Advances in the development of a single-shot live-attenuated chikungunya vaccine candidate

Joint International Tropical Medicine Meeting 2022

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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

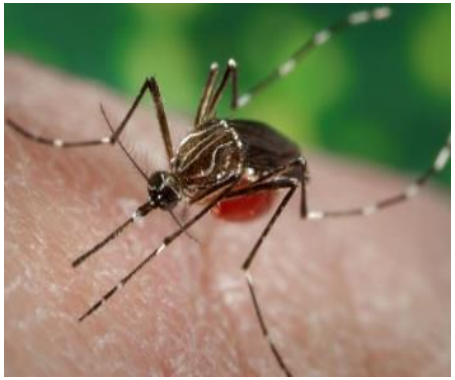
- **Highly specialized and targeted approach to development of unique prophylactic vaccines**
- **Advanced pipeline of differentiated clinical-stage assets** designed to address large target populations
- **Highly experienced leadership team with vaccine development and regulatory expertise;** clear 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 nine-month 2022 revenues of ~ €250 million, ~3.5-fold increase compared to 2021**
- **Strong cash position: €261 million at the end of September 2022, excluding recent global offering proceeds**

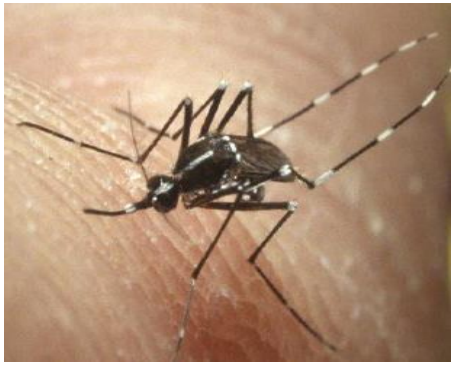
Valneva has an Advanced Clinical Pipeline and Three Approved Products[1]

[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

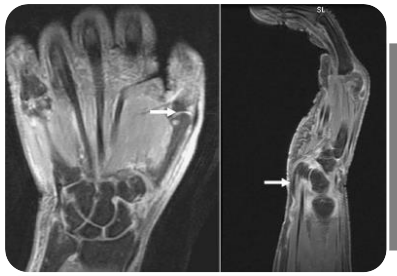
Chikungunya means “to become contorted” in Kimakonde, describing sufferers’ stooped appearance

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

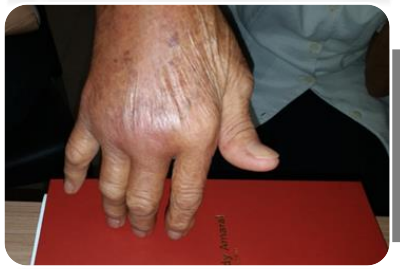
Chronic Chikungunya negatively impacts quality of life

Persistent rheumatologic disease

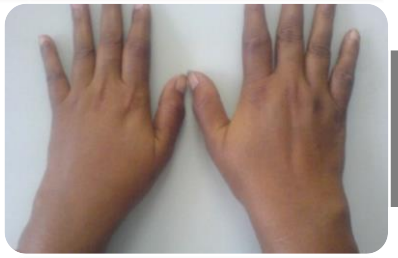
Post-CHIKV Rheumatism - 2 forms -	Effect of Arthritis/Polyarthritis	Impact on Quality of Daily Life
Mechanical musculoskeletal disorders	Long-term joint pain	• **Rising from chair** • **Walking** • **Picking up objects** • **Opening a bottle** • **Self care** • **Physical impact on leisure time and limitations 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 (Seroresponse 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

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":**

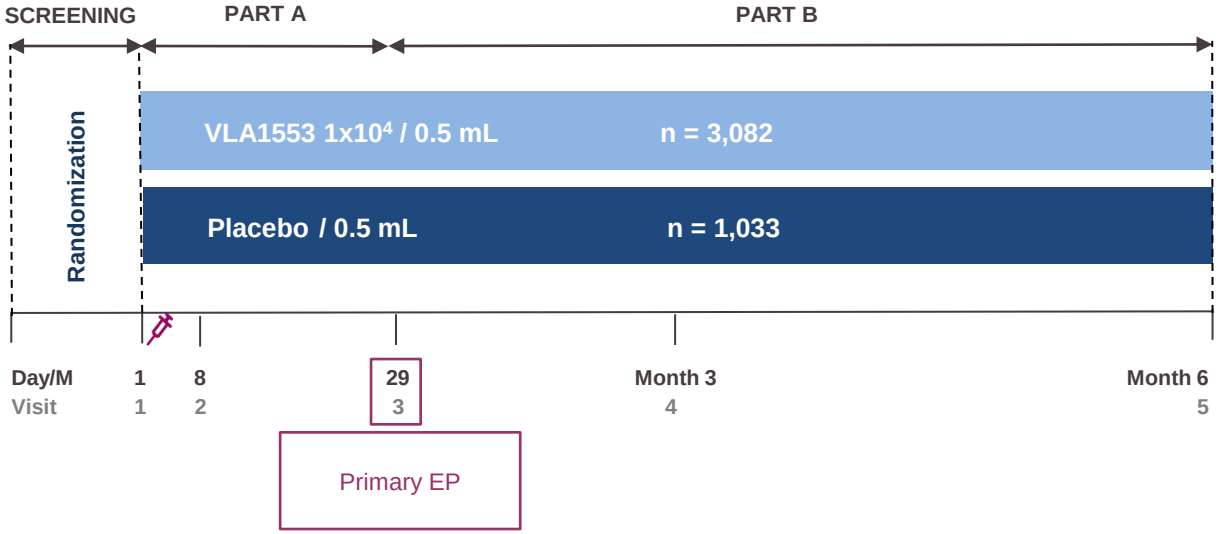
  - Rate of subjects achieving a **neutralizing antibody titer of ≥150 in a $\mu PRNT_{50}$** assay[2]

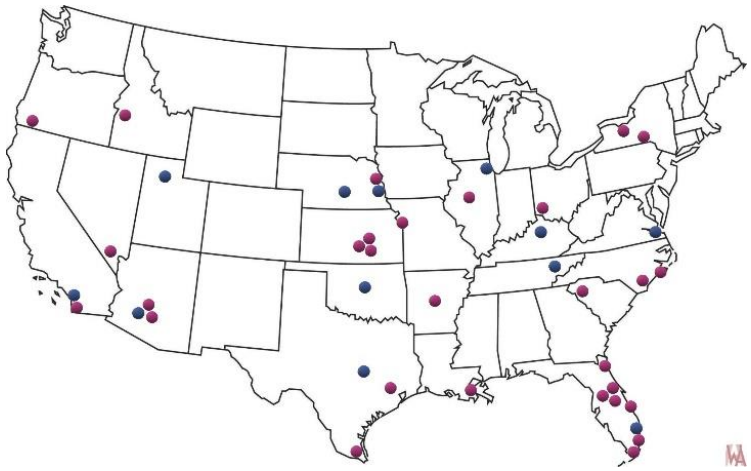
1 VRBPAC Meeting, Nov 2019. 2 Bettis et al, PLoS Negl Trop Dis 16(1): e0010069
2 Roques P, et al. Effectiveness of CHIKV vaccine VLA1553 demonstrated by passive transfer of human sera. JCI Insight. 2022 Jul 22;7(14):e160173. doi: 10.1172/jci.insight.160173. PMID: 35700051; PMCID: PMC9431671.

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
  - FDA non-acceptance threshold: Lower bound of the 95%CI for the seroresponse rate at Day 29 needed to exceed 70%
- **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)
- 3:1 Randomization to VLA1553 and Placebo
- Immunogenicity subset: first 462 participants enrolled at selected sites





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

n = number of participants in the safety population

Demographic Data (VLA1553-301)

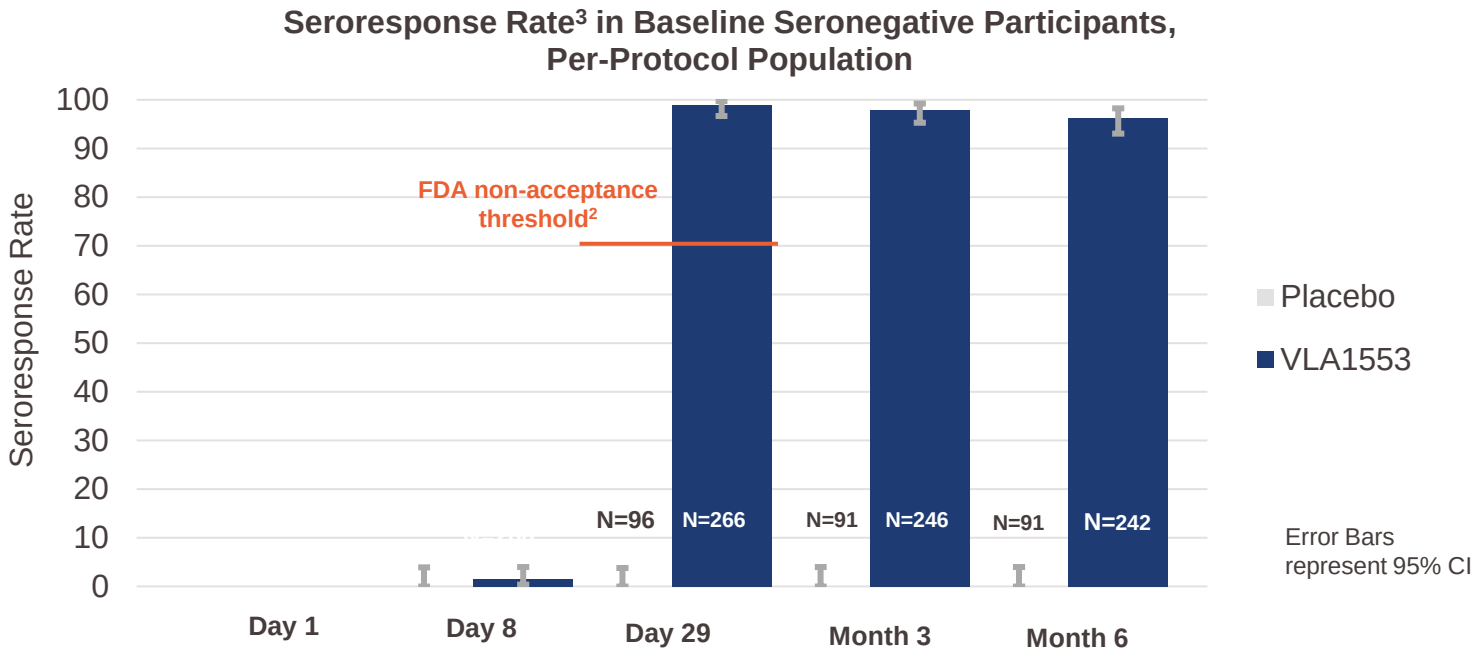
Similar baseline characteristics between VLA1553 group and Placebo

	VLA1553 N=3,082	**Placebo** N=1,033
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 (VLA1553-301)

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

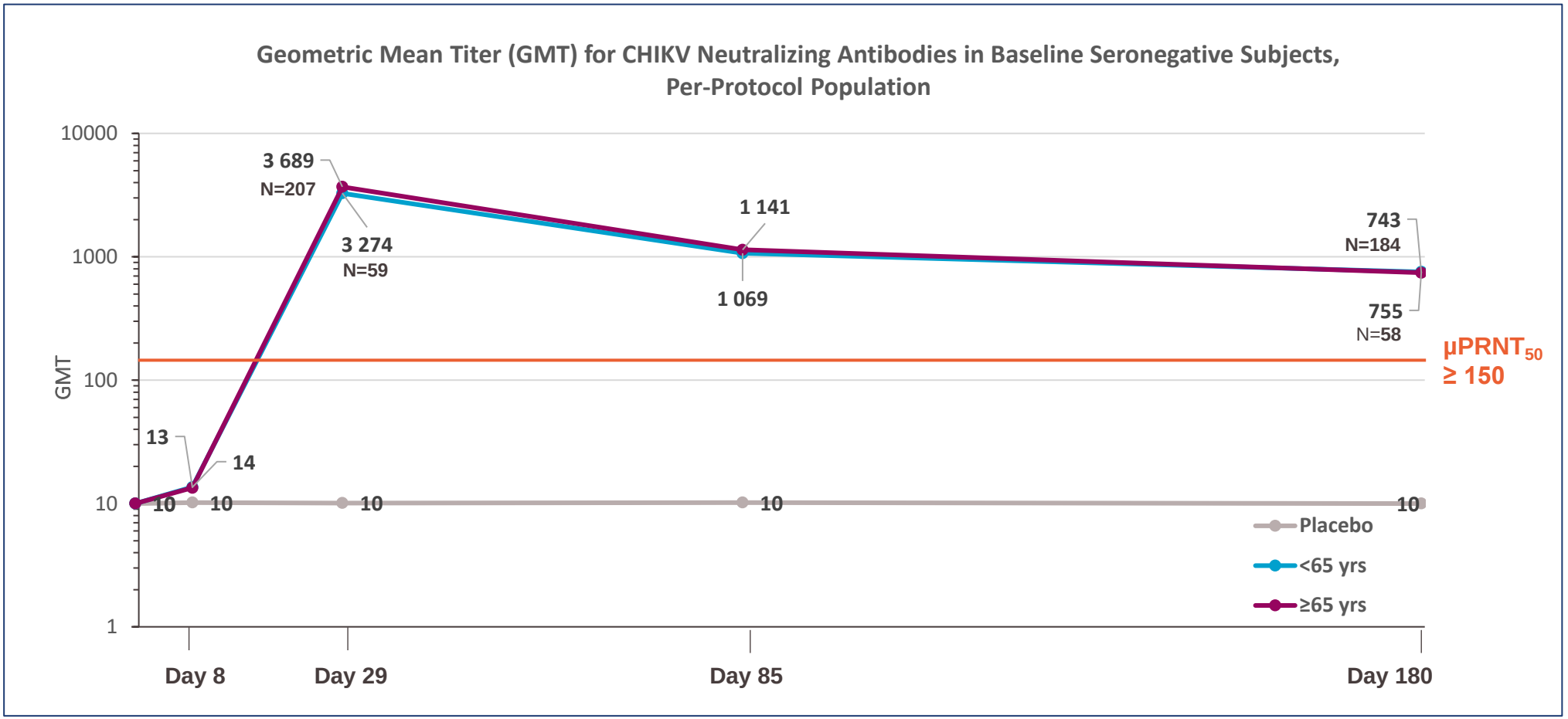


- **Per-Protocol population: 362 / 462 participants from immunogenicity set**
- **Day 29 Seroresponse rate (SRR):**
  - **98.9% (263/266, 95% CI: 96.7- 99.8) vs placebo 0% (0/96, 95%CI 0.0 - 3.8)**
- **High SRR was maintained after six months at 96.3% (233/242, 95% CI: 93.1 - 98.3)**

1 CHIKV neutralizing antibody titer ≥150 by $\mu PRNT_{50}$; 2 The lower bound of the 95% Confidence Interval for the SRR at Day 29 in the VLA1553 group needed to exceed 70%; 3 The proportion of participants with seroresponse, determined by $\mu PRNT_{50}$ for baseline negative participants 28 days post-vaccination

Neutralizing Antibodies By Age Group (VLA1553-301)

Equally immunogenic in participants 18-64 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 Lower Limit of Quantification).

Seroresponse Rate in Older Participants (VLA1553-301)

99.0% in Immunogenicity Elderly Population

	18-64 years		≥ 65 years	
Subjects with Seroresponse	**VLA1553** N=269	**Placebo** N=94	**VLA1553** N=107	**Placebo** N=33
Day 29[a] n (%)	251 **248 (98.8)**	88 **1 (1.1)**	104 **103 (99.0)**	33 **0**
Day 180[a] n (%)	241 **233 (96.7)**	87 **2 (2.3)**	104 **99 (95.2)**	33 **0**

- **Immunogenicity Elderly Population: ≥ 65 years 107/376 VLA1553 participants**
- **Day 29 Seroresponse rate (SRR):**
  - **99.0% (103/104, 95% CI: 94.8 – 100.0) vs placebo 0% (0/33, 95%CI 0.0 – 10.6)**
- **High SRR was maintained after six months at 95.2% (99/104, 95%CI: 89.1 - 98.4)**

a. Number of µPRNT baseline negative (<20) subjects with non-missing titers at the specified time point.
Percentages are based on the number of subjects with non-missing titers at the visit.
Seroresponse is defined as $\mu PRNT_{50} \geq 150$ for µPRNT baseline negative (<20) subjects.

Summary of Adverse Event (AE) Rates (VLA1553-301)

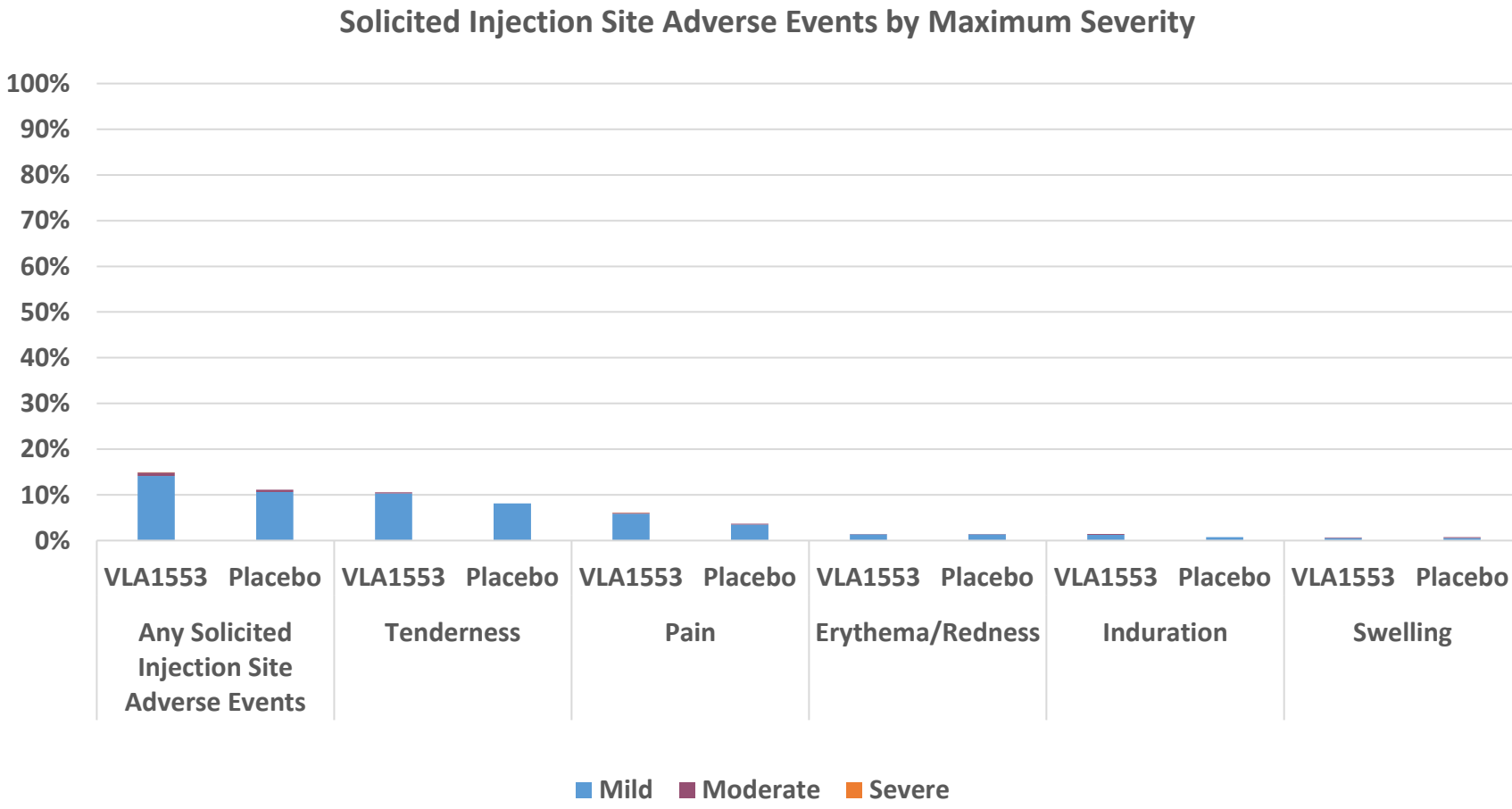
VLA1553 vaccine candidate generally well tolerated

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

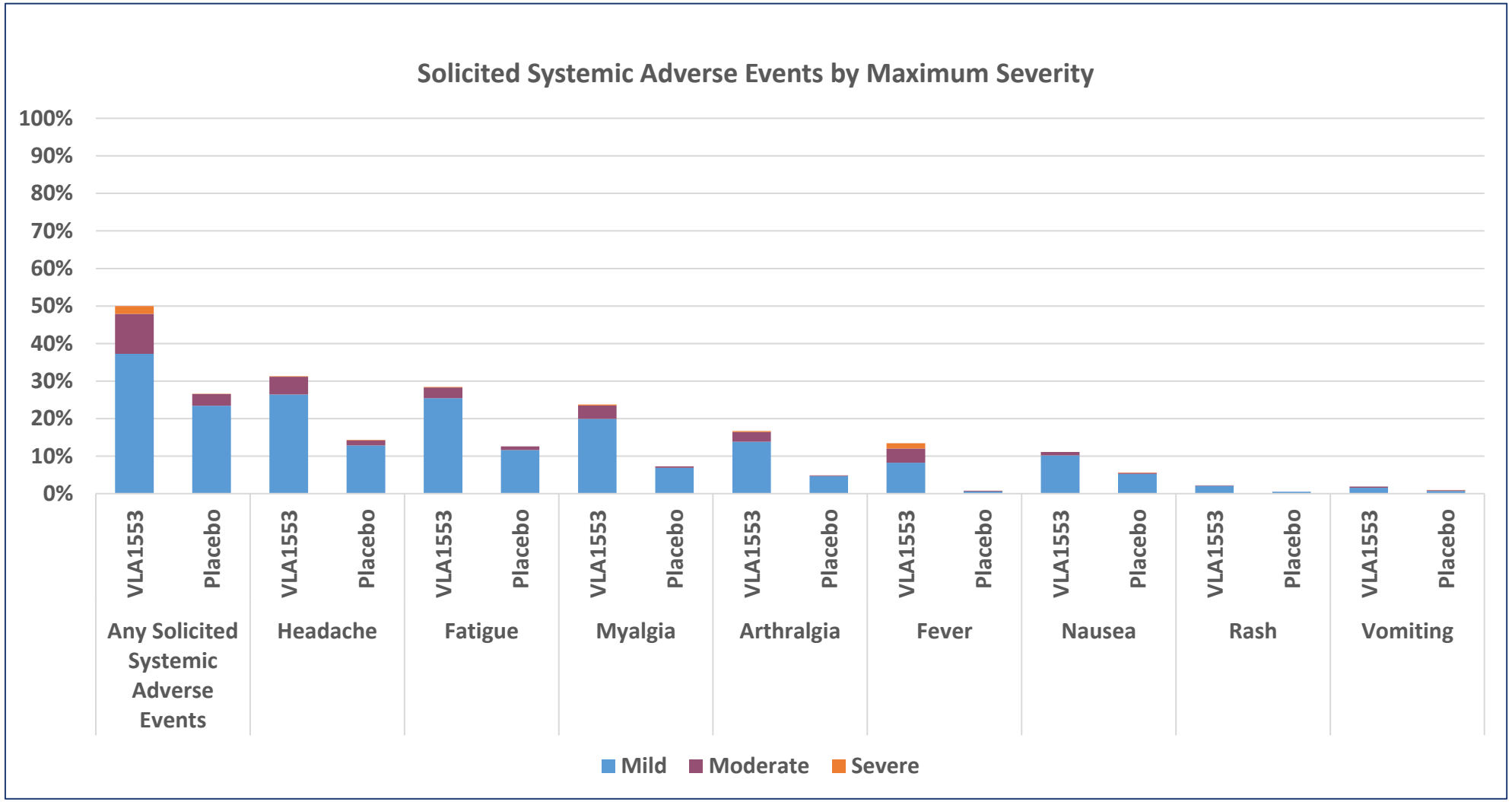
Pivotal Phase 3 Solicited Local AE Within 10 Days After Vaccination (VLA1553-301)

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



VLA1553 Chikungunya Vaccine Candidate

Summary

- **VLA1553 met primary endpoint in a pivotal immunogenicity phase 3 study**
  - Serological endpoint, μPRNT$_{50}$ titer ≥150, agreed by FDA to support accelerated approval
  - **Single dose induced seroresponse in 98.9%** of participants at Day 29
  - Seroresponse was **sustained in 96.3%** of participants at **Day 180**
  - Similar GMT and SRR induced in participants aged 18-64 or ≥65 years of age
- **VLA1553 was generally well tolerated across age groups**
  - Independent DSMB 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)
- **Safety profile comparable with other licensed vaccines[1]**
- **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

1 E.g. compare FDA prescribing information Comirnaty, Bexsero, Shingrix, YF-VAX, all accessible at https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states

ACKNOWLEDGEMENTS

+ Study Participants, Clinical Trial Sites and Vendors

+ Valneva VLA1553 Project Team and Clinical Study Teams

+ Herwig Kollaritsch, Lin Chen, Eva-Maria Poellabauer, DSMB Committee

+ Najwa Khuri-Bulos, SPEAC (Safety Platform for Emerging Vaccines) DSMB Observer

+ Pierre Roques, Roger Le Grand and colleagues from Université Paris-Saclay, INSERM, CEA, France

+ Development of VLA1553 is funded in part by CEPI and EU Horizon 2020

CEPI

Horizon 2020

Thank you.

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