One step closer to a chikungunya vaccine: update on Valneva's live-attenuated vaccine candidate

World Vaccine Congress Europe

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valneva

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Valneva in Summary

Fully integrated specialty vaccine company focused on development and commercialization of **prophylactic vaccines for infectious diseases** with significant unmet medical need

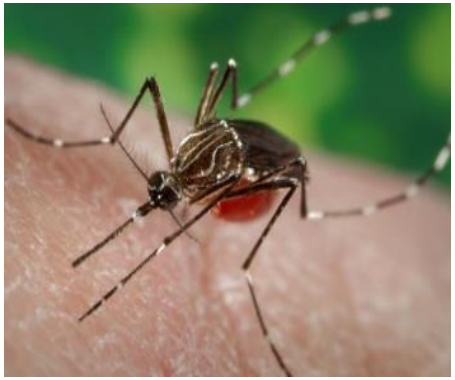
- **Highly specialized and targeted approach to development of unique prophylactic vaccines**
- **Advanced pipeline of differentiated clinical-stage assets** designed to address large target populations
- **Highly experienced leadership team with vaccine development and regulatory expertise;** clear demonstrated ability of rapidly moving new vaccines through the clinic to commercialization
- **Highly developed, nimble and sophisticated manufacturing infrastructure**
- **Specialist sales infrastructure: three commercialized vaccines; distribution rights for third-party vaccines**

- **Total revenues of €93.2 million in H1 2022 vs. €47.5 million in H1 2021; FY 2022 revenue guidance of ~€340 to €360 million**
- **Cash position of €336.2 million on June 30, 2022**

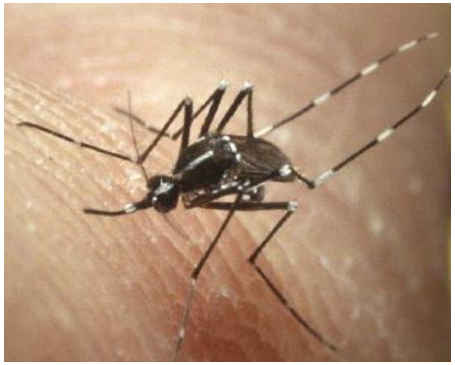
Valneva has an Advanced Clinical Pipeline and Three Approved Products[1]

[1]As of June 24, 2022, VLA2001 has received emergency use authorization in Bahrain and in the United Arab Emirates, as well as Conditional Marketing Authorization in the UK and standard marketing authorization in Europe.[2] VLA1553 received Fast Track designation from the FDA, PRIME designation from the European Medicines Agency and is also potentially eligible for a U.S. Priority Review Voucher. [3] VLA15 received Fast Track designation from the FDA [4] 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]
- Often causes large, explosive outbreaks with high attack rates, affecting one-third to three-quarters of the population[1]; difficult to predict next outbreaks[2]
- 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]
- Highest areas of risk of infection for travelers include the Americas, parts of Africa, and Southeast Asia[3]
- Returning infected travelers can trigger local transmission in areas where relevant mosquitoes are established (e.g. Southern U.S./Europe)[2]
- High burden of disease: outbreaks can have substantial health-economic impact; infection can progress to severe chronic symptoms in many patients[4]

No cure; treatment is symptomatic and supportive only

Without a vaccine, prevention is limited to protection against mosquito bites and vector control

1. Staples et al. CDC Yellow Book 2020, Chapter 4 . 2. Bettis et al. PLOS Neglected Tropical Diseases 2022;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.

High acute morbidity: can lead to chronic, incapacitating effects

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]
- Viremic 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 (4% to 78%)[5,6]

- Pattern similar to rheumatoid arthritis
  - Characterized by peripheral spondylarthritis, undifferentiated arthritis, fibromyalgia, neuropathic chronic pain
- Fatigue is another main persistent symptom, can last for months to years[7,8]
- Risk factors for developing chronic symptoms:[(6,9)]
  - >45 years of age
  - High viral load during acute phase
  - Severe immunologic response in post-viremic phase
- Chronic disease negatively impacts quality of life and ability to work

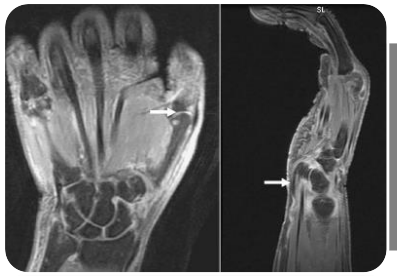
Chikungunya means “to become contorted” in Kimakonde, describing sufferers’ stooped appearance

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. Rodríguez-Morales AJ et al . Arthritis Care Res 2016;68:849-58 6. Martí-Carvajal A et al. PLoS One 2017;12:e0179028 7. Manimunda SP, et al. Trans R Soc Trop Med Hyg 2010; 104: 392–99. 8. Soumahoro MK, et al. PLoS One 2009;4:e7800. 9. Zaid A et al. Arthritis Rheumatol 2018;70:484-95

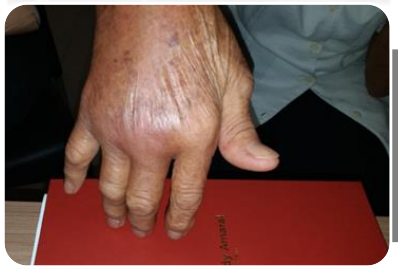
Chronic Chikungunya negatively impacts quality of life

Persistent rheumatologic disease

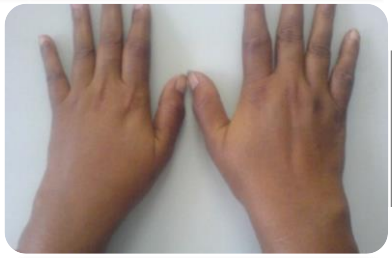
Post-CHIKV Rheumatism - 2 forms -	Effect of Arthritis/Polyarthritis	Impact on Quality of Daily Life
Mechanical musculoskeletal disorders	Long-term joint pain	• **Rising from chair** • **Walking** • **Picking up objects** • **Opening a bottle** • **Self care** • **Physical impact on leisure time and limitations on activity**
	Stiffness after immobility[1,4]	
	Multiple joints affected, ie., spine, shoulder, elbow, wrist, hand, hip, knee, ankles, feet	
Chronic inflammatory arthritis	Can be triggered by change in temperature and physical effort[5]	
	May require surgery	



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



2 years after CHIKV infection: Intense arthritis of metacarpophalangeal joints and wrist[3]



Symmetrical inflammatory polyarthritis[2]

1. Fabrice S, et al. Medicine: 2007;86:123-137. 2. Mohan A, et al. Indian J Dermatol. 2010; 55: 54–63. 3. Amaral J, et al. Viruses. 2019;11:289. 4. Tritsch S. et al. J Rheum. 2020;47:1267-74. 5. Schilte C. et al. PLOS Negl Trop Dis. 2013;7:e2137.

VLA1553 at a Glance

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

Vaccine Candidate VLA1553

- **Live-attenuated** CHIKV vaccine candidate, **single** dose, i.m., **lyophilized**
- Based on **La Reunion strain** of East Central South African genotype
- **Attenuation by reverse genetics,** 60aa deletion within the non-structural nsP3 protein

Development Status

- **Pivotal** Phase 3 Trial: **Primary Endpoint (Seroprotection Rate) met**
- **Lot-to-Lot consistency** Trial: **Primary Endpoint met**
- Antibody persistence trial ongoing
- Adolescents trial in Brazil ongoing

Regulatory Milestones

- FDA: **Fast Track and Breakthrough designations granted**
  - **Rolling submission** of Biologics License Application (BLA) commenced in Aug 2022
- EMA: **PRIME** designation 2020
- Investigational vaccine candidate, not approved for use in any jurisdiction

Target Populations & Geographic Reach

- **Non-endemic** countries: Travelers / Military / Outbreak preparedness in US, EU, CAN
- **Endemic** use: Partnered with CEPI and Instituto Butantan, technology transfer

Note:.

Licensure Pathway for Chikungunya Vaccines

Accelerated approval pathway agreed with regulators for chikungunya vaccines

- **Classical efficacy studies for chikungunya vaccines are considered unfeasible**[1,2]
  - Unpredictable and short-lived outbreaks
  - Logistical boundaries
  - Acceptable timeframes & cost barriers

- **In the US, 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":**

  - Rate of subjects achieving a **neutralizing antibody titer of ≥150 in a μPRNT$_{50}$** assay[2]

1 VRBPAC Meeting, Nov 2019. 2 Bettis et al, PLoS Negl Trop Dis 16(1): e0010069
2 Roques P, et al. Effectiveness of CHIKV vaccine VLA1553 demonstrated by passive transfer of human sera. JCI Insight. 2022 Jul 22;7(14):e160173. doi: 10.1172/jci.insight.160173. PMID: 35700051; PMCID: PMC9431671.

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 $\mu PRNT_{50} \geq 150$**

Further evidence[1]:

Protective titer determined in a **prospective seroepidemiological study** 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.

Overview of Clinical Studies

Three clinical trials completed

Phase 1:

- **Phase 1 study[1]:**
  - **120 healthy adults** aged 18-45 years
  - **Three dose levels** of vaccine studied
  - Included a **re-vaccination** as homologous viral challenge
  - Study generated **safety, immunogenicity, and viremia** data

Phase 3:

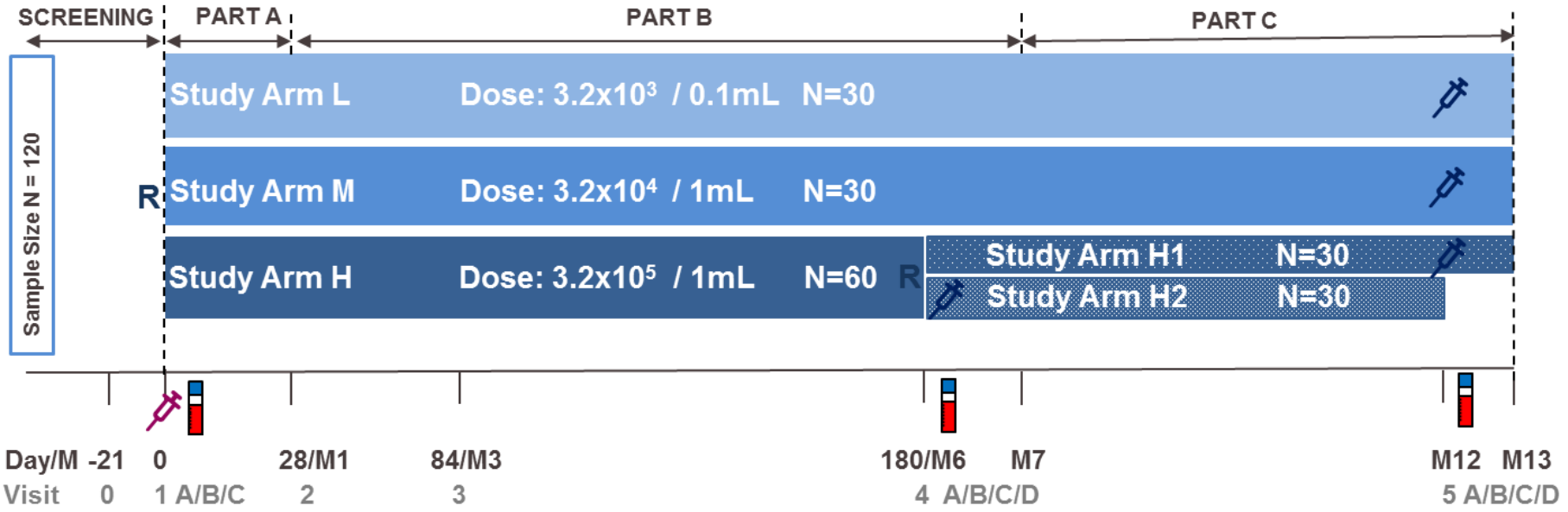
- **Pivotal Phase 3 study:**
  - **4,115 participants** aged ≥18 years
  - RCT comparing **VLA1553 to placebo**
  - Study generated **safety and immunogenicity** data
- **L2L consistency study:**
  - **408 participants** aged **18-45 years**
  - RCT comparing **3 lots of VLA1553**

1 Wressnigg et al. 2020; Lancet Infect Dis 20:1193-1203.

Phase 1 Study VLA1553-101 – Study Design

Observer-blinded, randomized, multicenter, dose-escalation study

- **120 healthy volunteers** aged 18 to 45 years, US
- **3 Dose Levels:** approx. $3x10^3$ (Low), $3x10^4$ (Medium), $3x10^5$ (High) $TCID_{50}$,
- **Intramuscular** immunization, liquid formulation
- **Serological assay:** μNT_{50} – target strain VLA1553



Re-vaccination at Month 6 (Study Arm "H2") or 12 with highest dose: Indirect homologous viral “challenge”

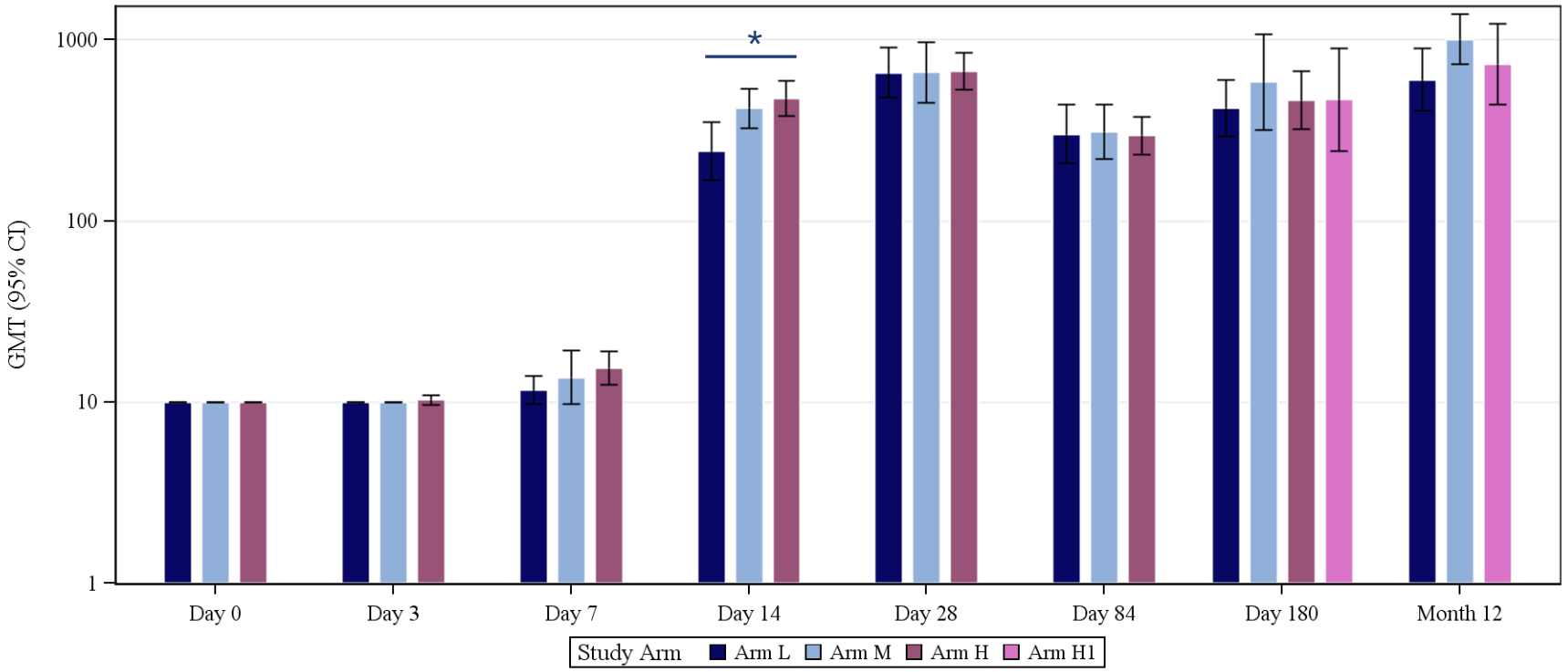
* safety including viremia on Days 0/3/7/14 post-vaccination

* vaccination with the highest dose

1 Wressnigg et al. 2020; Lancet Infect Dis 20:1193-1203.

Phase 1 VLA1553-101 – Immunogenicity data

Sustained CHIKV-specific Neutralizing Antibodies (GMT) after Single Vaccination

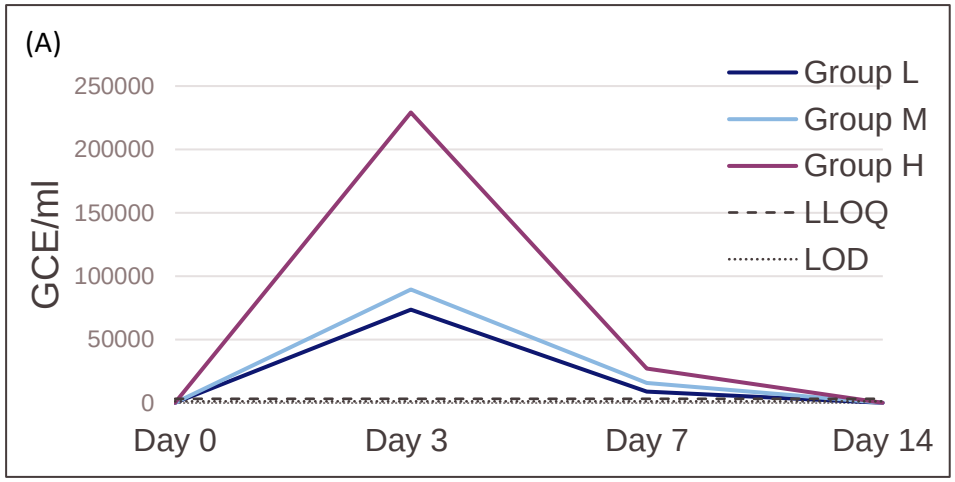


* ANOVA
Arm L vs. M p = 0.0348
Arm L vs. H p = 0.0020

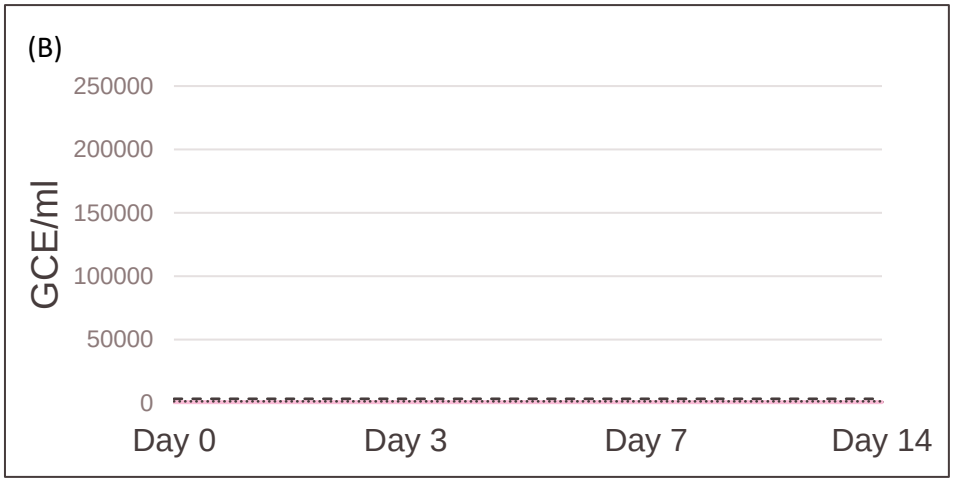
Phase 1 VLA1553-101 – Safety

Plasma Viremia abolished after Re-Vaccination

Single Dose



Re-vaccination



Numbers indicate mean Genome Copy Equivalents (GCE) / mL
Limit of Detection (LOD): 1087 GCE/mL,
Lower Limit of Quantification (LLOQ): 3261 GCE/mL.
Time points with no available results in the treatment group are plotted at 0.

Summary of VLA1553-101 Phase 1 data

Results supported direct progression into Phase 3

- **Excellent immunogenicity** profile in all dose groups after a single dose – **medium dose** selected for further development
- **100% seroconversion*** at Day 14 in all dose groups, **sustained at 100% until Month 12** – data generated with **µNT$_{50}$ assay**
  - **100% seroresponse rate** after re-testing with Phase 3 µPRNT$_{50}$ assay
- **Absence of anamnestic neutralizing antibody response following re-vaccination** - single dose sufficient to induce sustaining high titer neutralizing antibodies at all dose levels
- After **re-vaccination** (“intrinsic human viral challenge”) **vaccinees were protected from vaccine induced viremia** and associated clinical symptoms as early indication of VLA1553’s efficacy

As antibody levels reached plateau in all dose groups after one shot, no further dose and schedule data needed to be generated in a Phase 2 study

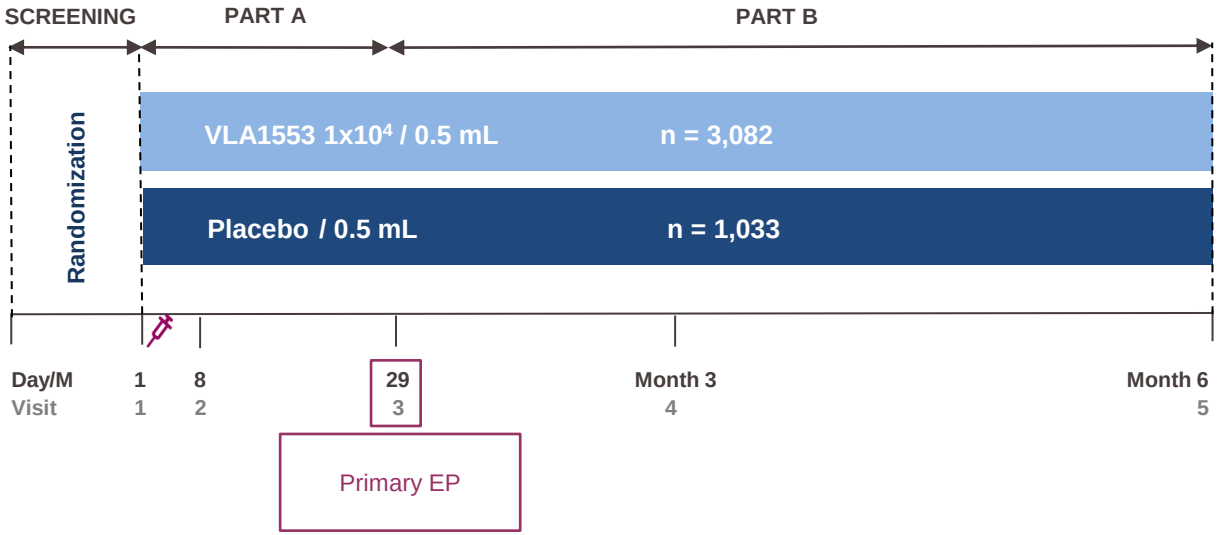
*Seroconversion defined as the proportion of subjects achieving a CHIKV-specific neutralizing antibody titer of NT$_{50}$ ≥20.

1 Wressnigg et al. 2020; Lancet Infect Dis 20:1193-1203.

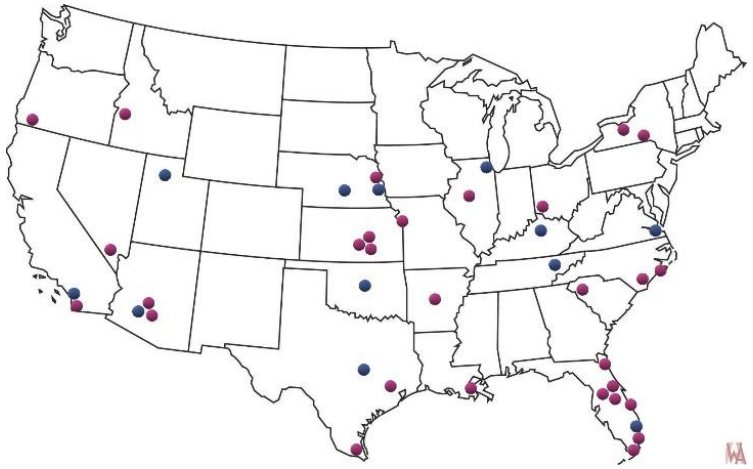
VLA1553-301 Pivotal Study Design

Multicenter, randomized, placebo-controlled double-blind Phase 3 study in 4,115 adults aged 18 years and above, conducted in US

- **Primary Endpoint:** Proportion of participants with seroresponse (CHIKV neutralizing antibody titer ≥150 by μPRNT$_{50}$) for baseline negative participants 28 days post-vaccination
- **Solicited adverse events** captured for **10 days** following vaccination
- Recruitment stratified by age, younger (18-64 years, N=3,652) and older adults (≥65 years, N=463)
- Immunogenicity subset: first 500 participants enrolled at selected sites



n = number of participants in the safety population



Blue = Immunogenicity Sites
Purple = Non-Immunogenicity Sites
(i.e. not enrolling participants within the immunogenicity subset)

Demographic Data

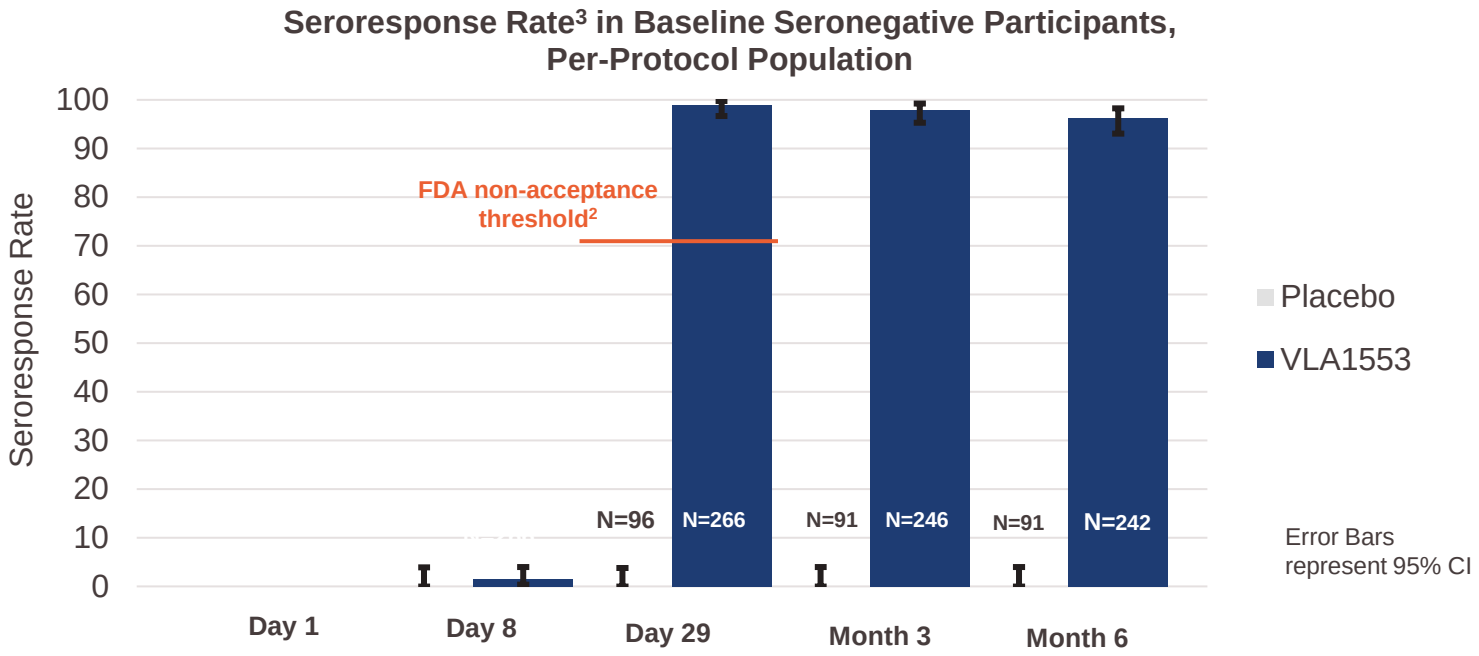
Similar baseline characteristics between VLA1553 group and Placebo

	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

Pivotal Study Met Primary Endpoint

Induced seroresponse[1] in 98.9% of participants; exceeding FDA threshold[2]

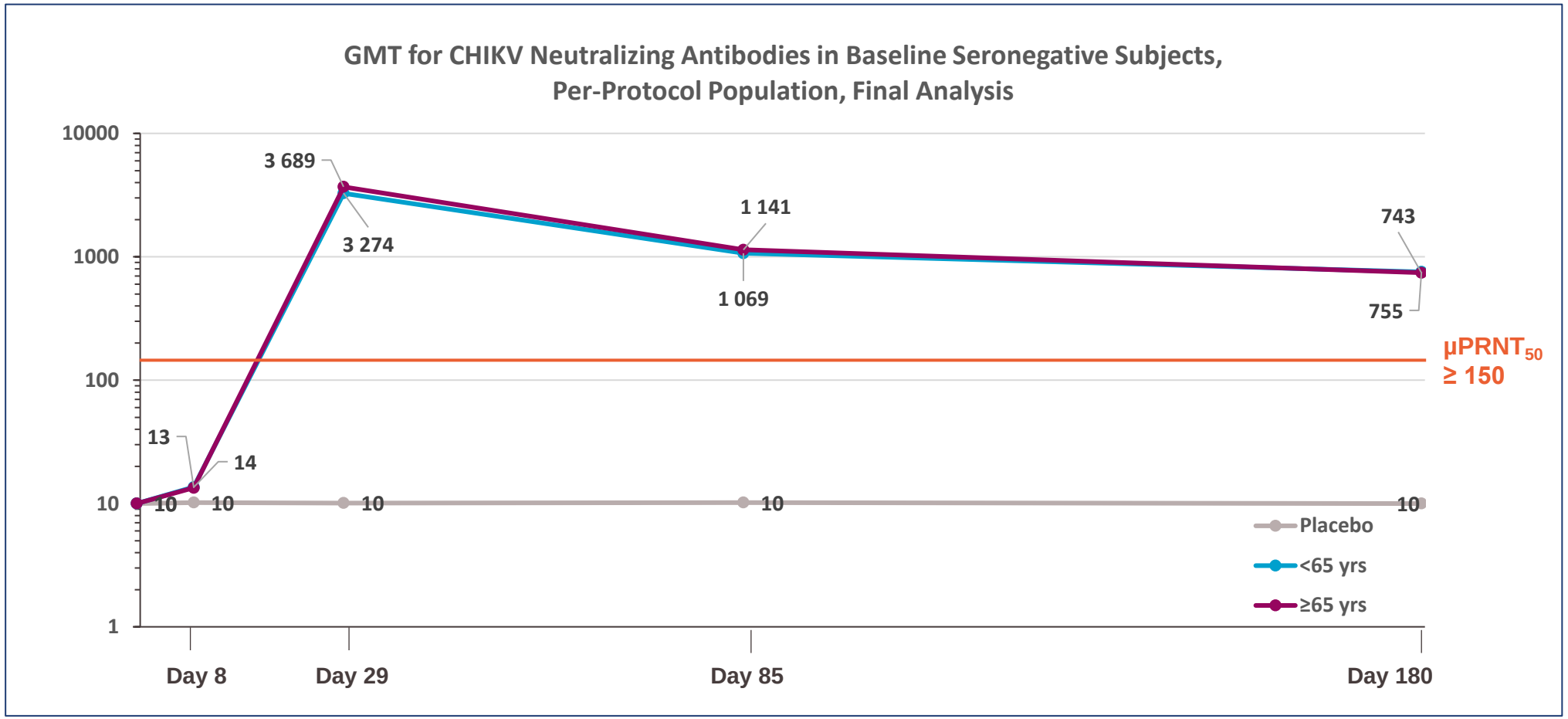


- **Seroresponse rate (SRR) was 98.9% (263/266, 95% CI: 96.7 - 99.8), vs placebo 0% [95%CI 0.0 - 3.8]**
- **High SRR was maintained after six months at 96.3% (233/242)**

1 CHIKV neutralizing antibody titer ≥150 by µPRNT$_{50}$; 2 The lower bound of the 95% Confidence Interval for the SRR at Day 29 in the VLA1553 group needed to exceed 70% Neutralizing antibody titers determined using a µPRNT$_{50}$ assay; 3 The proportion of participants with seroresponse, determined by µPRNT (Micro Plaque Reduction Neutralization Test) for baseline negative participants 28 days post-vaccination

Neutralizing Antibodies By Age Group

Equally immunogenic in participants younger or ≥65 years



Chikungunya virus neutralizing antibody titers were determined using a $\mu PRNT_{50}$ assay. Values below the quantification limit are set to 10 (Half LLOQ).

Summary of Immunogenicity Data

Both Phase 3 trials met primary endpoints

Pivotal trial VLA1553-301

- Seroresponse[1] in 98.9% of participants 28 days after a single vaccination
- Immunogenicity profile was maintained at Day 180 with seroresponse in 96.3% of participants
- Vaccine candidate induced peak neutralizing antibody GMTs ≥3,200 in both age groups
- Equally high GMTs and seroresponse rates in trial participants ≥65 years of age or <65 years

Lot-to-Lot consistency study VLA1553-302

- GMT Ratio confidence intervals were all within the defined acceptance margins of 0.67 and 1.5
- Seroresponse[1] in 97.8% of participants 28 days after a single vaccination and 96.0% at Day 180
- Confirmed the immunogenicity profile of the pivotal study

1 CHIKV neutralizing antibody titer ≥150 determined by $\mu PRNT_{50}$ (Micro Plaque Reduction Neutralization Test) for baseline negative participants

Pivotal Phase 3: Summary of Adverse Events Rates

VLA1553 vaccine candidate generally well tolerated

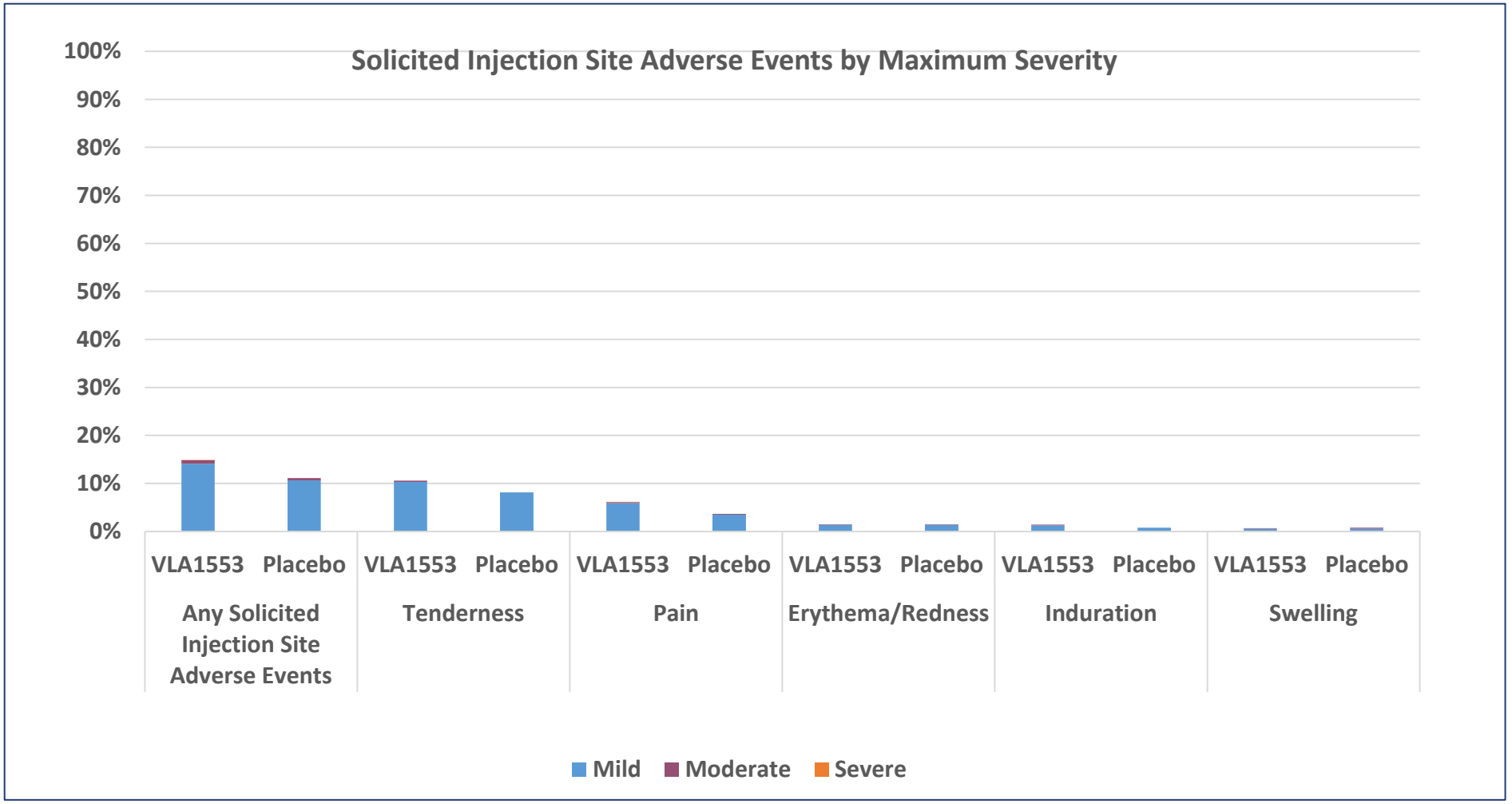
Adverse Event Category	VLA1553 N=3082 n (%)	Placebo N=1033 n (%)
Any Adverse Events [95% CI] p-value[a]	**1926 (62.5)** [60.8, 64.2]	**463 (44.8)** [41.8, 47.9] *<0.0001*
Any Related Adverse Events [95% CI] p-value[a]	**1575 (51.1)** [49.3, 52.9]	**322 (31.2)** [28.4, 34.1] *<0.0001*
Any Related Severe Adverse Events [95% CI] p-value[a]	**62 (2.0)** [1.5, 2.6]	**1 (0.1)** [0.0, 0.5] *<0.0001*

- Two related SAEs (Myalgia, Syndrome of inappropriate antidiuretic hormone secretion) reported for VLA1553, both fully recovered
- Monitoring for AESI:
  - Symptoms suggesting acute chikungunya, including combinations of solicited AEs (Fever, Arthralgia, Rash)
  - 10 cases reported, 9 confirmed by DSMB to meet definition
  - Most symptoms were mild or moderate, 5 subjects w/ severe fever; 21 of 28 symptoms were solicited adverse events, most commonly fever and arthralgia, majority of symptoms self-limited 2-4 days

a P-value from Fisher's Exact test for difference between the study arms.

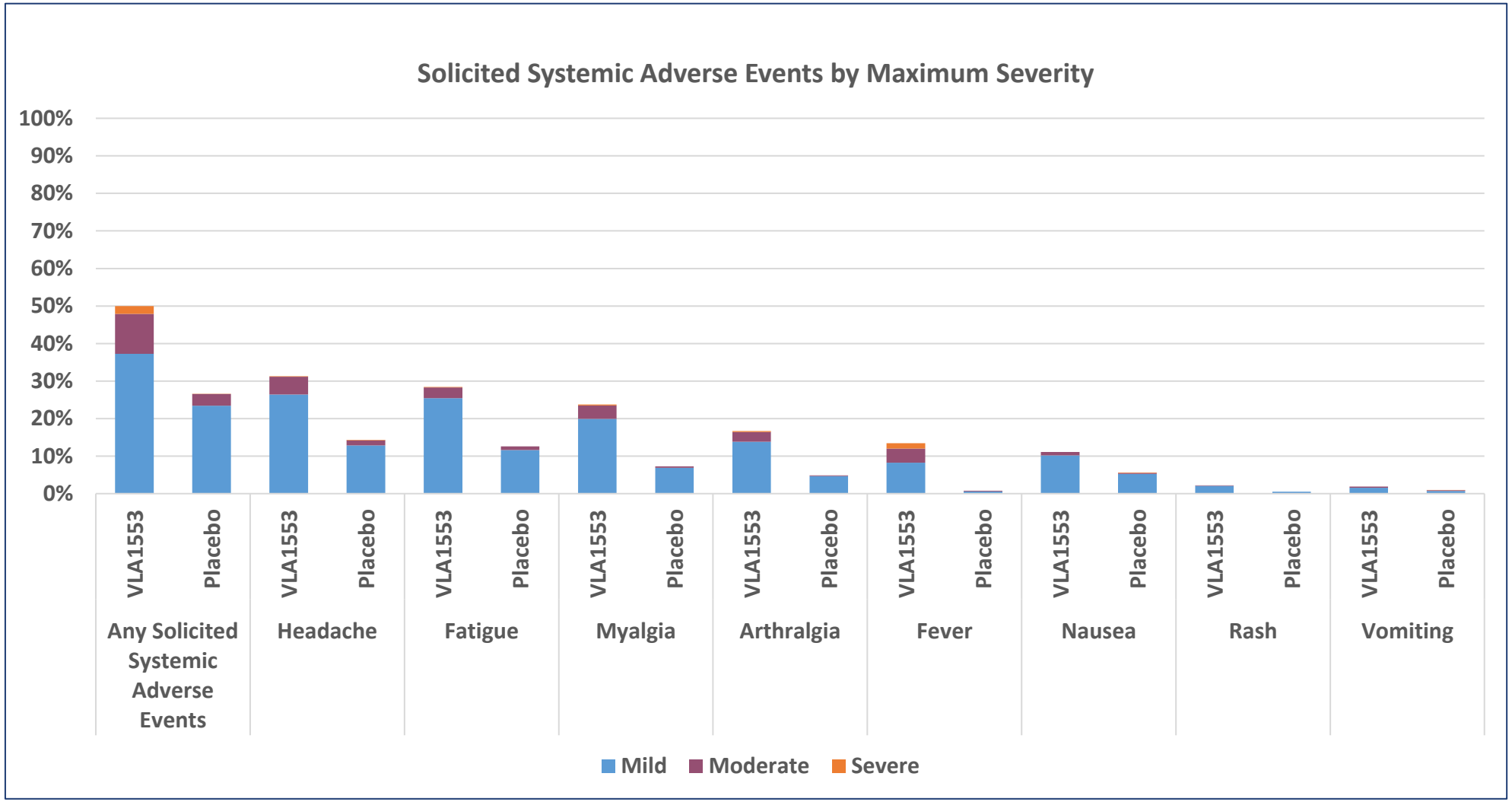
Pivotal Phase 3 Solicited Local Adverse Events Within 10 Days After Vaccination

Local AEs in 15% of Participants, Majority of AEs Mild-Moderate



Pivotal Phase 3 Solicited Systemic Adverse Events Within 10 Days After Vaccination

Generally Well Tolerated, Majority of AEs Mild-Moderate



Safety Summary

VLA1553 was generally well tolerated

- **Independent DSMB** continuously evaluated safety data and **did not identify any safety concern**
- **Majority of solicited AE mild or moderate, resolved within 3 days, 2.1% severe solicited AE (most commonly fever)**
  - Approx. 50% solicited systemic AE; headache, fatigue and myalgia most common (>20% of participants)
  - Approx. 15% solicited local AE
- **Treatment-related unsolicited AE in 9.8%; majority mild or moderate; most frequent (≥1% in VLA1553 group) chills and (transient) neutropenia**
- **VLA1553 was equally well tolerated across age groups**
- **Lot-to-Lot study showed a similar safety profile**
- **Safety profile was consistent with results in a preceding Phase 1 clinical trial and comparable with other vaccines**

Summary

- **Chikungunya is a major public health concern** w/o available vaccine or specific treatment

- **VLA1553 vaccine candidate induced robust and sustained immune response**
  - Single dose induced **seroresponse in 98.9%** of participants at Day 28
  - Seroresponse was **sustained in 96.3%** of participants at **Day 180**
  - Similar GMT and SRR induced in participants aged <65 years or ≥65 years

- **VLA1553 was generally well tolerated across age groups**
  - Independent DSMB continuously evaluated safety data and did not identify any safety concern
  - **Majority of AEs mild or moderate** and resolved within 3 days, 2.1% severe solicited AEs (most commonly fever)
- **Rolling BLA Submission to FDA initiated**

VLA1553 is an investigational chikungunya vaccine candidate and is not approved for use in the United States or any other jurisdiction

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CEPI

Horizon 2020

Thank you.

valneva