PROGRESS OF CLINICAL DEVELOPMENT OF A LIVE-ATTENUATED SINGLE SHOT CHIKUNGUNYA VACCINE CANDIDATE

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BACKGROUND

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 outbreak, as well as for the general population living in endemic regions. Due to the sporadic epidemic occurrence of chikungunya, an immunological surrogate to assess clinical efficacy was accepted by regulators (FDA).

METHODS

A blinded, randomized phase 1 clinical trial evaluated the safety and immunogenicity of three dose levels of VLA1553, administered as a single intramuscular immunization in 120 participants (NCT03382964; VLA1553-101)[1]. This was followed by a pivotal phase 3 double-blinded, multicenter randomized trial that enrolled 4,115 adults to receive the selected final VLA1553 dose or placebo (NCT04546724; VLA1553-301). A further phase 3 trial evaluated bioequivalence between three lots of VLA1553 in 408 healthy adults randomized to each lot 1:1:1 (NCT04786444; VLA1553-302). Safety and immunogenicity data were collected for 29 days post vaccination in both trials.

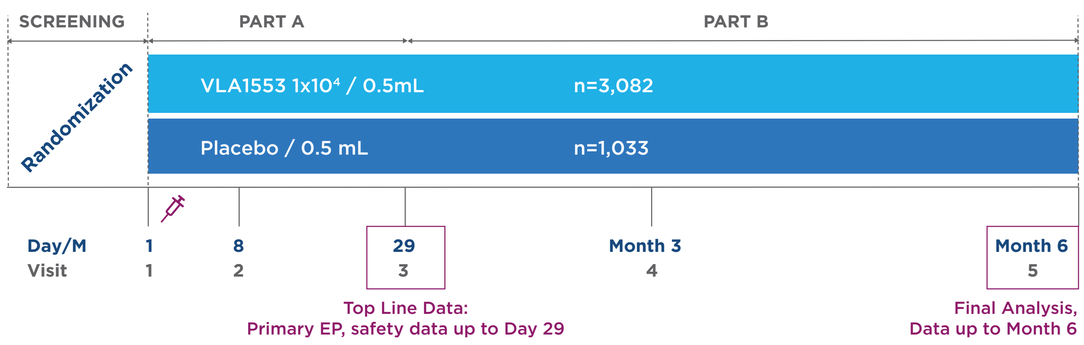
RESULTS

The first pivotal trial VLA1553-301 met its primary endpoint with 98.5% of participants achieving seroprotection (264 of 268 participants in the per-protocol immunogenicity subgroup, 95% CI: 96.2-99.6). VLA1553 was also well tolerated with a favorable safety profile. The bioequivalence study VLA1553-302 showed no significant differences between lots with regard to antibody titers. VLA1553 was also highly immunogenic as seroprotection was achieved in 97.7% of participants. Furthermore, the safety profile was consistent between lots and with the preceding pivotal phase 3 trial VLA1553-301.

CONCLUSION

The absence of observed differences between lots confirmed clinical equivalence as well as manufacturing consistency. This data along with positive results from VLA1553-301 places VLA1553 as an effective candidate for the prevention of disease caused by the CHIKV.

Study design: Pivotal Phase 3 Trial VLA1553-301



Primary Objective

+ To evaluate immunogenicity and safety of the final dose of the live-attenuated CHIKV vaccine candidate (VLA1553) 28 days following vaccination in a population aged 18 years and above after a single immunization.

Primary Endpoint

+ Proportion of subjects with a seroprotective CHIKV neutralizing antibody titer for baseline negative subjects 28 days post-vaccination.

Seroprotective titer: Surrogate of protection agreed upon with FDA to support licensure via accelerated approval pathway
Recruitment stratified by age, younger adults (18-64 years) and older adults (65 years and above)

Pivotal Phase 3 Trial (VLA1553-301) Day 29 Top Line Immunogenicity Data: Primary Endpoint Met

Seroprotection Rate for CHIKV-Specific Neutralizing Antibodies at Day 29

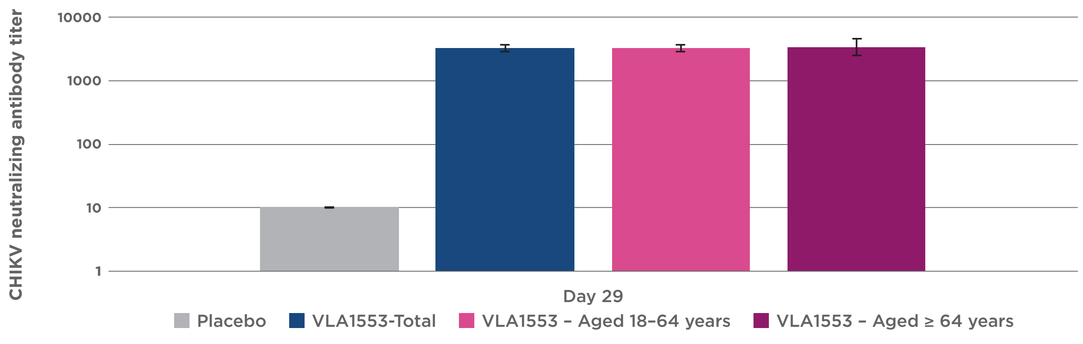
	18–64 years		≥ 65 years		Total	
	VLA1553 N=209	Placebo N=73	VLA1553 N=59	Placebo N=23	VLA1553 N=268	Placebo N=96
Total[a] n	209	73	59	23	268	96
Subjects with Seroprotection n (%)	**206 (98.6)**	**0**	**58 (98.3)**	**0**	**264 (98.5)**	**0**
95% CI for Seroprotection Rate	[95.9, 99.7]	[0.0, 4.9]	[90.9, 100.0]	[0.0, 14.8]	[96.2, 99.6]	[0.0, 3.8]
Difference in Seroprotection Rate[b]	98.6		98.3		98.5	
95% CI	[97.0, 100.0]		[95.0, 100.0]		[97.1, 100.0]	
p-value[c]	**<0.0001**		**<0.0001**		**<0.0001**	

a. Number of baseline negative subjects with non-missing titers at Day 29.
b. Differences, p-values and associated confidence intervals are presented for the VLA1553 arm minus Placebo treatment arm.
c. P-value from Fisher's Exact test.

Percentages are based on the number of baseline negative subjects with non-missing titers at the visit.Seroprotection threshold for baseline negative subjects has been agreed upon with FDATwo-sided 95% exact (Clopper-Pearson) confidence intervals presented.

Pivotal Phase 3 Trial (VLA1553-301) Day 29 Top Line Immunogenicity Data: Primary Endpoint Met

GMT FOR CHIKV NEUTRALIZING ANTIBODIES IN BASELINE SERONEGATIVE SUBJECTS, PER-PROTOCOL POPULATION



Chikungunya virus neutralizing antibody titers were determined using a $\mu PRNT_{50}$ assay. Values below the quantification limit are set to 10. Error Bars represent 95%CI

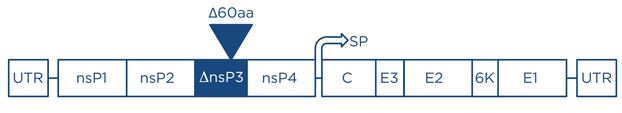
PIVOTAL PHASE 3 TRIAL (VLA1553-301) DAY 29 TOP LINE IMMUNOGENICITY DATA: KEY CONCLUSIONS

+ Pivotal study VLA1553-301 **met its primary endpoint**.
+ VLA1553 induced **protective levels of antibodies in 98.5% of participants** after a single vaccination.
+ **The seroprotection rate, based on a surrogate of protection agreed with regulators to support accelerated approval, was 98.5%** (95%CI: 96.2- 99.6; 264 of 268 participants in the per-protocol subset tested for immunogenicity).
+ Seroprotection rate **significantly exceeded regulators requirement** for licensure of >70%*.
+ Vaccine was highly immunogenic with a **neutralizing antibody GMT of 3,270, and at least 64-fold increase in antibody titers in 257 of 268 participants** (95.9%) at Day 29.
+ The vaccine was also **remarkably immunogenic in older adults**, with equally high GMTs and seroprotection rates, when compared with adults <65 years.
+ The compelling immunogenicity profile from the preceding Phase 1 clinical trial was confirmed.

* The lower bound of the 95%CI for the SPR needed to exceed the non-acceptance threshold of 70%

Attenuation principle[2]

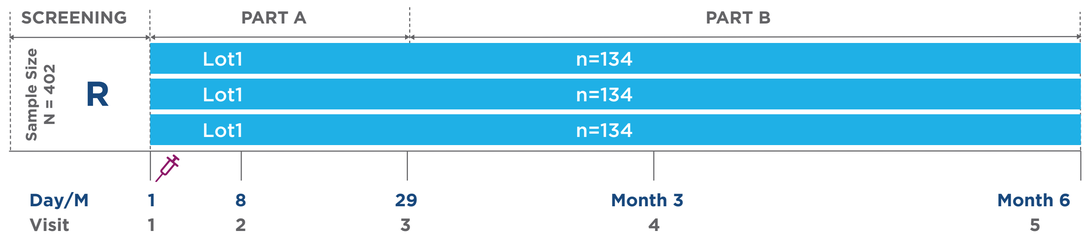
LIVE-ATTENUATED CHIKV VACCINE



Δ5nsP3 = VLA1553

+ Based on La Reunion strain of ECS African strain of Indian Ocean lineage with cross-protective immunity against Asian isolate which is now spreading rapidly across the Americas
+ 60aa deletion in gene encoding nsP3
+ No change of deletion detectable after up to 20 passages on Vero Cells
+ Slightly reduced plaque size as compared to CHIKV clone LR2006-OPY1
+ Reduced replication ($1.2x10^7$ pfu/mL) as compared to CHIKV clone LR2006-OPY1 ($4.4x10^8$ pfu/mL)

Study design: Pivotal Phase 3 Lot to Lot Trial VLA1553-302



Part A analysis provides unblinded immunogenicity and safety data up to Day 29

Primary Objective

+ To demonstrate Lot-to-Lot manufacturing consistency of a live-attenuated CHIKV vaccine candidate (VLA1553) 28 days following vaccination in a healthy population aged 18 to 45 years after a single immunization

Primary Endpoint

+ Geometric mean titer (GMT) of CHIKV-specific neutralizing antibodies as determined by microneutralization (µPRNT) assay on Day 29 post-vaccination in subjects who tested negative for CHIKV antibodies at baseline.

Pivotal Phase 3 Lot to Lot Trial (VLA1553-302) Day 29 Top Line Immunogenicity Data: Primary Endpoint Met

Summary and Analysis of GMTs for CHIKV-Specific Neutralizing Antibodies at Day 29

	VLA1553 Lot 1 N=121	VLA1553 Lot 2 N=116	VLA1553 Lot 3 N=120	All Subjects N=357
n[a]	121	116	120	357
Geometric Mean	**2535.4**	**2786.9**	**2530.7**	**2612.9**
95% CI for GM	[2036.10, 3157.12]	[2319.55, 3348.30]	[2065.09, 3101.25]	[2326.15, 2934.94]
Min, Max	10, 21668	10, 17398	10, 40999	10, 40999
Difference in GMT[b] (Primary Endpoint)				
Comparison	Lot 2 - Lot 1	Lot 3 - Lot 2	Lot 3 - Lot 1	
Difference in GMT Ratios (=Difference in LS Mean) (SE)[c]	**1.10 (1.16)**	**0.91 (1.16)**	**1.00 (1.15)**	
95% Confidence Intervalc	[0.83, 1.46]	[0.68, 1.21]	[0.75, 1.32]	
p-value[c]	0.5152	0.5079	0.9897	
p-value[d]	0.9855	0.8869	0.9830	

GMT = geometric mean titer; GM = geometric mean; std = standard deviation; LS = least squares; SE = standard error; n = number of subjects with available result;
a. n is the number of subjects that contribute data at least once in the primary analysis model.
b. LS means, standard errors, confidence intervals, and p-values are from an analysis of covariance (ANCOVA) model with fixed factor for Lot and study center as a covariate.
c. p-values, LS mean differences and associated confidence intervals are presented for the comparison stated in each column..

Note: The ANCOVA model is applied to the log-transformed titers, and back-transformed results are displayed for the LS mean and difference. The difference in GMT is a ratio of the LS means.

PIVOTAL PHASE 3 LOT TO LOT TRIAL (VLA1553-302) DAY 29 TOP LINE IMMUNOGENICITY DATA: KEY CONCLUSIONS

+ Pivotal study VLA1553-302 **met its primary endpoint**.
+ No significant differences were observed between lots with regards to antibody titer; **the confidence intervals on the GMT ratios of all lots were in the defined acceptance margins of 0.67 and 1.5**.
+ **The seroprotection rate, based on a surrogate of protection agreed with regulators to support accelerated approval, was on average 97.7%** (95%CI: 95.6, 99.0;) **in the per-protocol analysis set**.
+ Seroprotection rate **significantly exceeded regulators requirement** for licensure of >70%*.
+ Vaccine was highly immunogenic with an average **neutralizing antibody GMT of 2613, and at least 64-fold increase in antibody titers in 343 of 357 participants** (96.1%) at Day 29.
+ **Overall the seroconversion rate was 97.5%** (95% CI 95.3, 98.8 348 of 357 participants in the per-protocol analysis set).
+ Study VLA1553-302 confirmed clinical equivalence as well as manufacturing consistency of three lots.

* The lower bound of the 95%CI for the SPR needed to exceed the non-acceptance threshold of 70%

Summary of Day 29 Top Line Safety Data - Comparison of the VLA1553-301 and VLA1553-302 trials

Solicited Injection Site AEs	Solicited Systemic AEs:	UnsolicitedAEs	SAE/AESIs:
VLA1553-301			
+ Solicited injection site AEs were reported by **14.8%** of participants; + 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 were reported by **49.6%** of participants; + Most solicited systemic AEs were **mild or moderate**; + 1.5 % of participants reported related severe solicited AEs, predominantly **fever**; + The most common (≥ 20%) related solicited systemic AE was **headache**.	+ Unsolicited AEs were reported by **20.7%** of participants, **0.6%** were severe; + Related unsolicited AEs were experienced by **8.9%** of participants, **0.2%** were severe	+ In the VLA1553 treatment group, **2 out of 25 SAEs** were assessed as probably related by the investigator; + In **10 participants** vaccinated with VLA1553 events meeting the AESI criteria were reported.
VLA1553-302 (Lot to Lot)			
+ Solicited injection site AEs were reported by **19.4%** of participants; + All of the solicited local AEs **were mild or moderate**; + The **most common** (≥ 10%) related solicited local AE was **tenderness**; + **No significant differences** in solicited local AE occurrences were seen between lots.	+ Solicited systemic AEs were reported by **56.9%** of participants; + Most solicited systemic AEs were **mild or moderate**; + The **most common** (≥ 20%) related solicited systemic AE was **Fatigue**; + **No significant differences** in solicited systemic AE occurrences were seen between lots.	+ Unsolicited AEs were reported by **25.2%** of participants, **1%** were severe; + Related unsolicited AEs were experienced by **(15.2%)** of participants, **0%** thereof were reported as severe related; + **No significant differences** in related unsolicited AE occurrences were seen between lots.	+ **2 SAEs** were assessed unrelated by the investigator; + **One participant** vaccinated with VLA1553 had events meeting the AESI criteria (arthralgia and fever).

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References: 1 *Wressnigg N, Hochreiter R, Zoihsl O, Fritzer A, Bézay N et al. Single-shot Live-Attenuated Chikungunya Vaccine in Healthy Adults: A Phase 1, Randomised Controlled Trial. Lancet Infect Dis. 2020 Oct;20(10):1193-1203.* | 2 *Hallengard et al. 2013, J Virol. 88(5):2858-66*