ONE STEP CLOSER TO A SINGLE-SHOT CHIKUNGUNYA VACCINE: update on Valneva's live-attenuated vaccine candidate

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Valneva Summary and Core Strengths

Fully integrated specialty vaccine company focused on development, manufacturing 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 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**

Advanced, Focused and Differentiated Clinical Pipeline and promising early stage targets

R&D pipeline overview

	Program	Discovery	Pre-Clinical	Phase 1	Phase 2	Phase 3	Commercial	Next Inflection Point	Development Partners
R&D Portfolio	**VLA1553[2]:** Chikungunya						*Potentially eligible for PRV*	Potential BLA approval 3Q 23	*CEPI/ Butantan (LMIC)*
	VLA15[3]: Lyme disease							Working with regulatory authorities on potential modifications of the clinical trial plan	Pfizer
	VLA84: Clostridium difficile							Developed to EoP2/ on-hold	*Open to partnering*
	VLA1601: Zika							Potential clinical re-entry end 2023/ early 2024	-
	VLA1554: hMPV							Initial pre-clinical PoC completed	*Partnering under evaluation*
	VLA2112: EBV							Antigen identification by end 2023	-
	Campylobacter							Pre-clinical entry subject to gating criteria	
	Parvovirus							Pre-clinical entry subject to gating criteria	

Chikungunya Vaccine Candidate – VLA1553*

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

VLA1553 at a Glance

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

CHIKV Vaccine Candidate 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 – Completed Phase 3

- **Pivotal** Phase 3 Trial: **Primary Endpoint (Seroresponse Rate) met**
- **Lot-to-Lot consistency** Trial: **Primary Endpoint met**
- Antibody persistence trial ongoing: positive 12 months data
- Adolescents trial in Brazil ongoing

Regulatory Milestones

- FDA: **Fast Track and Breakthrough designations granted**
  - Rolling submission of Biologics License Application (BLA) completed in Dec 2022, filing acceptance for **priority review** in Feb 2023
- EMA: **PRIME** designation 2020

Target Populations & Geographic Reach

- **Non-endemic** countries: Travelers / Military / Outbreak preparedness in U.S., 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 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. 2 Bettis et al, PLoS Negl Trop Dis 16(1): e0010069

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 provide data for initial licensure

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[2]** data

Phase 3:

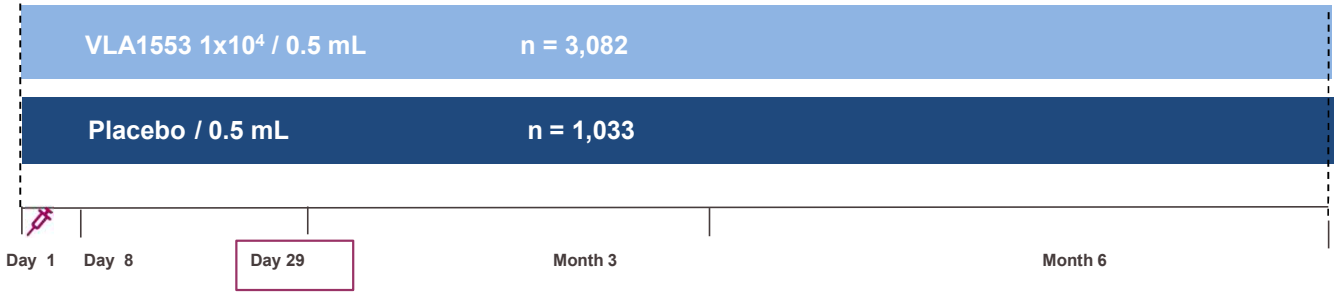
- **Pivotal Phase 3 study[3]:**
  - **4,115 participants** aged ≥18 years
  - RCT comparing **VLA1553 to placebo**
  - Study generated **safety and immunogenicity** data
- **Lot-to-Lot consistency study[4]:**
  - **408 participants** aged **18-45 years**
  - RCT comparing **3 lots of VLA1553**

1 Wressnigg et al. 2020; Lancet Infect Dis 20:1193-1203. 2 Viremia tested by RT-qPCR, readout: CHIKV genome copy equivalents (GCE) detected per 1mL of initial specimen. 3 NCT04546724 ClinicalTrials.gov Record. Available at: https://clinicaltrials.gov/ct2/show/NCT04546724. Accessed: January 2023. 4 VLA1553-302 ClinicalTrials.gov Record. Available at: https://clinicaltrials.gov/ct2/show/NCT04786444. Accessed: January 2023

Pivotal Study Design (VLA1553-301)

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 µPRNT50) among 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
- Subset of participants is being followed for long-term safety and antibody persistence in study VLA1553-303



n = number of participants in the safety population

Demographic Data

Similar baseline characteristics between VLA1553 group and Placebo

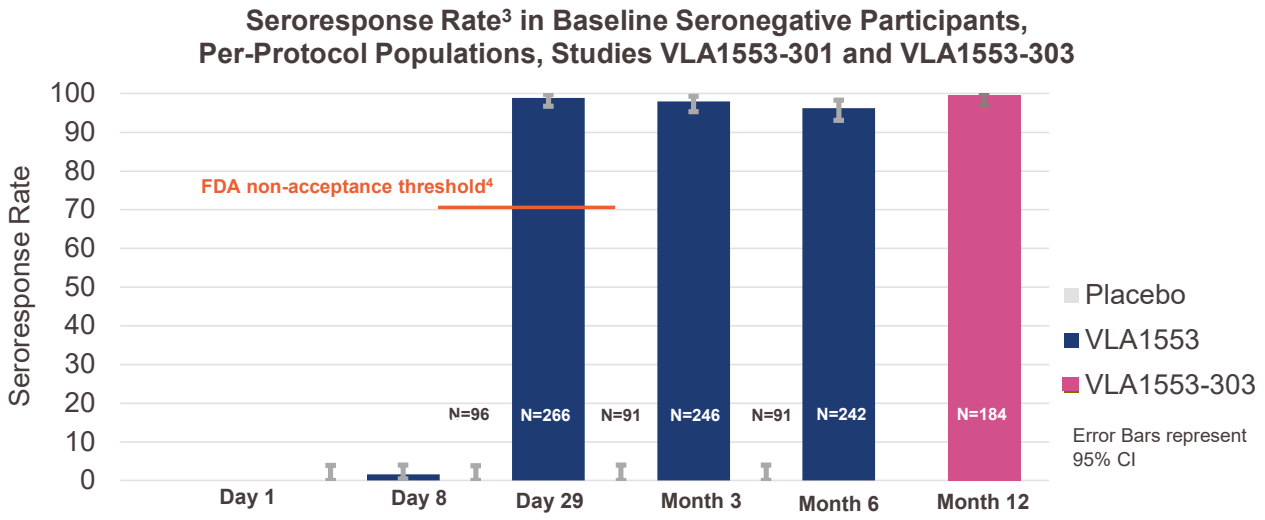
	VLA1553 N=3082	Placebo N=1033
Gender n (%)		
Female	1682 (54.6)	569 (55.1)
Male	1400 (45.4)	464 (44.9)
Race n (%)		
American Indian or Alaskan Native	27 (0.9)	5 (0.5)
Asian	51 (1.7)	17 (1.6)
Black or African American	451 (14.6)	122 (11.8)
Native Hawaiian or Other Pacific Islander	13 (0.4)	5 (0.5)
White	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;

Seroresponse[1] in 99% of Participants, Retained After 12 Months

12-month persistence data from a subset of pivotal trial confirm earlier findings[2]



- **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 12 months after vaccination at 99.5% (183/184, 95% CI: 97 – 100)**

1 CHIKV neutralizing antibody titer ≥150 by $\mu PRNT_{50}$; 2 Wressnigg et al, Lancet ID 2020; 3 The proportion of participants with seroresponse, determined by $\mu PRNT_{50}$ for baseline negative participants 28 days post-vaccination; 4 The lower bound of the 95% Confidence Interval for the SRR at Day 29 in the VLA1553 group needed to exceed 70%
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High Seroresponse Rate Confirmed in Older Participants

Additional data in adults ≥65 Years

Subjects with Seroresponse	18-64 years		≥ 65 years	
	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**

- **107 participants aged ≥65 years were included in a secondary analysis population**
- **Day 29 Seroresponse rate:**
  - **99.0% (103/104, 95% CI: 94.8 – 100.0)**
- **High rate 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.

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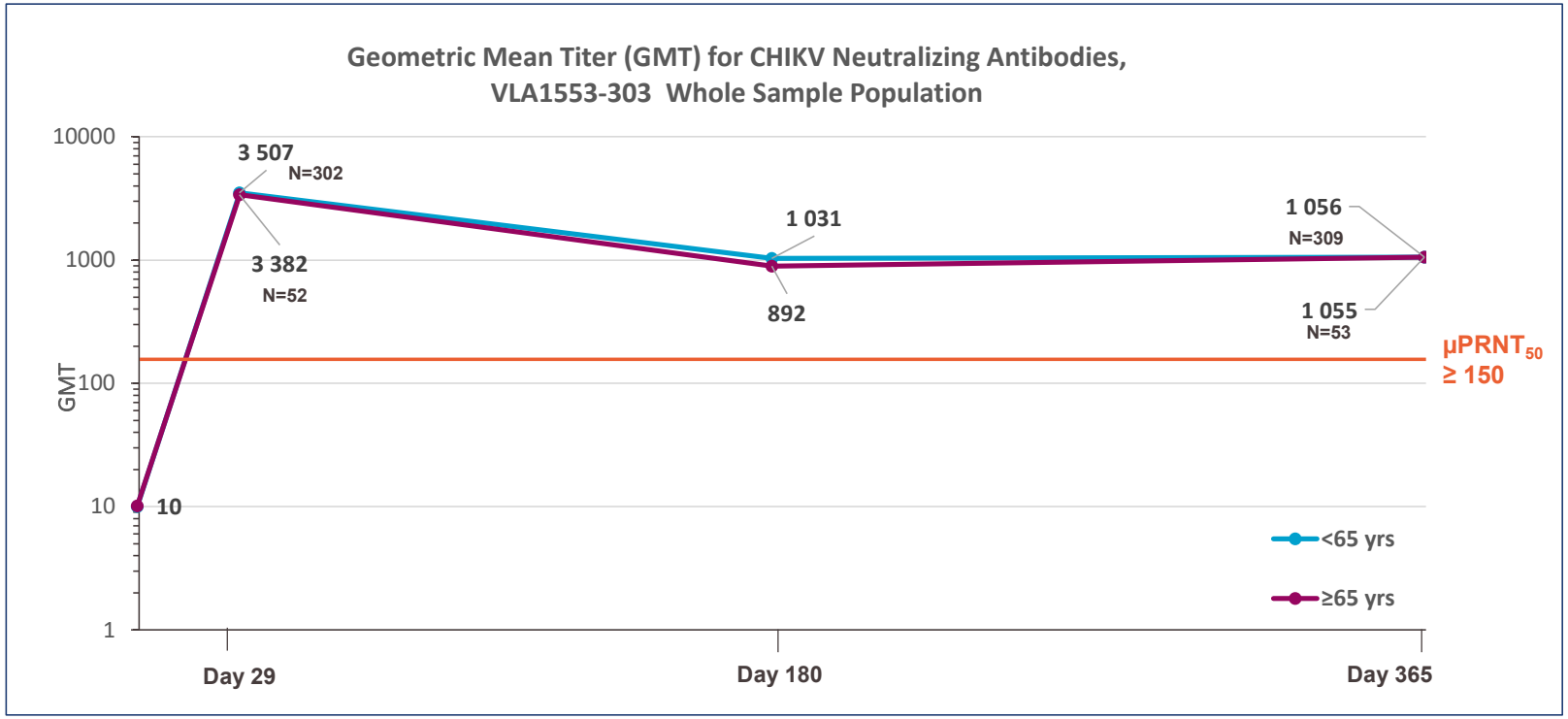
Stable Neutralizing Antibodies During 12 Months Follow-up (VLA1553-303)

Comparable titers in participants 18-64 or ≥65 years throughout study



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Investor Day Slides, December 06, 2022. Available at https://valneva.com/wp-content/uploads/2022/12/VALNEVA_Investor-Day-2022_vFinal.pdf Accessed: 23 March 2023

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*

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

- 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: Adverse Events Rates by Age (VLA1553-301)

Similar AE profiles in participants 18-64 or ≥65 years

	18-64 years		≥ 65 years	
AE Category	**VLA1553** (N=2,736) n (%)	**Placebo** (N=916) n (%)	**VLA1553** (N=346) n (%)	**Placebo** (N=117) n (%)
Any AE	**1708 (62.4)**	407 (44.4)	**218 (63.0)**	56 (47.9)
Any Related AE	**1415 (51.7)**	292 (31.9)	**160 (46.2)**	30 (25.6)
Any Severe[a] AE	**94 (3.4)**	10 (1.1)	**10 (2.9)**	4 (3.4)
Any Related Severe[a] AE	**58 (2.1)**	1 (0.1)	**4 (1.2)**	0

a Severe (grade 3): incapable of work or usual activity and requiring medical intervention. Injection site AEs and systemic AEs were rated based on the FDA Guidance on Toxicity Grading Scales

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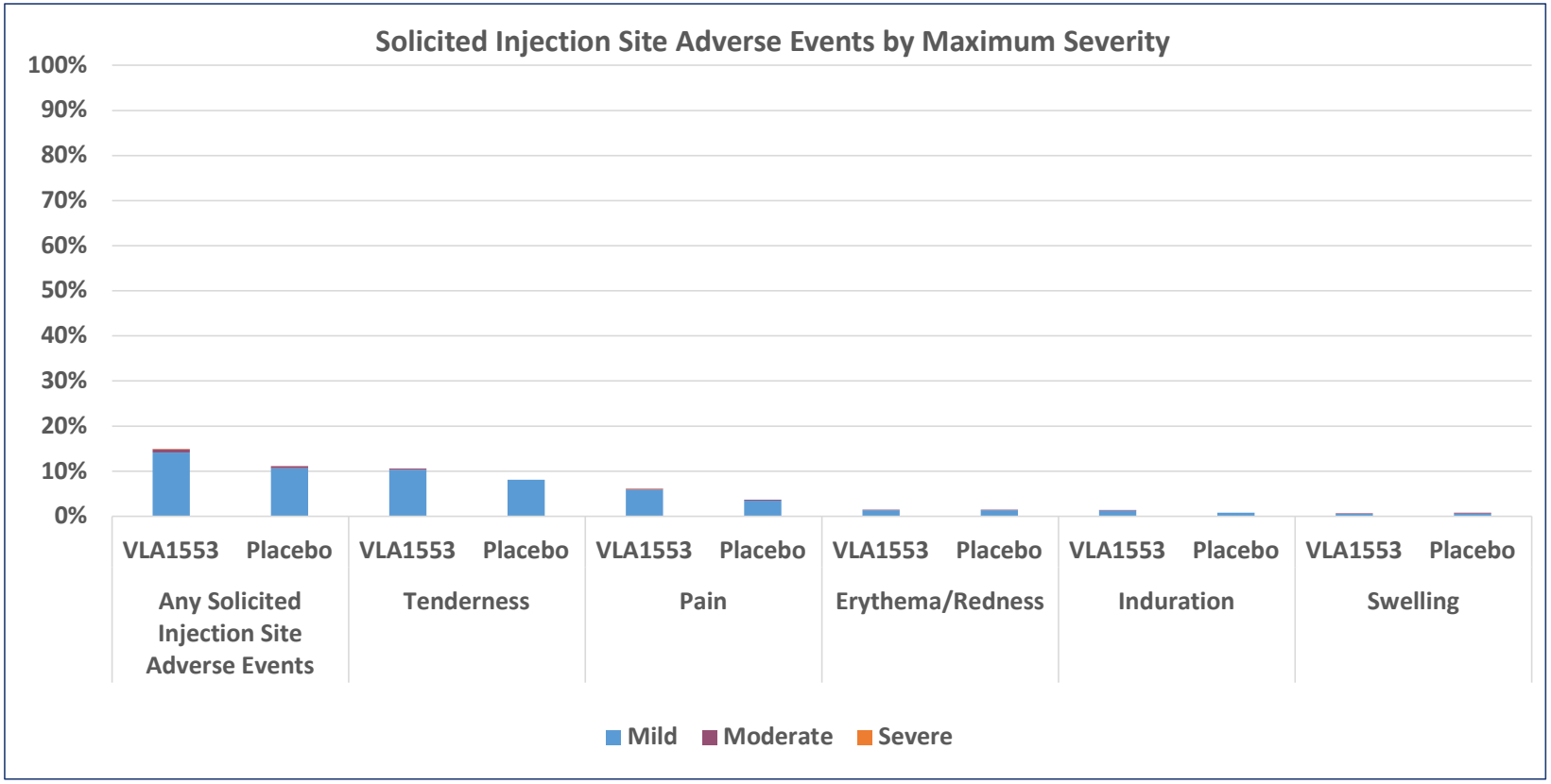
Pivotal Phase 3 Solicited Local Adverse Events Within 10 Days After Vaccination

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



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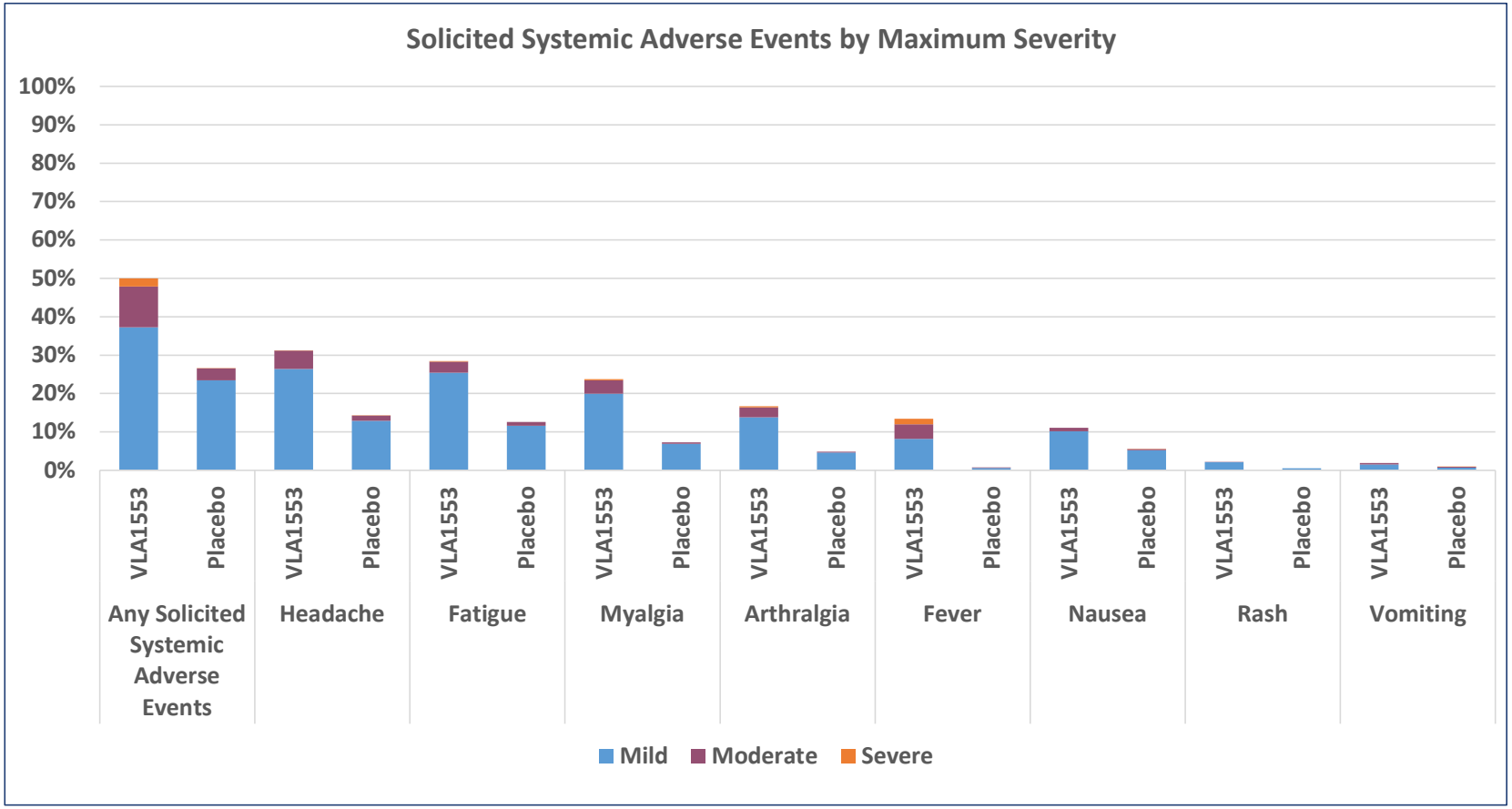
Pivotal Phase 3 Solicited Systemic Adverse Events Within 10 Days After Vaccination

Generally well tolerated, majority of AEs mild-moderate



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VLA1553: Clinical Data Highlights[1,2]

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

Immunogenicity Data	Safety Data[1]
▪ Seroresponse[3] Rate (SRR) in 99% of participants after a single vaccination ▪ Immunogenicity profile maintained over time: 99% SRR after 12 months[4] ▪ Older adults (≥ 65 years) achieved similar SRR and neutralizing antibody titers as younger adults (<65 years)[1,4] ▪ 100% seroconversion after 14 days and sustained to Month 12 in preceding trial[2]	▪ 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 ▪ Majority of solicited adverse events mild or moderate. 2.0% of study participants reported severe solicited adverse events, most commonly fever.

1 Valneva Successfully Completes Pivotal Phase 3 Trial of Single-Shot Chikungunya Vaccine Candidate. **2** Wressnigg et al, Lancet ID: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30238-3/fulltext; **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

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 vaccine candidate 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 patient age** (VLA1553-301)[5] and **persists for at least 12 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. Safety and immunogenicity of a single-shot live-attenuated chikungunya vaccine: a double-blind, multicenter, randomized, placebo-controlled phase 3 trial. Lancet. [Accepted]. 6. Valneva Reports Positive 12-Month Antibody Persistence Data for Single-Shot Chikungunya Vaccine Candidate 7 Valneva Successfully Completes Pivotal Phase 3 Trial of Single-Shot Chikungunya Vaccine Candidate.

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