Chikungunya: Phase 3 clinical development of a single-shot live-attenuated vaccine candidate

American Society of Tropical Medicine & Hygiene

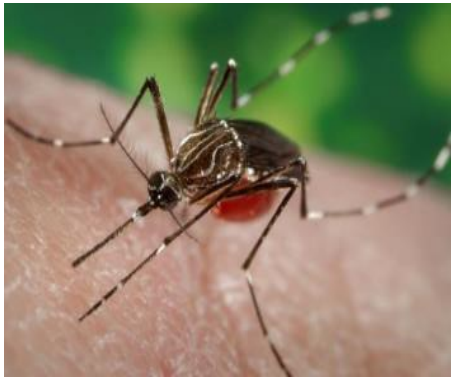
Vera Bürger
Director Clinical Strategy, Project Lead Chikungunya Vaccine Development

valneva

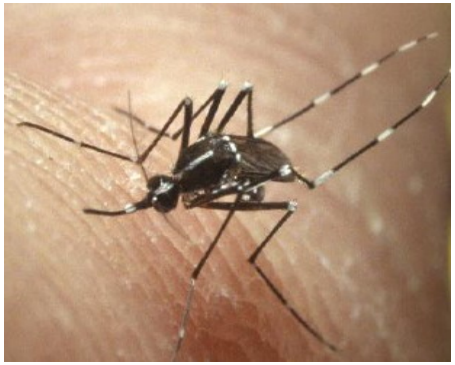
Disclaimer

This presentation does not contain or constitute an offer of, or the solicitation of an offer to buy or subscribe for, Valneva SE shares to any person in the USA or in any jurisdiction to whom or in which such offer or solicitation is unlawful.
Valneva is a European company. Information distributed is subject to European disclosure requirements that are different from those of the United States. Financial statements and information may be prepared according to accounting standards which may not be comparable to those used generally by companies in the United States.
This presentation includes only summary information provided as of the date of this presentation only and does not purport to be comprehensive. Any information in this presentation is purely indicative and subject to modification at any time without notice. Valneva does not warrant the completeness, accuracy or correctness of the information or opinions contained in this presentation. None of Valneva, or any of its affiliates, directors, officers, advisors and employees is under any obligation to update such information or shall bear any liability for any loss arising from any use of this presentation. The information has not been subject to independent verification and is qualified in its entirety by the business, financial and other information that Valneva is required to publish in accordance with the rules, regulations and practices applicable to companies listed on Euronext Paris and the NASDAQ Global Select Market, including in particular the risk factors described in Valneva's universal registration document filed with the French Financial Markets Authority (Autorité des Marchés Financiers, or AMF) on March 23, 2022, as completed by an amendment to the 2021 universal registration document filed with the AMF on September 30, 2022 under number D. 22-0140-A01, and the Form 20-F filed with the U.S. Securities and Exchange Commission (SEC) on March 24, 2022, as well as the information in any other periodic report and in any other press release, which are available free of charge on the websites of Valneva (www.valneva.com) and/or the AMF (www.amf-france.org) and SEC (www.sec.gov).
Certain information and statements included in this presentation are not historical facts but are forward-looking statements, including statements with respect to revenue guidance, the progress, timing, completion results of research, development and clinical trials for product candidates and estimates for future performance. The forward-looking statements (a) are based on current beliefs, expectations and assumptions, including, without limitation, assumptions regarding present and future business strategies and the environment in which Valneva operates, and involve known and unknown risk, uncertainties and other factors, which may cause actual results, performance or achievements to be materially different from those expressed or implied by these forward-looking statements, (b) speak only as of the date this presentation is released, and (c) are for illustrative purposes only. Investors are cautioned that forward-looking information and statements are not guarantees of future performances and are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of Valneva.

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.

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":**

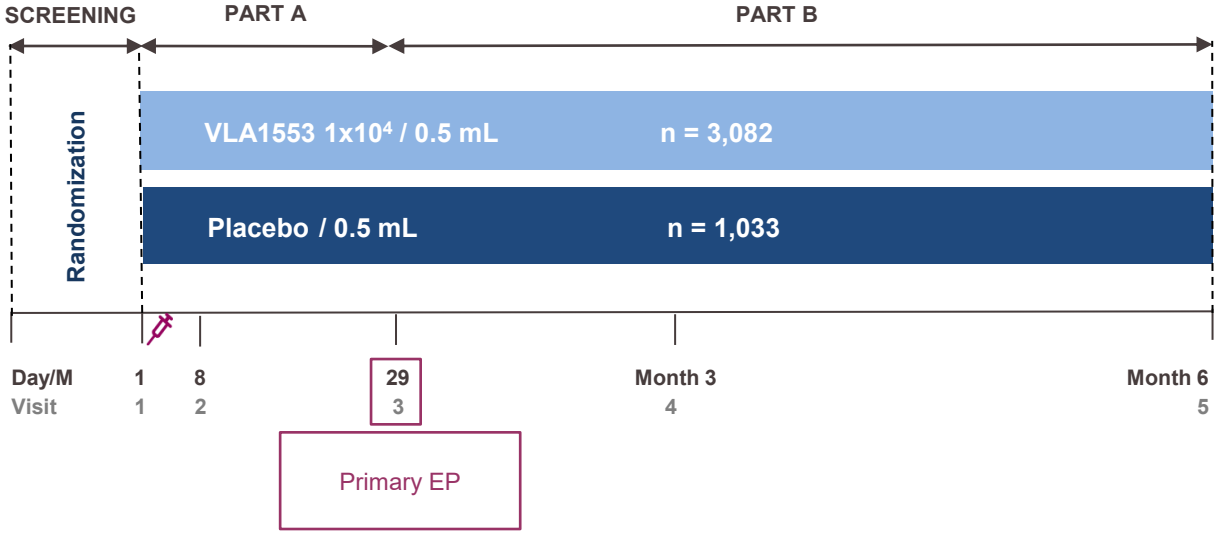
  - Rate of subjects achieving a **neutralizing antibody titer of ≥150 in a $\mu PRNT_{50}$** assay[2]

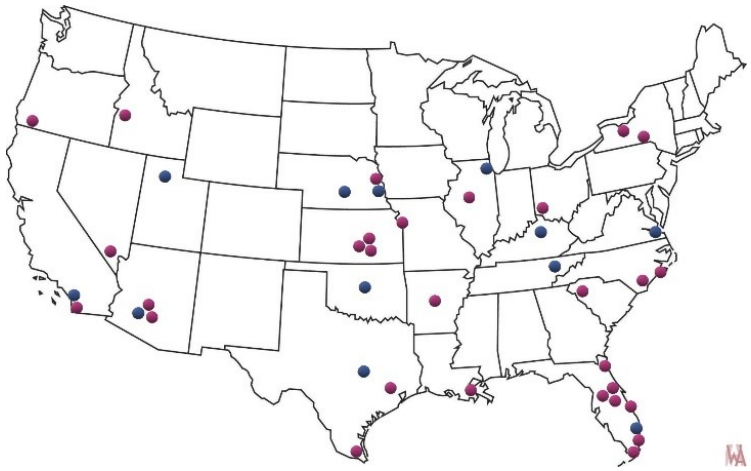
1 VRBPAC Meeting, Nov 2019. 2 Bettis et al, PLoS Negl Trop Dis 16(1): e0010069
2 Roques P, et al. Effectiveness of CHIKV vaccine VLA1553 demonstrated by passive transfer of human sera. JCI Insight. 2022 Jul 22;7(14):e160173. doi: 10.1172/jci.insight.160173. PMID: 35700051; PMCID: PMC9431671.

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



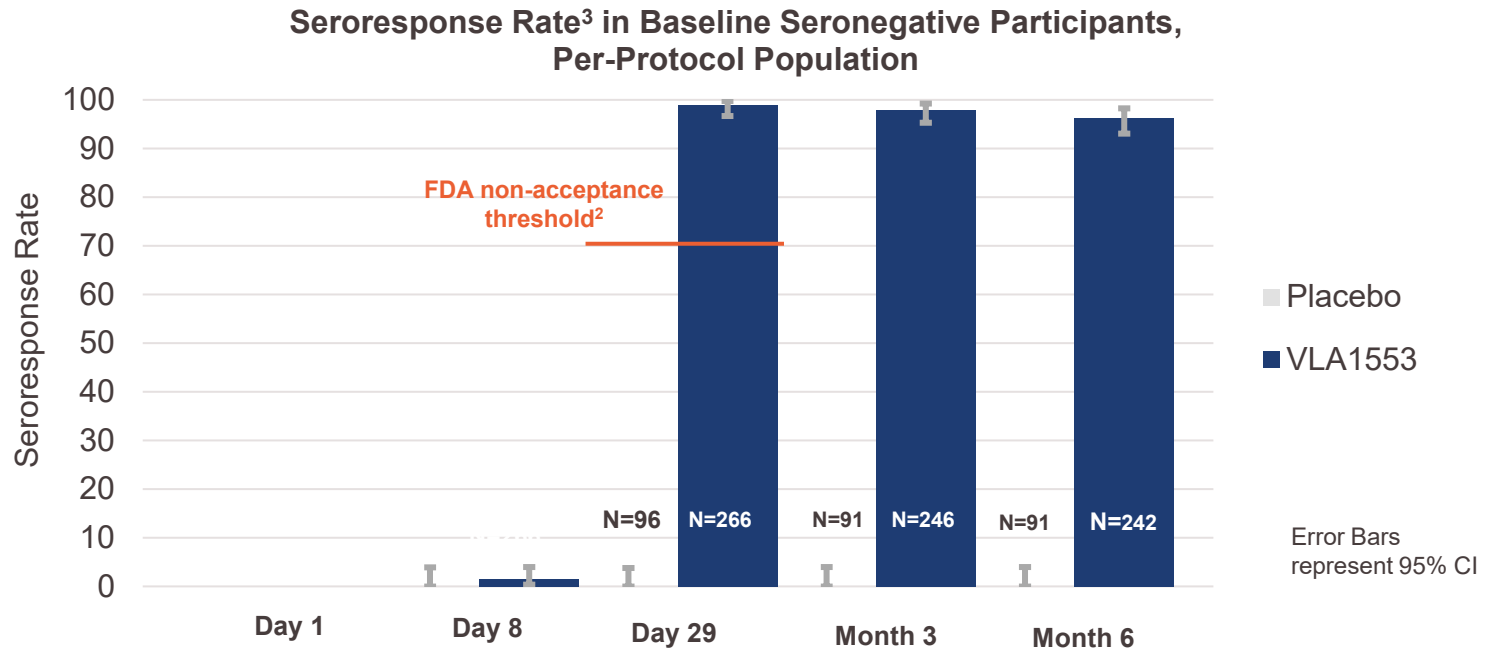


Blue = Immunogenicity Sites
Purple = Non-Immunogenicity Sites
(i.e. not enrolling participants within the immunogenicity subset)

n = number of participants in the safety population

Pivotal Study Met Primary Endpoint (VLA1553-301)

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

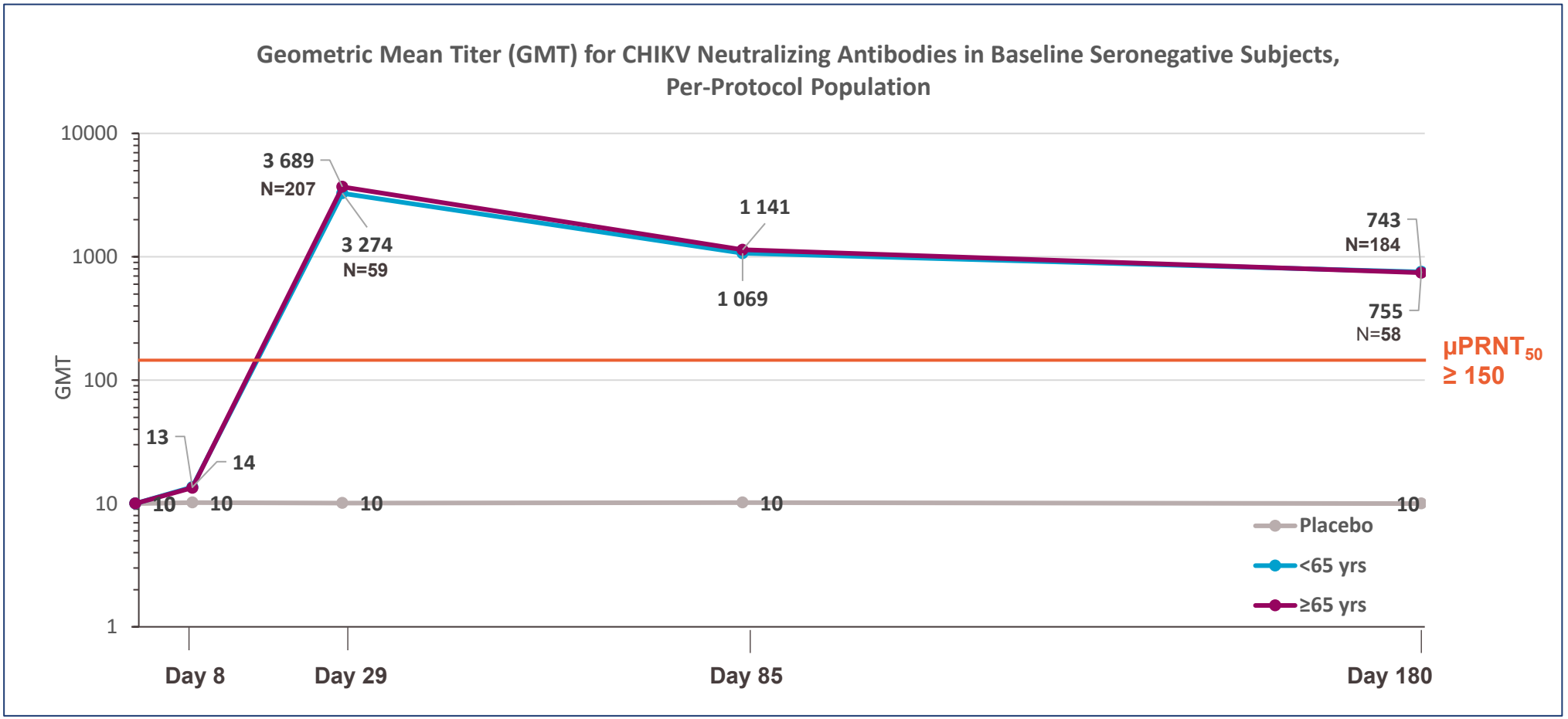


- **Per-Protocol population: 362 / 462 participants from immunogenicity set**
- **Day 29 Seroresponse rate (SRR):**
  - **98.9% (263/266, 95% CI: 96.7- 99.8) vs placebo 0% (0/96, 95%CI 0.0 - 3.8)**
- **High SRR was maintained after six months at 96.3% (233/242, 95% CI: 93.1 - 98.3)**

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)

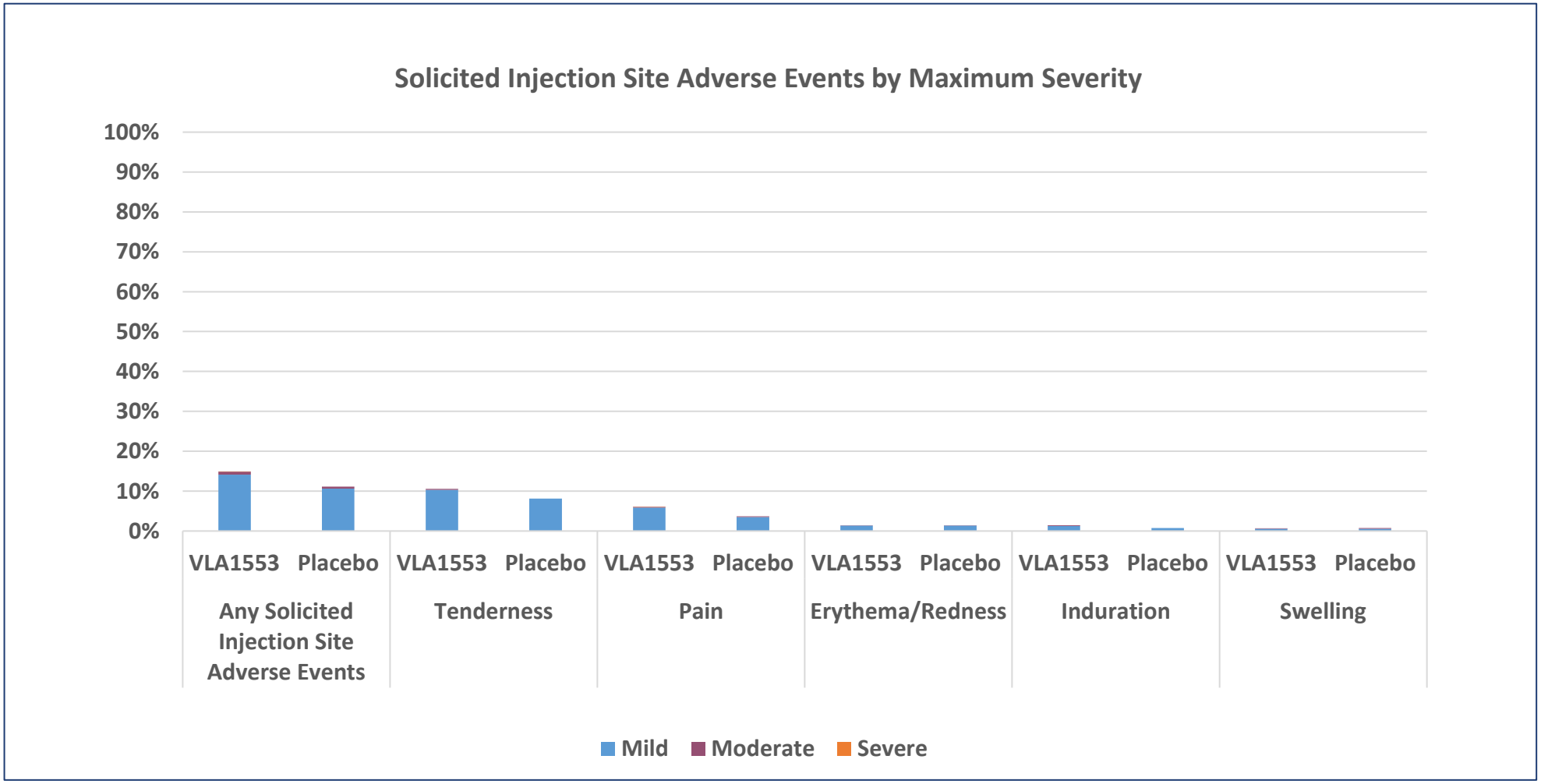
VLA1553 vaccine candidate generally well tolerated

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

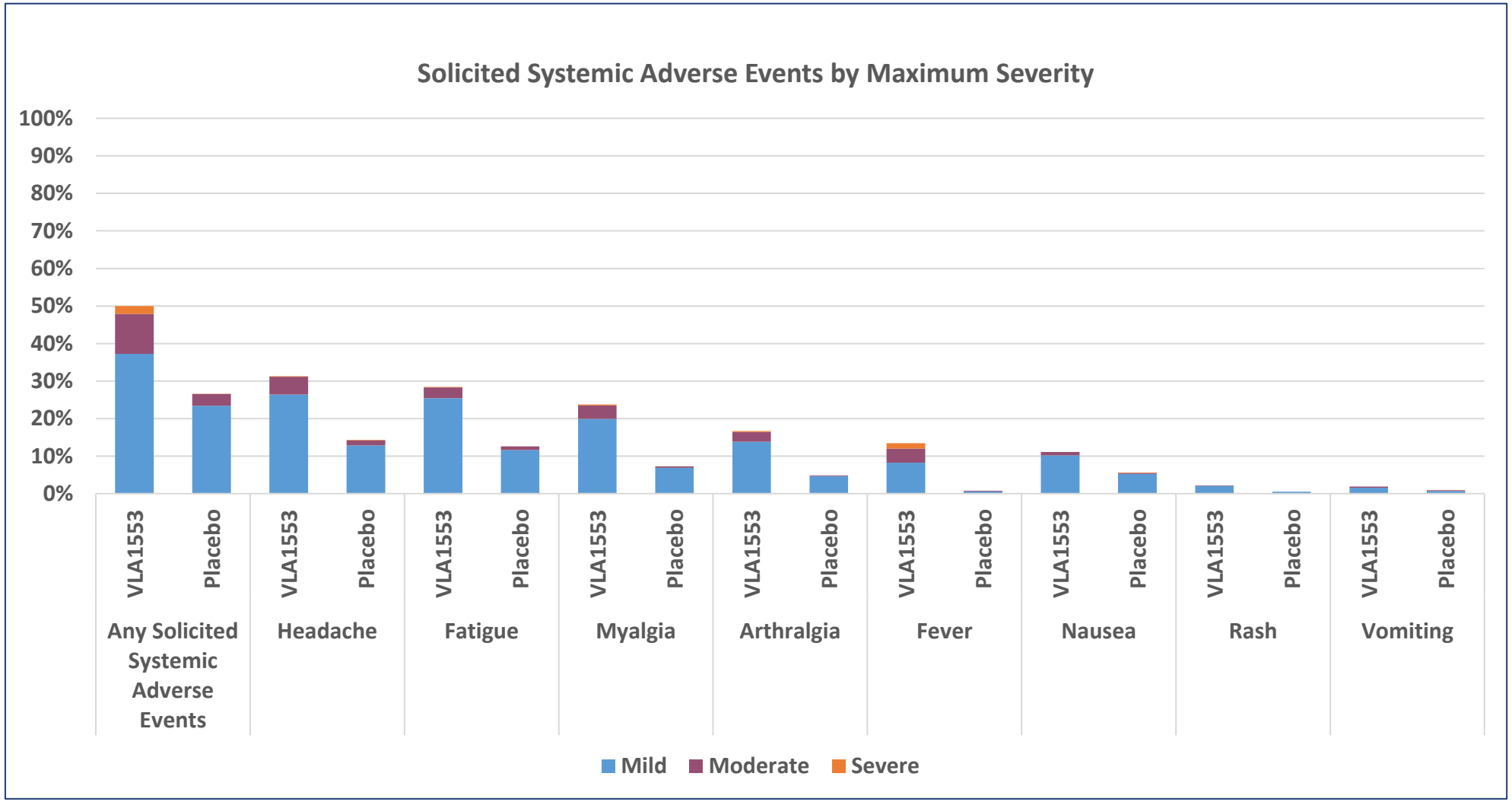
Pivotal Phase 3 Solicited Local AE Within 10 Days After Vaccination (VLA1553-301)

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 accelable 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.

valneva