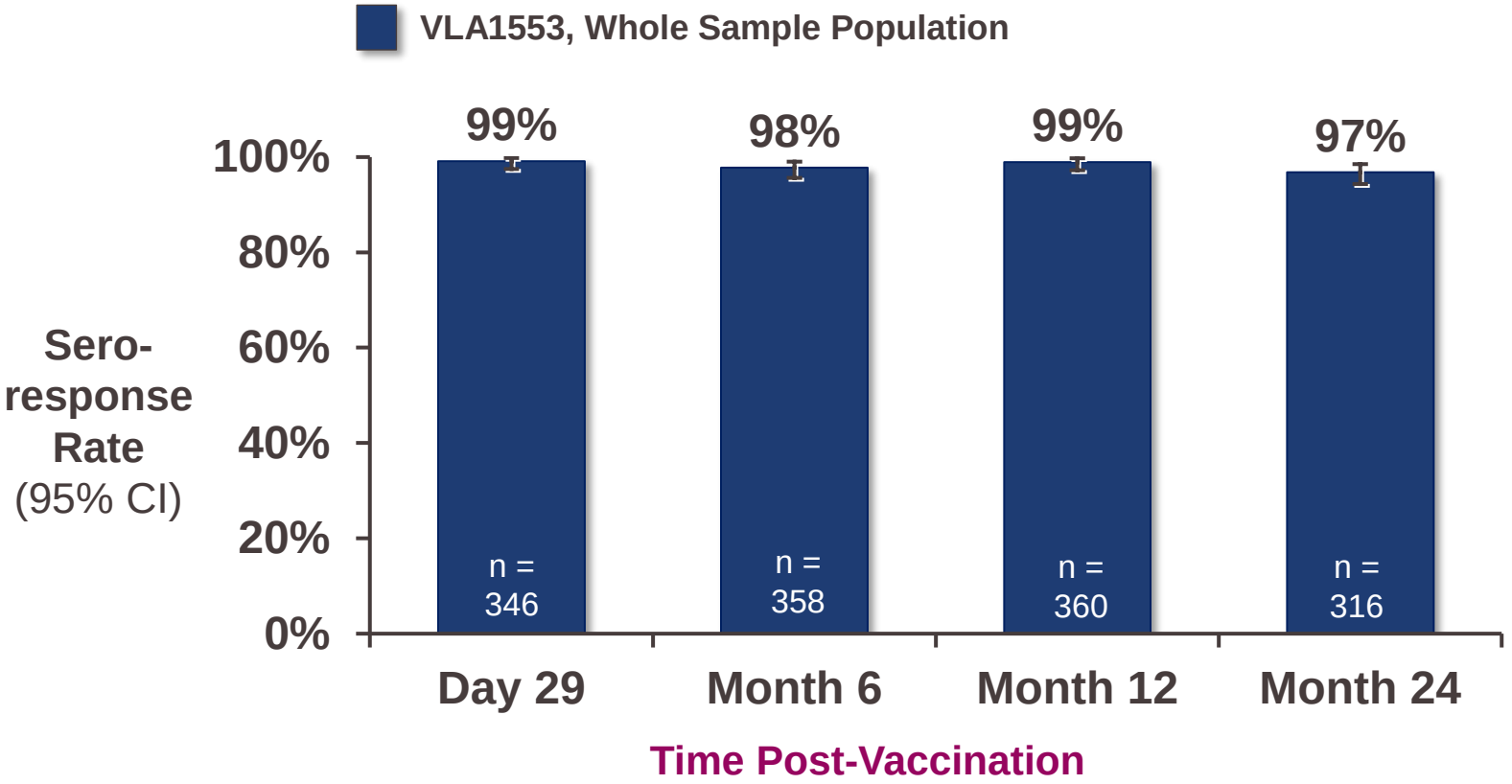
N = number of participants in the intention-to-treat population

VLA1553-303 Demographic Data

	18-64 Years N=310	>=65 Years N=53	All Subjects N=363
Sex n (%)			
Female	177 (57.1)	30 (56.6)	207 (57.0)
Male	133 (42.9)	23 (43.4)	156 (43.0)
Race n (%)			
American Indian or Alaskan Native	2 (0.6)	0	2 (0.6)
Asian	6 (1.9)	0	6 (1.7)
Black or African American	44 (14.2)	8 (15.1)	52 (14.3)
Native Hawaiian or Other Pacific Islander	2 (0.6)	1 (1.9)	3 (0.8)
White	237 (76.5)	43 (81.1)	280 (77.1)
Other	19 (6.1)	1 (1.9)	20 (5.5)
Age (years)			
Mean	44.1 (12.02)	68.7 (3.37)	47.7 (14.15)
(Min/Max)	18, 64	65, 78	18, 78
Age Group n (%)			
18 years – 64 years	310 (100)	53 (100)	310 (85.4)
≥ 65 years			53 (14.6)

VLA1553-303: seroresponse[1] in 97% of Participants Retained After 24 Months

Data support the anticipated long-term durability of the immune response after a single dose

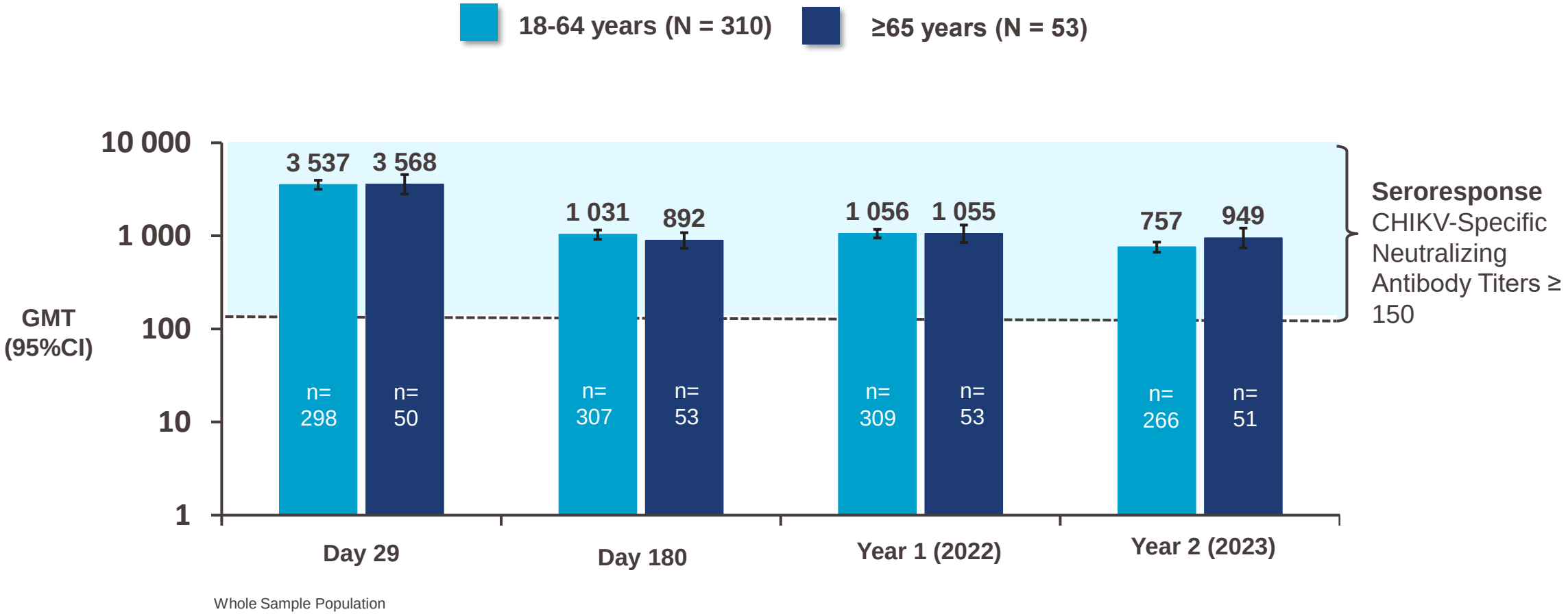


Seroresponse = CHIKV-specific neutralizing antibody titers ≥ 150

Sources: Buerger et at, presented at CISTM 2023; Valneva Press Release Dec 4, 2023 https://valneva.com/press-release/valneva-reports-positive-24-month-antibody-persistence-data-for-its-single-shot-chikungunya-vaccine-ixchiq/

VLA1553-303: Comparable Titers Retained in Participants 18-64 or ≥65 Years

In older adults aged ≥ 65 years, antibody persistence was similar as in younger adults



VLA1553-303 Serious Adverse Events from Month 6 until Year 2

No SAE deemed related to VLA1553 administration

	System Organ Class Preferred Term [n (%)]	18-64 Years N=310	>=65 Years N=53	All Subjects N=363
	Any SAE [n (%) m]	7 (**2.3**) 8	2 (**3.8**) 2	9 (2.5) 10
Month 6 - 12	**Pelvic Fracture**	1 (0.3)	0	1 (0.3)
	Intracranial Aneurysm	0	1 (1.9)	1 (0.3)
	Seizure	1 (0.3)	0	1 (0.3)
	Upper abdominal pain	1 (0.3)	0	1 (0.3)
Year 2	**Gun shot wound**	1 (0.3)	0	1 (0.3)
	Overdose	1 (0.3)	0	1 (0.3)
	Apallic syndrome	1 (0.3)	0	1 (0.3)
	Coronary artery disease	0	1 (1.9)	1 (0.3)
	Myocardial infarction	1 (0.3)	0	1 (0.3)
	Cholecystitis	1 (0.3)	0	1 (0.3)

Table 14.3.2.1, WS Population

Serious AEs (SAEs): results in death, life threatening, requires/prolongs hospitalization, results in significant disability, congenital defect, medical important condition.

n = number of subjects with an event
Row Any SAE displays n (%) m.
m = number of events

Conclusions

- It is estimated that **over three quarters of the world's population** live in areas at-risk of CHIKV transmission[1]
- Chikungunya epidemics are characterized by **large, explosive outbreaks with high attack rates** that often overwhelm local health systems[2]
- **Travel to, from and within Europe or the US can contribute to the spread of CHIKV** and poses a public health threat in the region[3] especially if coinfections occur with other vector-borne diseases, such as dengue[4]
- A single immunization with VLA1553 induced a **strong and robust immune response** with a seroresponse rate of 98.9% (VLA1553-301)[5]
- Immunogenicity was shown to be **unaffected by participant age** (VLA1553-301)[5] and **persists for at least 24 months** (VLA1553-303)[6]
- VLA1553 was generally well tolerated (VLA1553-301)[7]

CHIKV = chikungunya virus.

1. Puntasecca CJ, et al. PLoS Negl Trop Dis. 2021; 15(3): e0009055; 2. Paul BJ and Sadan S. Rheumatol Ther. 2018;5:317-326; 3. Gossner CM, et al. Emerging Infectious Diseases. 2020;26(6):1067; 4. Salam N, et al. BMC Public Health. 2018;18:710; 5. Schneider M, et al. Lancet. 2023;401(10394):2138-2147; 6. Valneva Reports Positive 24-Month Antibody Data for its Single-Shot Chikungunya Vaccine IXCHIQ®; 7 Valneva Successfully Completes Pivotal Phase 3 Trial of Single-Shot Chikungunya Vaccine Candidate.

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CEPI

Horizon 2020

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Danke
Tack

valneva