# CHIKUNGUNYA: SAFETY UP TO DAY 29 OF PHASE 3 CLINICAL DEVELOPMENT OF A SINGLE-SHOT LIVE-ATTENUATED VACCINE

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## BACKGROUND

*Chikungunya is a mosquito-transmitted outbreak disease with potentially debilitating consequences and no available causative treatments or preventative vaccines.*

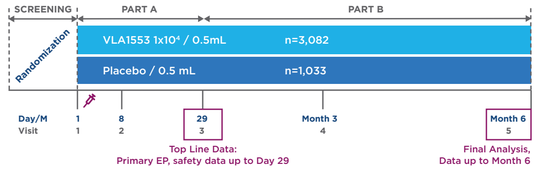
*Chikungunya disease has been reported in over 100 countries worldwide with more than three million suspected cases alone in the Americas resulting in chronic and incapacitating arthralgia accompanied by an acute febrile disease with headache, muscle pain and skin rashes affecting all gender and age groups.*

*Coinciding with an adaptation enabling unusually efficient transmission by Aedes albopictus mosquitoes, the virus re-emerged in 2004 and rapidly spread over Africa, Asia, the Americas and locally also in Europe since then.*

*VLA1553 is a live-attenuated chikungunya virus (CHIKV) vaccine candidate designed for active immunization as a prophylactic measure for travelers to endemic areas or areas at risk for an upcoming outbreak, as well as for the general population living in endemic regions.*

## METHODS *STUDY DESIGN*

*VLA1553-301 Pivotal Study Design:*
*Multicenter, randomized, placebo-controlled double-blind Phase 3 trial*

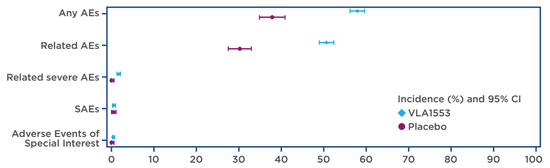



+ 4,115 adults aged 18 years and above, conducted in US
+ Primary Objective: immunogenicity and **safety** of the final dose of VLA1553 28 days following vaccination
+ NCT: 04546724
+ Single-dose vaccination Day 1
+ Solicited adverse events (AEs) captured for 10 days following vaccination and unsolicited AE throughout the study
+ Recruitment stratified by age, younger adults (18–64 years) and older adults (65 years and above)

n = number of subjects in the safety population, M = Month

## RESULTS *SUMMARY OF ADVERSE EVENTS*

*Top Line Data - Summary of AEs up to Day 29 (Safety Population)*




AE = adverse event; SAE = serious adverse event.
Note: Each participant is only counted once per incidence.
Related adverse events are those recorded as 'Probably Related' or 'Possibly Related' on the CRF.
Adverse events of special interest are those as assessed by the investigator.

## SUMMARY

TOP LINE DATA –
PRELIMINARY DAY 29 STATISTICAL ANALYSIS

**Solicited Injection Site AEs:**

+ Solicited injection site AEs were reported by approximately 15% of subjects vaccinated with VLA1553;
+ Most of solicited local AEs were mild, one severe event of pain was reported;
+ The most common (≥ 10%) solicited local AE was tenderness.

**Solicited Systemic AEs:**

+ Solicited systemic AEs were reported by approximately 50% of subjects receiving VLA1553;
+ Most solicited systemic AEs were mild or moderate;
+ 46 (1.5%) subjects reported related severe solicited AEs, predominantly fever (27 subjects), arthralgia (9 subjects), myalgia (8 subjects), fatigue (4 subjects), and headache (3 subjects);
+ The most common (≥ 20%) related solicited systemic AEs were headache, fatigue and myalgia.

**Unsolicited AEs:**

+ Related unsolicited AEs were experienced in less than 10%.

**SAEs/AESIs:**

+ SAEs were observed at similar rates in the VLA1553 and placebo groups.
+ In the VLA1553 treatment group, 2 out of 25 SAEs were assessed as probably related by the investigator;
+ In 10 subjects vaccinated with VLA1553 events meeting the AESI criteria were reported.

*Adverse Events of Special Interest* (Safety Population)*

| | VLA1553 N=3082<br>n (%) m<br>[95% CI] | Placebo N=1033<br>n (%) m<br>[95% CI] | All Participants N=4115<br>n (%) m<br>[95% CI]<br>p-value |
|---|---|---|---|
| Any AESI as assessed by investigator | 10 (0.3)<br>[0.2, 0.6] | 1 (0.1)<br>[0.0, 0.5] | 11 (0.3)<br>[0.1, 0.5]<br>0.3106 |

+ In total 11 participants met the criteria of adverse event of special interest, 10 participants received VLA1553;
+ Most of the events were mild or moderate, 3 subjects had severe fever;
+ 20 of 27 symptoms were captured as solicited adverse event;
+ Majority of events were self-limited after 2-4 days.

*defined as: 1. Fever (≥38.0 °C / 100.4 °F) AND 2. Acute (poly)arthralgia/arthritis, back pain and/or neurological symptoms and/or cardiac symptoms OR rash, polyadenopathies AND 3. Onset of symptoms 2 to 21 days after vaccination AND 4. Duration of event ≥ 3 days

*Related Serious Adverse Events (Safety Population)*

| | VLA1553 N=3082<br>n (%) m<br>[95% CI] | Placebo N=1033<br>n (%) m<br>[95% CI] | All Participants N=4115<br>n (%) m<br>[95% CI]<br>p-value |
|---|---|---|---|
| Any SAE | 14 (0.5) 25<br>[0.2, 0.8] | 4 (0.4) 5<br>[0.1, 1.0] | 18 (0.4) 30<br>[0.3, 0.7]<br>>0.9999 |
| Any related SAE | 2 (0.1) 2<br>[0.0, 0.2] | 0<br>[0.0, 0.4] | 2 (0.0) 2<br>[0.0, 0.2]<br>>0.9999 |

**CASE #1 – 58 years female**

+ Event: Myalgia
+ Vaccination 03 NOV
+ Onset 04 NOV;
  Hospitalization: 06 NOV – 11 NOV
+ Outcome: recovered 03 DEC
  Participant has a history of fibromyalgia
  No other trigger for myalgia could be identified

**CASE #2 – 66 years male**

+ Event: Syndrome of inappropriate antidiuretic hormone secretion
+ Vaccination 17 NOV
+ Onset 27 NOV;
  Hospitalization: 27 NOV – 30 NOV
+ Outcome: recovered 02 DEC
  Appeared to be related to prolongued fever/symptoms post-vaccination

*Overview of systemic AEs up to Day 11* by Age Strata (Safety Population)*

| | 18-64 years | | ≥ 65 years | |
|---|---|---|---|---|
| | VLA1553<br>N=2736<br>%<br>[95% CI] | Placebo<br>N=916<br>%<br>[95% CI]<br>p-value | VLA1553<br>N=346<br>%<br>[95% CI] | Placebo<br>N=117<br>%<br>[95% CI]<br>p-value |
| Any solicited systemic AE | 50.4<br>[48.5, 52.3] | 27.3<br>[24.4, 30.3]<br><0.0001 | 43.6<br>[38.3, 49.0] | 19.7<br>[12.9, 28.0]<br><0.0001 |
| Headache | 31.8<br>[30.0, 33.5] | 14.7<br>[12.5, 17.2] | 23.7<br>[19.3, 28.5] | 11.1<br>[6.1, 18.3] |
| Fatigue | 28.1<br>[26.4, 29.8] | 13.2<br>[11.1, 15.6] | 26.0<br>[21.5, 31.0] | 6.0<br>[2.4, 11.9] |
| Myalgia | 23.1<br>[21.5, 24.7] | 6.9<br>[5.3, 8.7] | 25.1<br>[20.7, 30.1] | 6.8<br>[3.0, 13.0] |
| Arthralgia | 16.2<br>[14.8, 17.6] | 4.9<br>[3.6, 6.5] | 13.9<br>[10.4, 18.0] | 3.4<br>[0.9, 8.5] |
| Fever | 13.3<br>[12.1, 14.7] | 0.7<br>[0.2, 1.4] | 11.6<br>[8.4, 15.4] | 0.9<br>[0.0, 4.7] |
| Nausea | 11.1<br>[10.0, 12.4] | 5.9<br>[4.5, 7.6] | 8.7<br>[5.9, 12.1] | 1.7<br>[0.2, 6.0] |
| Rash | 2.3<br>[1.8, 2.9] | 0.5<br>[0.2, 1.3] | 1.2<br>[0.3, 2.9] | 0.9<br>[0.0, 4.7] |
| Vomiting | 1.9<br>[1.4, 2.4] | 1.1<br>[0.5, 2.0] | 2.0<br>[0.8, 4.1] | 0<br>[0.0, 3.1] |

Solicited AEs captured via Participant eDiary for up to 10 days post vaccination.
a. P-value from Fisher's exact test for difference between the treatment arms.

## CHIKUNGUNYA VACCINE CANDIDATE *VLA1553*

*Vaccine Candidate 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

1 Hallengärd et al. 2013. J Virology 88:2858–2866.

## PRELIMINARY SAFETY SUMMARY AND CONCLUSIONS

+ VLA1553 was generally well tolerated.
+ An independent DSMB continuously evaluated safety data during the study and did not identify any safety concern;
+ The majority of solicited adverse events were mild or moderate and resolved in average within 3 days;
+ Approximately 50% of study participants experienced solicited systemic adverse events; headache, fatigue and myalgia were most common (seen in more than 20% of subjects);
+ Local tolerability profile was compelling with approximately 15% of participants experiencing solicited local adverse events;
+ Rate of unsolicited adverse events considered treatment-related up to Day 29 was 8.9% (275/3,082 participants); majority was mild or moderate; most frequently reported (≥ 1% in VLA1553 Study Arm) were chills and (transient) neutropenia;
+ VLA1553 was equally well tolerated in older adults;
+ The safety profile was consistent with results in a preceding Phase 1 clinical trial and comparable with other vaccines;
+ A final safety analysis will be performed once 6-months follow-up visits have been concluded.

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