Chikungunya
A reemerged tropical disease
Development of a live-attenuated vaccine

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valneva

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Chikungunya: A Major Unmet Medical Need

VLA1553 is a unique, single-shot vaccine candidate

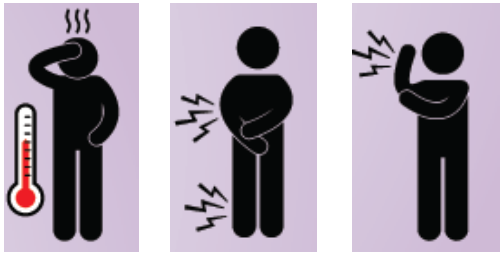
1. **Mosquito-borne viral disease caused by the Chikungunya virus (CHIKV), an Alphavirus, transmitted by *Aedes* mosquitoes (*A. aegypti* and *A. albopictus*)**
2. **Causes clinical cases in 72-92% of infected humans who can develop serious, long-term health impairments[1]**
3. **Outbreaks in Asia, Africa, Europe & the Americas (as of today > 2.2 million reported cases in the Americas)[2]**
4. **Currently no preventive vaccine or effective antiviral treatments exist for Chikungunya**
5. **Three main strains: the African, East-Central South African (ECSA) and Asian strains, as well as the Indian Ocean Lineage (IOL) strain which is a sub-strain of the ECSA virus**
6. **VLA1553 is a monovalent, single dose, live-attenuated prophylactic vaccine targeting Chikungunya virus neutralization[3]**

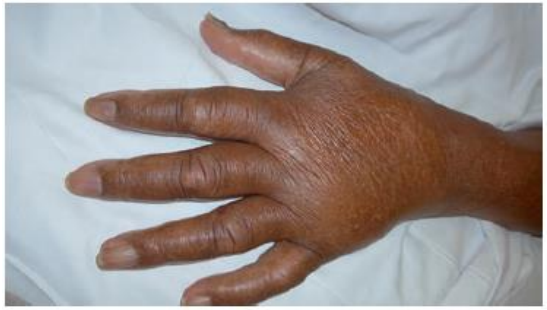
__1__ Simon et al. Curr Infect Dis, 2011); __2__ PAHA/WHO data: Number of reported cases of Chikungunya Fever in the Americas; __3__ Hallengärd et al. 2013. J Virology 88:2858–2866
***Photo credit**: James Gathany*

Chikungunya Disease Symptoms

Affecting Women and Men of All Ages

Most common clinical symptoms:





Acute arthritis and distal edema

Severe arthritis (black arrow) and tenosynovitis (white arrow)

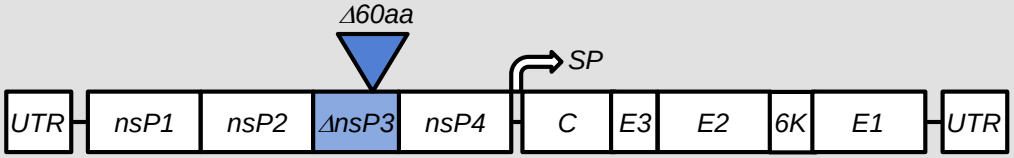
+ Majority of infected people become symptomatic (60-80%)
+ Incubation period usually 4–7 days (range 1–12 days)
+ Acute onset of high fever (in 90% of patients) and polyarthralgia (in 95% of patients) are the primary clinical findings
+ Joint symptoms usually symmetric, often occuring in hands and feet; severe and debilitating, lasting for weeks to months to years
+ Other symptoms: Headache, myalgia (for 7-10 days), arthritis, conjunctivitis, nausea/vomiting, maculopapular rash (for ~1 wk, in 40-50% of patients)
+ No treatment available

***Source**: CDC; Suhrbier et al. Nature, 2012; Simon et al. Curr Infect Dis, 2011; Pictures: Springer 2016;*

Chikungunya Vaccine Candidate

VLA1553 Short Profile

Live-attenuated CHIKV vaccine



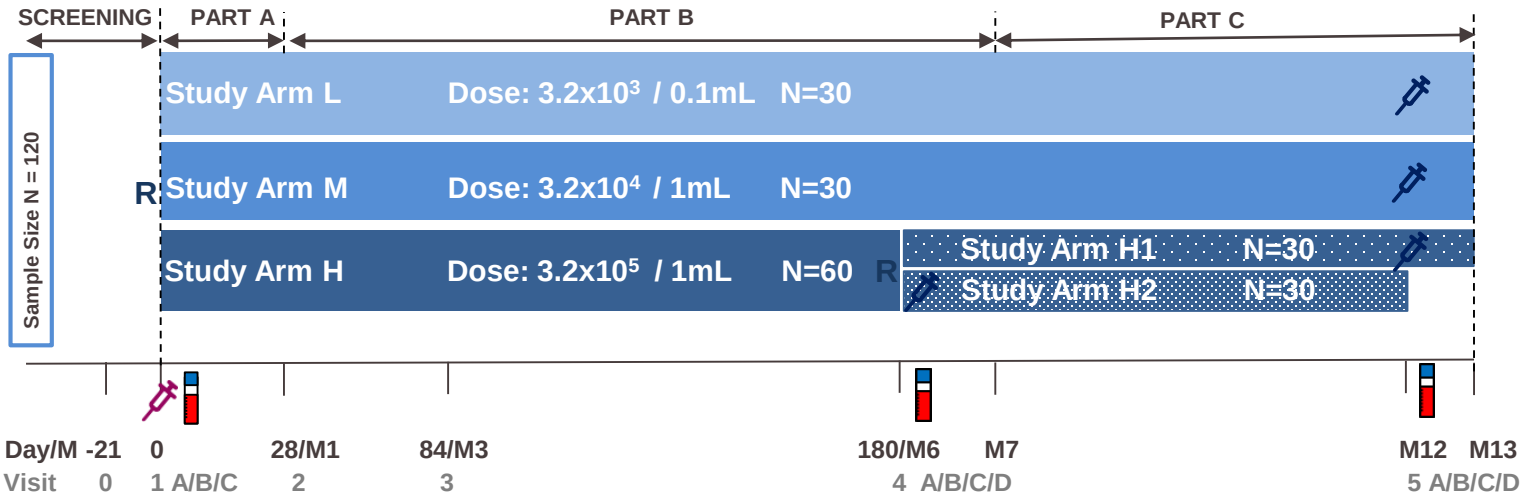
Δ5nsP3 = VLA1553

+ Based on La Reunion strain of East Central South African genotype
+ Attenuation by reverse genetics resulting in 60aa deletion within the C-terminal part of the non-structural nsP3 gene of the viral replicase complex which leads to a reduced replication capability of the virus in vivo.[1]
+ Reversion to wild-type impossible
+ Vero cell-culture derived
+ Purified by centrifugation, ultrafiltration, batch-chromatography and sucrose gradient centrifugation
+ Wild-type challenge studies in immunized Non-Human Primates demonstrated protection from viremia and disease.[2]

1 Hallengärd et al. 2013. J Virology 88:2858–2866. 2 Roques et al., 2017. J Clin Invest Insight.

Chikungunya Vaccine - Phase I Clinical Study
Blinded, Randomized, Dose-Escalation Study

+ Study Population: 120 healthy volunteers aged 18 to 45 years
+ Dosage: Single-dose vaccination with $3.2x10^3$ $TCID_{50}$ (Group L, 0.1ml), $3.2x10^4$ $TCID_{50}$ (M, 1ml), $3.2x10^5$ $TCID_{50}$ (H, 1ml)
+ Immunization route: i.m.
+ Primary Objective: Safety and tolerability after a single vaccination
+ Secondary Objectives: Safety up to 12 months, Immunogenicity, Optimal Dose and Antibody Persistence
+ Challenge (Re-vaccination with highest dose) at Month 6 or 12
  (1) to show that single-shot is sufficient to induce sterilizing immunity;
  (2) to serve as human viral challenge demonstrating that subjects are protected from viremia, as an indicator of early vaccine efficacy.



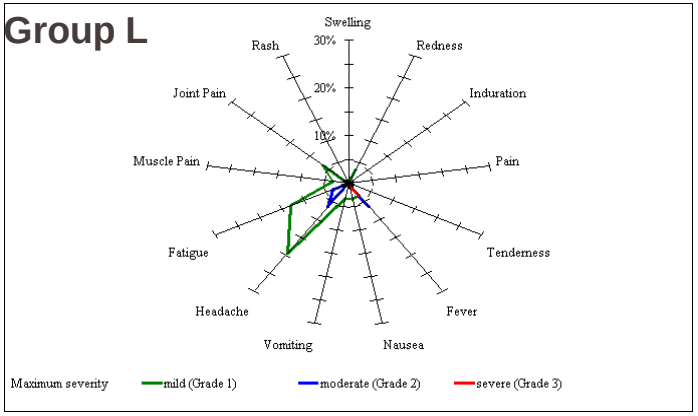
Clinicaltrials.gov ; No. NCT03382964

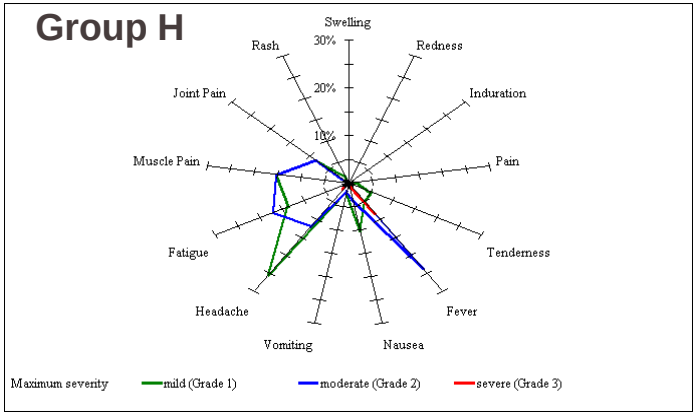
* safety including viremia on Days 0/3/7/14 post-vaccination

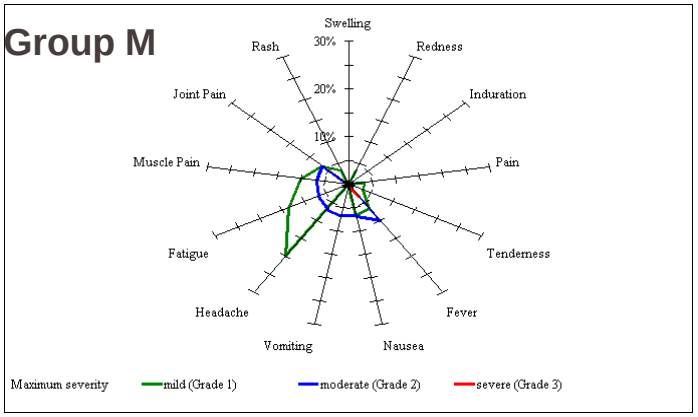
* vaccination with the highest dose

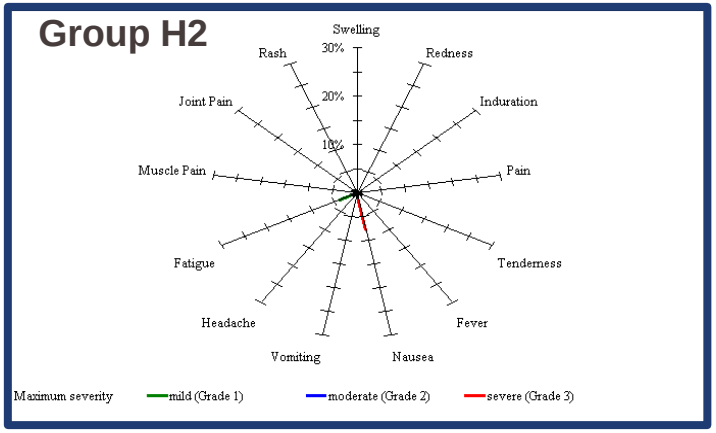
Chikungunya Phase 1 - Safety

Subjects with solicited AEs after Vaccination by Maximum Severity





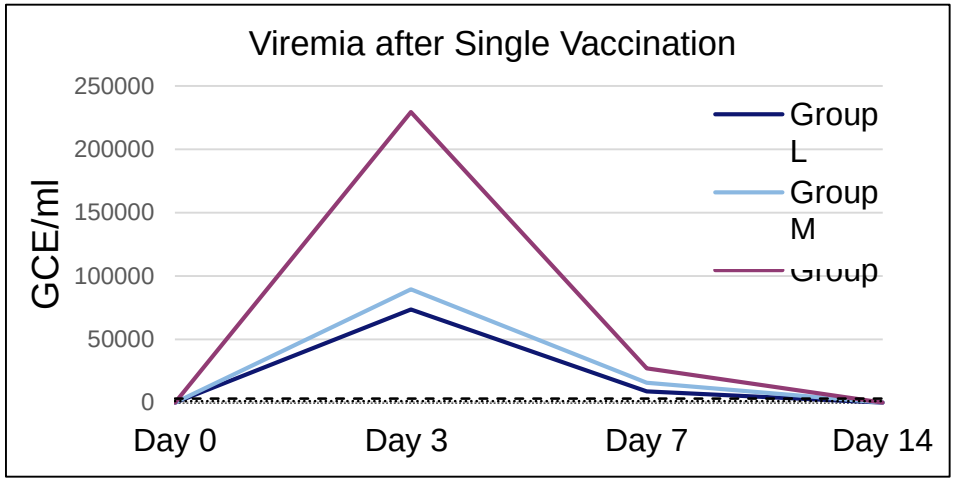


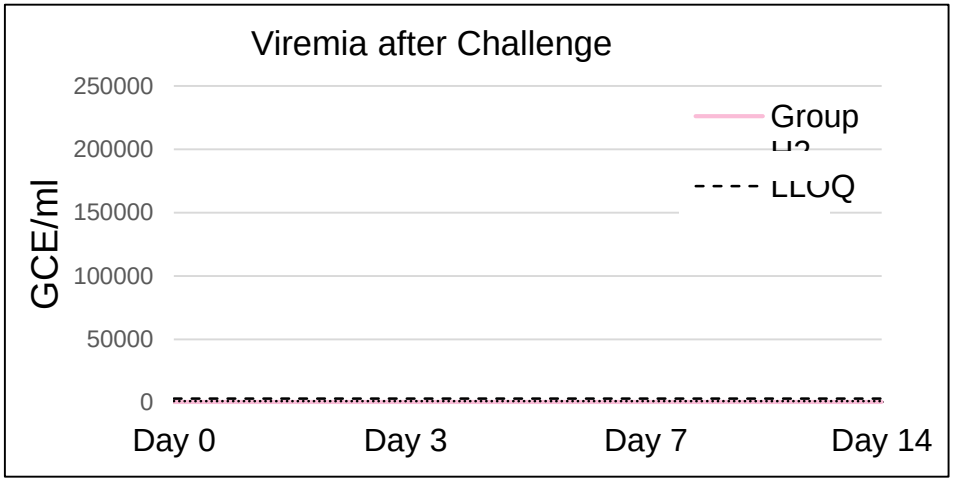


Radar plots of solicited injection site and systemic Aes within 14 days after Single Vaccination (Groups L, M, H) and Challenge (Group H2).

Chikungunya Phase 1 - Safety

Viremia at Days 0, 3, 7 and 14 after Single Vaccination and Challenge

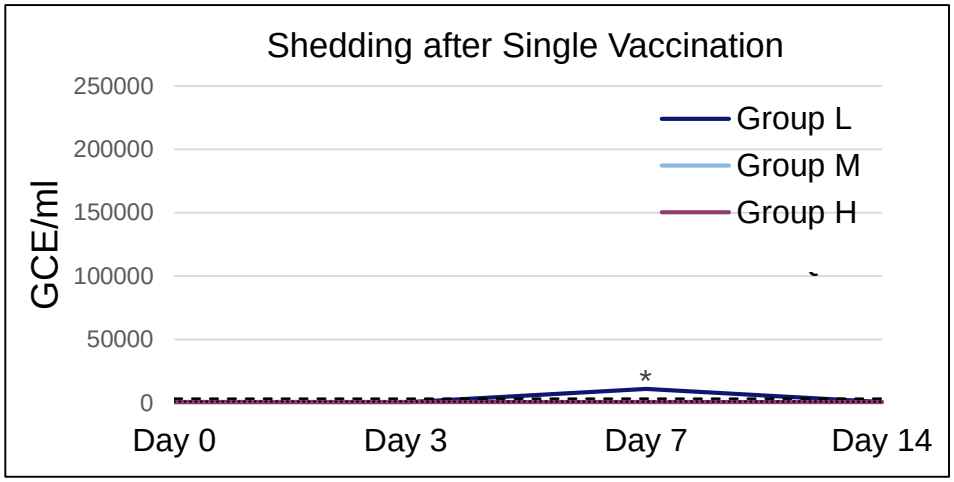


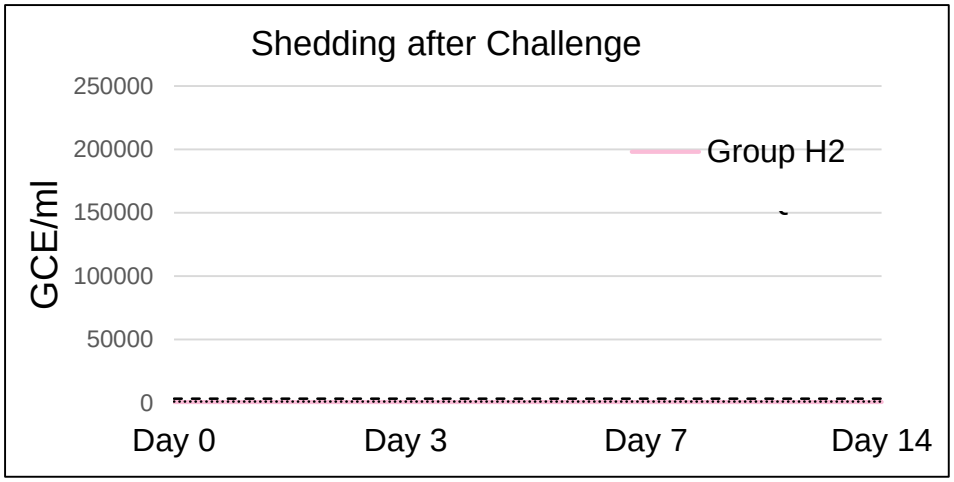


Viremia in plasma at Days 0, 3, 7 and 14 after Single Vaccination and Challenge (B). Limit of Detection (dotted line): 1087 GCE/mL, Lower Limit of Quantification (dashed line): 3261 GCE/mL. Time points with no available results in the treatment group are imputed with 500. GCE/mL – Genome copy equivalents per mL determined by quantitative real-time PCR

Chikungunya Phase 1 - Safety

Urinary Shedding at Days 0, 3, 7 and 14 after Single Vaccination and Challenge

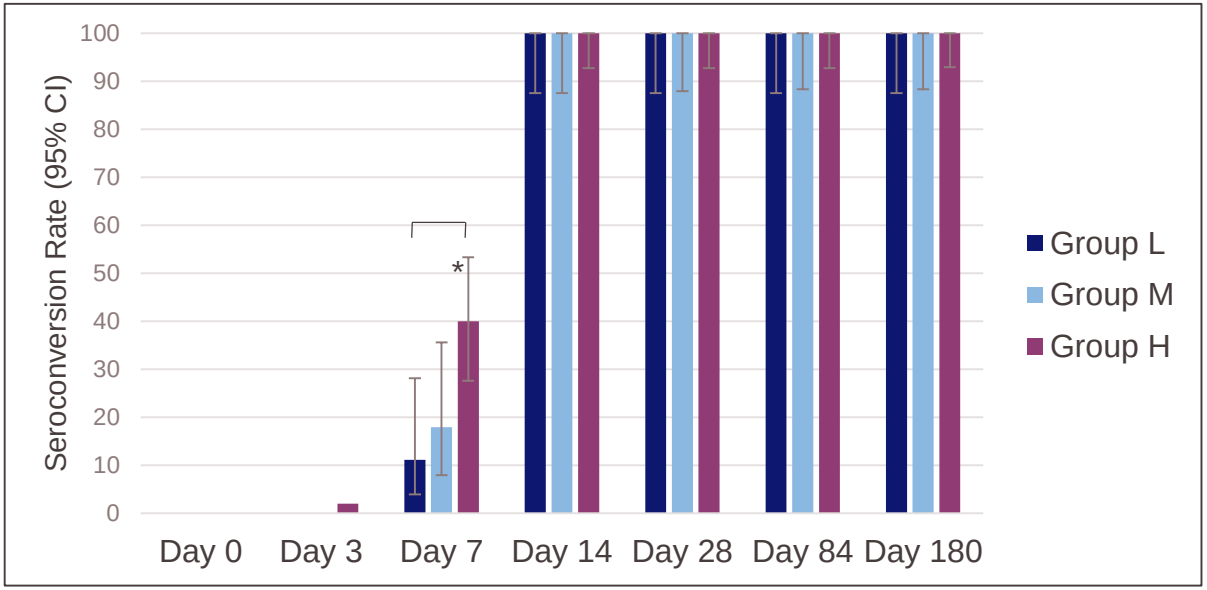




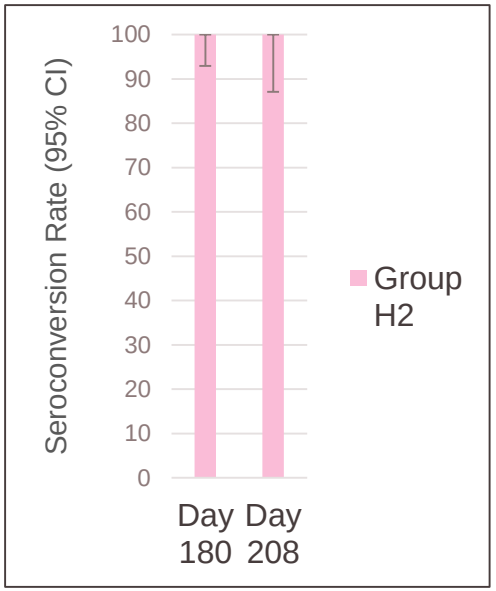
Shedding in urine at Days 0, 3, 7 and 14 after Single Vaccination and Challenge. Limit of Detection (dotted line): 1087 GCE/mL, Lower Limit of Quantification (dashed line): 3261 GCE/mL.
Time points with no available results in the treatment group are imputed with 500. GCE/mL – Genome copy equivalents per mL determined by quantitative real-time PCR
* Single subject

Chikungunya Phase 1 - Immunogenicity

CHIKV-specific Seroconversion Rates after Single Vaccination



Assessment of Neutralizing Antibodies after Single Vaccination. Seroconversion rates assessed by CHIKV-specific microneutralization assay compared to baseline. Seroconversion is defined as proportion of subjects achieving a CHIKV-specific antibody titer of at least 20 (NT50≥20).* Pairwise test p=0.0092



Assessment of Neutralizing Antibodies after Challenge at 6 months. Seroconversion defined as proportion of subjects achieving a CHIKV-specific antibody titer of at least 20 (NT50≥20) compared to baseline.

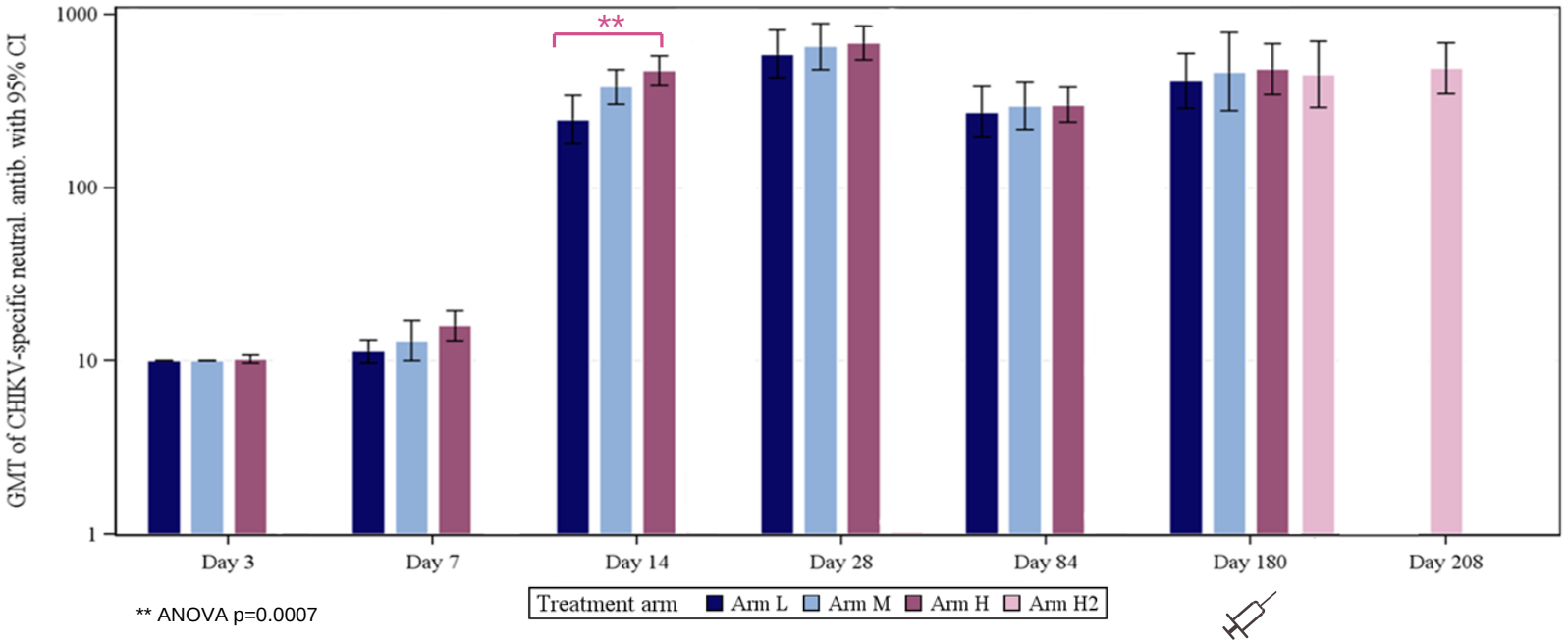
Single-Dose Vaccination sufficient to induce sustaining high titer neutralizing antibodies

		Group H2 (N=26)
≤ 4-fold increase	n /Nm (%)	25 /26 (96.2)
	[95% CI]	[81.1, 99.3]

Rate of subjects within ≤ 4-fold increase in antibody titers from the day of Challenge to Day 28 after Challenge. Sterilizing immunity characterized by a ≤ 4-fold rise in antibody titers as compared to pre-vaccination titers.

Chikungunya Phase 1 - Immunogenicity

CHIKV-specific neutralizing antibodies (GMT) after Single Vaccination and Challenge



** ANOVA p=0.0007

Chikungunya Phase 1 Study – Interim results
Excellent immunogenicity and Safety Profile up to Month 7

Immunogenicity

- 100% Seroconversion Rate achieved already at Day 14 after a single vaccination in all dose groups
  - and fully sustained at 100% after six months
- Single vaccination of VLA1553 is sufficient to induce sustaining, high titer, neutralizing antibodies

Excellent immunogenicity profile after single vaccination

Safety

- Generally safe in all dose groups
- Well-tolerated in the low and medium doses
  - Superior safety profile, including viremia, in low and medium doses compared to highest dose
- Excellent local tolerability
- No vaccine related Serious Adverse Events or Adverse Events of Special Interest up to Month 7

Excellent safety profile in low and medium dose groups

SCR defined as proportion of subjects achieving a CHIKV-specific neutralizing antibody titre as $NT_{50} \geq 20$;

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