23 July 2026
EMADOC-1700519818-3178068
Human Medicines Division

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

IXCHIQ

Chikungunya vaccine (live)

Procedure no: EMA/PAM/0000341806

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start date	25 May 2026	25 May 2026
☐	CHMP Rapporteur AR	29 June 2026	18 June 2026
☐	CHMP comments	13 July 2026	n/a
☐	Updated CHMP Rapporteur AR	16 July 2026	n/a
☒	CHMP outcome	23 July 2026	23 July 2026

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1. Introduction

On 15 April 2026, the MAH submitted a completed paediatric study for Ixchiq, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that 'A randomized, observer-blinded, dose response phase 2 study to assess the safety and immunogenicity of two different dose levels of a live attenuated chikungunya virus vaccine candidate (VLA1553) in healthy children aged 1 to 11 years' (VLA1553-221) is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

In this study the VLA1553 vaccine in two different doses or Nimenrix in the control group will be administered to study participants.

VLA1553

The VLA1553 vaccine will be tested both as full dose formulation (4.0 log 10 TCID50 per 0.5mL) and as a half dose formulation (3.7 log 10 TCID50 per 0.5mL).

One full dose (0.5 mL) of the VLA1553 vaccine contains between 3.2 log 10 and 4.4 log 10 TCID50 per dose (target dose 4.0 log 10 TCID50 per 0.5 mL).

One half dose (0.5 mL) of the VLA1553 vaccine contains between 2.9 log 10 and 4.1 log 10 TCID50 per dose (target dose 3.7 log 10 TCID50 per 0.5 mL).

Table 1. Composition of the VLA1553 full dose lyophilized Drug Product

Active substance	
Live-attenuated CHIKV	**Target $TCID_{50}$/dose**
	4.0 log 10 $TCID_{50}$
Excipients and buffer components	**Freeze Dried Formulation/ dose**
di-Potassium Hydrogen Phosphate	0.313 mg
Potassium di-Hydrogen Phosphate	0.098 mg
Trisodium citrate dihydrate	3.68 mg
Sucrose	25 mg
Magnesium Chloride hexahydrate	0.51 mg
D-Sorbitol	2.5 mg
L-Methionine	0.75 mg
Recombinant Human Albumin	0.01% (equals 0.05mg)
pH	7.3

Table 2. Composition of the VLA1553 half dose lyophilized Drug Product

Active substance	
Live-attenuated CHIKV	**Target $TCID_{50}$/dose** 3.7 log 10 TCID50
Excipients and buffer components	**Freeze Dried Formulation/ dose**
di-Potassium Hydrogen Phosphate	0.157 mg
Potassium di-Hydrogen Phosphate	0.048 mg
Trisodium citrate dihydrate	1.84 mg
Sucrose	12.5 mg
Magnesium Chloride hexahydrate	0.255 mg
D-Sorbitol	1.25 mg
L-Methionine	0.375 mg
Recombinant Human Albumin	0.005% (equals 0.025mg)
pH	7.3

Nimenrix

Nimenrix is a conjugate vaccine indicated for the active immunization of individuals from the age of 6 weeks against invasive meningococcal disease caused by Neisseria meningitidis groups A, C, W-135, and Y.

Nimenrix is present as powder and solvent for solution for injection in pre-filled syringe.

The reconstituted vaccine is a clear colourless solution.

Nimenrix should be used in accordance with available official recommendations. Primary immunization in infants from 6 months of age, children, adolescents and adults: a single 0.5 mL dose should be administered.

Table 3. Composition of Nimenrix

	Nimenrix	
Formulation:	MenA (5 µg)-TT MenC(5 µg)-TT MenW135(5 µg)-TT MenY(5 µg)-TT	Sodium chloride; Water for injections q.s. 0.5 mL
Presentation:	Powder for solution for injection (vial)	Solution for solution for injection
Type:	Biologic/Combination Product	
Route of administration:	Intramuscular injection (i.m.)	
Location	Upper arm for Stratum A and B; thigh for Stratum C	
Directionality	Anterolateral	
Number of doses to be administered:	1	
Volume to be administered:	0.5 mL	

Assessment

The investigational vaccine evaluated in this study was VLA1553, a live-attenuated chikungunya vaccine (commercialized as Ixchiq). The study investigated VLA1553 in paediatric subjects aged 1–11 years using a full-dose (4.0 $\log_{10}$ $TCID_{50}$/0.5 mL) and a half-dose (3.7 $\log_{10}$ $TCID_{50}$/0.5 mL) formulation.

The clinical relevance of comparing a half versus full dose is unclear, as the theoretical difference in potency falls within the variability of the assay (average error range of about 0.6 log TCID50/ml) and manufacturing process (titer loss during manufacturing varies from 0.4 to 0.9 log TCID50/ml). It is therefore unlikely that the half dose will translate into a meaningful difference in the actual administered dose, reactogenicity/safety and immune response. The rationale for evaluating these two dose levels in children 1-11 years of age has not been properly justified and it remains unclear whether this study will provide meaningful information to support the identification of an appropriate dose for this population. Nevertheless, this concern was already raised during the initial PIP evaluation, where the MAH indicated that lower dose levels are not technically feasible.

A MenACWY vaccine (Nimenrix) was used as a control vaccine and was used according to official recommendations.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- VLA1553-221: A randomized, observer-blinded, dose response phase 2 study to assess the safety and immunogenicity of two different dose levels of a live attenuated chikungunya virus vaccine candidate (VLA1553) in healthy children aged 1 to 11 years

2.3.2. Clinical study

VLA1553-221: A randomized, observer-blinded, dose response phase 2 study to assess the safety and immunogenicity of two different dose levels of a live attenuated chikungunya virus vaccine candidate (VLA1553) in healthy children aged 1 to 11 years

Description

This is a multicenter, prospective, randomized, observer-blinded, three arm, phase 2 clinical study evaluating the full dose formulation (target 4.0 log 10 TCID50 per 0.5mL) of VLA1553, half dose formulation (target 3.7 log 10 TCID50 per 0.5mL) and control (Nimenrix). The study was conducted in two countries considered endemic for chikungunya virus (Dominican Republic and Honduras).

At least 300 male and female healthy children aged 1 to 11 years will be enrolled and the overall distribution of participants will be 2:2:1 to the two VLA1553 dose groups (n=120 each) or control (Nimenrix) (n=60).

These volunteers will be screened for evidence of previous CHIKV exposure. Enrolment will then be stratified by CHIKV serostatus at baseline, targeting:

- Up to 10 % CHIKV seropositive subjects (i.e. IgM+/IgG+ or IgM-/IgG+)
- At least 90% CHIKV seronegative subjects (i.e. IgM-/IgG-)

Subjects who are IgM+/IgG- do not qualify for participation in this study.

Note: Generally subjects with any indeterminate Ig element at screening will be included in the study (i.e., IgM?/IgG- and IgM+/IgG? and IgM-/IgG?) and will be mapped to seropositive group. The clinical study design is displayed in the Figure below.

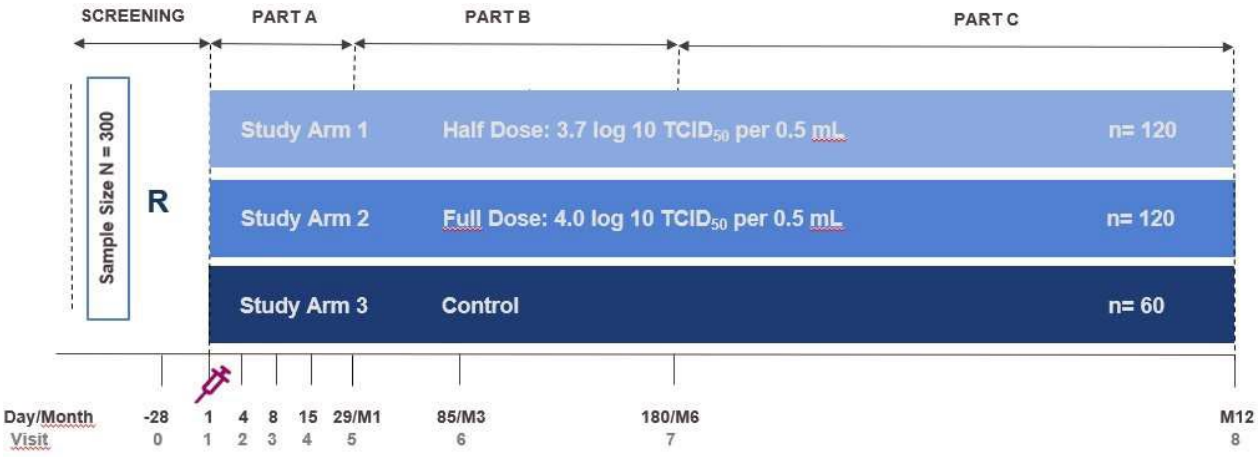


Figure 1. Phase 2 Clinical Study Design

Table 4. Participant Distribution

Study Arm	Dosage (TCID50/dose)	Stratum	Cohort I	Cohort II	Cohort III	Cohort IV	Total N
1	VLA1553 half dose 3.7 log 10	A (7 to 11 yrs.)	5*+35	-		-	40
		B (3 to 6 yrs.)	-	5*+35	-		40
		C (1 to 2 yrs.)	-	-	5*+35	-	40
2	VLA1553 full dose 4.0 log 10	A (7 to 11 yrs.)	-	5*+35		-	40
		B (3 to 6 yrs.)	-	-	5*+35		40
		C (1 to 2 yrs.)	-	-	-	5*+35	40
3	Control	A (7 to 11 yrs.)	10	10		-	20
		B (3 to 6 yrs.)	-	10	10		20
		C (1 to 2 yrs.)	-	-	10	10	20
		C (1 to 2 yrs.)	-	-	10	10	20

*Sentinel enrolment will be conducted in open-label fashion and sentinels recruited at a preferably single study site. Vaccinations in the following cohort can be started based on the previous cohort sentinels' review by the Data Safety Monitoring Board and recommendation to proceed with the study.

At Day 1 (Visit 1) VLA1553 or Nimenrix (control) will be administered intramuscularly (in deltoid muscle for Stratum A and B; anterolateral thigh muscle for Stratum C) as a single dose immunization. Participants will return to study site at Day 4 (i.e., Visit 2, three days after vaccination) and Day 8 (i.e. Visit 3, seven days after vaccination) for physical examination, safety evaluation and viremia assessments (as applicable). Furthermore, participants will visit study site at Day 15 (Visit 4), Day 29

(Visit 5), Month 3 (Day 85, Visit 6), Month 6 (Day 180, Visit 7) and Month 12 (Day 365) for safety evaluations and collection of samples for immunogenicity assessments. Safety laboratory evaluations will be done at Visit 5 (Day 29) from all participants of age Stratum A (7 to 11 yrs.) and all sentinel participants from Stratum B (3 to 6 yrs.) and Stratum C (1 to 2 yrs.). In addition, urinalysis will be done at every study visit from Day 1 (Visit 1) until Month 12 (Visit 8) from all participants, if possible. Viremia samples will be collected from all participants of Stratum A and sentinel participants from Stratum B and C only at Visit 1 to 8. Viremia samples from Day 1 - Day 15 (Visit 1- Visit 4) will be analysed. Should the sample on Day 15 (Visit 4) after vaccination test positive for viremia, the collected Day 29 (Visit 5) sample will be analysed. Other viremia samples will be tested for clinically indicated retrospective analysis.

Assessment

Study VLA1553-221 was a multicentre, randomised, observer-blinded, three-arm Phase 2 clinical trial designed to evaluate the safety and immunogenicity of VLA1553 in paediatric subjects aged 1 to 11 years. Participants were randomised in a 2:2:1 ratio to receive one of two VLA1553 dose levels (n=120 per group) or a control vaccine (Nimenrix; n=60).

Enrolment was stratified according to baseline CHIKV serostatus, with up to 10% of subjects allowed to be seropositive (defined as IgM+/IgG+ or IgM-/IgG+) and at least 90% required to be seronegative (defined as IgM-/IgG-). Proportions of CHIKV baseline seronegative and seropositive participants are not justified. However, from an immunological point of view, this is deemed adequate since seronegative participants are those who will benefit from vaccination. In contrast, this approach limits the assessment of safety in CHIKV baseline seropositive participants. This represents a limitation, as such data are particularly important in a population expected to derive limited or no clinical benefit from vaccination.

Within each treatment arm, participants were further stratified into three age strata: Stratum A (7 to 11 years), Stratum B (3 to 6 years), and Stratum C (1 to 2 years). In the VLA1553 groups, the number of participants per age stratum was planned to be approximately equal (approximately 40 subjects per stratum).

The study included an initial cohort of 30 sentinel participants who were enrolled in an open-label manner following an age de-escalation (step-down) approach. Subsequent participants were enrolled in a blinded manner.

The investigational vaccine and control were administered intramuscularly as a single-dose immunisation.

Resulting questions:

None.

Methods

Study participants

Inclusion criteria

Participants who meet ALL of the following criteria are eligible for this study:

1. Male or female healthy children aged 7 to 11 years for Stratum A, 3 to 6 years for Stratum B and 1 to 2 years for Stratum C at the time of vaccination;

2. Written informed consent by the participant's parent(s)/Legally Acceptable Representative(s) ((LAR(s)), according to local requirements, and written informed assent of the participant, if applicable;

3. Participant is seropositive for previous CHIKV exposure (i.e. IgM+/IgG+ or IgM-/IgG+) or seronegative (i.e. IgM-/IgG-); or participants with any indeterminate IgG element (IgM?/IgG- and IgM+/IgG? and IgM-/IgG?);

4. Participant is generally healthy as determined by the Investigator's clinical judgement based on medical history, physical examination and screening laboratory tests;

5. For participants in Stratum C 1 to 2 years: Participant was born at full term of pregnancy (≥37 weeks) with a birth weight ≥2.5 kg;

6. If participant is of childbearing potential (after onset of menarche) and if involved in activities that could result in pregnancy:

a) Participant has a negative pregnancy test (in accordance with local regulations) at screening (Visit 0) and Day 1 (Visit 1), respectively

b) Participant has practiced an adequate method of contraception during at least the 30 days before screening (Visit 0) and during the screening period

c) Participant agrees to employ adequate birth control measures for the first three months post-vaccination (i.e. until Day 85, Visit 6). This includes one of the following measures:

- Hormonal contraceptives (e.g. implants, birth control pills, patches);
- Intrauterine hormone-release systems;
- Barrier type of birth control measure (e.g. condoms, diaphragms, cervical caps);
- Vasectomy in the male sex partner ≥3 months prior to first vaccination;
- Same-sex relationships.

<u>Exclusion criteria</u>

Participants who meet ANY of the following criteria are NOT eligible for this study:

1. Participant who is IgM+/IgG- does not qualify for participation in this study.

2. Participant is taking medication or other treatment for unresolved symptoms attributed to a previous CHIKV infection; or has participated in a clinical study involving an investigational CHIKV vaccine;

3. Participant has an acute or recent infection (and who is not symptom-free in the week prior to the Screening Visit (Visit 0);

4. Parent(s)/LAR(s) or siblings have a known HIV infection;

5. Participant has received another live virus vaccine within 28 days or inactivated vaccine 16 within 14 days prior to vaccination in this study or plans to receive a live virus vaccine within 28 days or inactivated vaccine within 14 days after vaccination;

6. Participant has abnormal findings in any required study investigations (including medical history, physical examination, and clinical laboratory) considered clinically relevant by the Investigator which pose a risk for participation in the study based on his/her judgement;

7. Participant has an ongoing medical history of or currently has acute or progressive, unstable or uncontrolled clinical conditions (e.g. cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions) that poses a risk for participation in the study, based on Investigators clinical judgement. Examples include individuals with poorly controlled or unstable disease, ongoing suspected or active inflammation, or poor compliance with pharmacologic treatment, or presence of high-risk comorbidities (e.g. significant cardiopulmonary disease);

8. Participant has a history of immune-mediated or clinically relevant arthritis/arthralgia;

9. Participant has a history of malignancy;

10. Participant has a known or suspected defect of the immune system that can be expected to influence the immune response to the vaccine, such as Participants with congenital or acquired immunodeficiency, including infection with HIV, status post organ transplantation or immunosuppressive therapy within 4 weeks prior to Visit 1. Immuno-suppressive therapy is defined as administration of chronic (longer than 14 days) prednisone or equivalent ≥0.05 mg/kg/day within 4 weeks prior to study entry, radiation therapy or immunosuppressive cytotoxic drugs/ monoclonal antibodies in the previous 3 years; topical and inhaled steroids are allowed.

11. Participant has a history of any vaccine related contraindicating event (e.g., anaphylaxis, allergy to components of the candidate vaccine or the control vaccine, other known contraindications including febrile convulsions);

12. Participant presents with clinical conditions representing severe bleeding disorders and medications interfering with blood clotting;

13. Participant is pregnant (positive pregnancy test (in accordance with local regulations) at screening or Visit 1, respectively), lactating at the time of enrollment or unreliable contraception in female participants after onset of menarche and if involved in activities potentially leading to pregnancy;

14. Participant received blood-derived products (e.g. plasma) within 180 days prior to vaccination in this study;

15. Participant has a rash, dermatological condition or tattoos that would, in the opinion of the Investigator, interfere with injection site reaction rating;

16. Participant has participated in another clinical study involving an investigational medicinal product (IMP) or device within 30 days prior to vaccination or is scheduled to participate in another clinical study involving an IMP, or device during the course of this study;

17. Participant has any condition that, in the opinion of the Investigator, may compromise the participants well-being, might interfere with evaluation of study endpoints, or would limit the participant’s ability to complete the study;

18. Participant/participant’s parent(s)/LAR(s) is/are a member of the team conducting the study or in a dependent relationship with one of the study team members. Dependent relationships include close relatives (i.e., children, partner/spouse, siblings, parent(s)/LAR(s)s) as well as employees of the Investigator or site personnel conducting the study.

19. Participant has received the control vaccine prior to the study.

Assessment

The study enrolled generally healthy male and female paediatric participants aged 1 to 11 years at the time of vaccination. Participants were stratified into three age groups: Stratum A (7 to 11 years), Stratum B (3 to 6 years), and Stratum C (1 to 2 years).

Participants could be either seropositive for prior CHIKV exposure (defined as IgM+/IgG+ or IgM-/IgG+), seronegative (IgM-/IgG-), or present with indeterminate serological status (i.e. IgM?/IgG-, IgM+/IgG?, or IgM-/IgG?). Participants with an IgM+/IgG− serological profile, indicative of a recent CHIKV infection, were excluded from the study. The reason for including participants with a serostatus IgM?/IgG- or IgM+/IgG? is unclear as those participants could have experienced a recent CHIKV infection.

Resulting questions:

None.

Treatments

Refer to section 2.2.

Assessment

All participants received a single intramuscular administration of either the full dose (4.0 $\log_{10}$ $TCID_{50}$/0.5 mL) or a half dose (3.7 $\log_{10}$ $TCID_{50}$/0.5 mL) of the investigational vaccine VLA1553, or the control vaccine (Nimenrix).

Refer to section 2.2.

Resulting questions:

None.

Objectives and endpoints

Primary Objective	**Primary Endpoint**
Tolerability To evaluate the tolerability of the full dose and half dose formulation of the live-attenuated CHIKV vaccine (VLA1553) following vaccination in healthy children aged 1 to 11 years after a single immunization	Frequency and severity of solicited injection site and systemic reactions within 14 days post-vaccination
Secondary Objectives	**Secondary Endpoints**
Safety and dose optimization • To assess the safety of the full dose and half dose formulation of VLA1553 in healthy children aged 1 to 11 years after a single immunization • To identify the optimal dose level(s) of VLA1553 in healthy children aged 1 to 11 years	• Frequency and severity of any AE within 28 days post-vaccination • Frequency and severity of unsolicited AE until Month 6 (Day 180) and Month 12 (Day 365) post-vaccination • Frequency and severity of any SAE until Month 6 (Day 180) and Month 12 (Day 365) post- vaccination • Frequency and severity of any early onset AESI starting within 2 to 21 days post- vaccination (i.e. Day 3 – Day 22) • Frequency and severity of any late onset AESI during the entire trial starting 22 days post-vaccination (i.e. Day 23 – trial end) • Assessment of viremia on Days 1, 4, 8, and 15 and beyond as applicable

Immunogenicity • To assess the immunogenicity of the full dose and half dose formulation of VLA1553 in healthy children aged 1 to 11 years after a single immunization	• Immune response in baseline seronegative participants as measured by CHIKV-specific neutralizing antibody titers on Day 1, Day 15, Day 29, Day 85, Day 180 and Month 12 (Day 365) post-vaccination as determined by µPRNT assay • Proportion of participants with seroconversion* as compared to baseline at Day 15, Day 29, Day 85, Day 180 and Month 12 (Day 365) as determined by µPRNT assay • Proportion of participants with a seroresponse (defined as $\mu PRNT_{50}$ ≥150 for baseline negative participants) † on Day 15, Day 29, Day 85, Day 180 and Month 12 (Day 365) post-vaccination as determined by µPRNT assay • Fold increase of CHIKV-specific neutralizing antibody titers determined by µPRNT assay at Days 15, 29, 85, 180 and at Month 12 (Day 365) post-vaccination as compared to baseline • Proportion of participants reaching an at least 4-fold, 8-fold, 16-fold or 64-fold increase in CHIKV-specific neutralizing antibody titers compared to baseline at Day 15, Day 29, Day 85, Day 180 and Month 12 (Day 365) as measured by µPRNT assay • Antibody titers, seroresponse, seroconversion and fold increases for CHIKV-specific neutralizing antibodies, determined by µPRNT assay at Day 15, Day 29, Day 85, Day 180 and Month 12 (Day 365) post-vaccination stratified by baseline serostatus (based on µPRNT), age stratum and dose

Exploratory Objective	Exploratory Endpoint
To evaluate the efficacy of VLA1553 in pediatric participants in CHIKV endemic areas after a single immunization	Incidence of CHIKV infections with onset 15 days post-vaccination (i.e. Day 16) as evidenced by viremia by virus specific quantitative reverse transcription polymerase chain reaction (RT-qPCR), clinical diagnosis, and seroconversion by µPRNT for the entire trial period (measured in Stratum A and in sentinel participants of Stratum B and Stratum C) (Figure 1). Note: this endpoint is not included in this CTR Part A

Assessment

The aim of the study was to evaluate the tolerability, safety, and immunogenicity of two dose levels of VLA1553 in healthy children aged 1 to 11 years, in order to support dose selection for further clinical development in this age group.

The primary objective was to assess the tolerability of the full-dose and half-dose formulations of VLA1553. Solicited local reactions (injection site pain, tenderness, erythema/redness, induration, and swelling) and systemic reactions (nausea/vomiting, headache, fatigue, myalgia, arthralgia, and rash) were recorded within 14 days following vaccination.

Secondary objectives included further evaluation of safety and immunogenicity. Safety assessments comprised the recording of unsolicited adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs; defined as a cluster of symptoms associated with CHIKV infection) up to 12 months post-vaccination. Viraemia was assessed on Days 1, 4, 8, and 15, and beyond as applicable.

Immunogenicity endpoints included the evaluation of CHIKV-specific neutralising antibody titres measured by µPRNT assay at Day 1 (baseline), Day 15, Day 29, Day 85, Day 180, and Month 12. Additional parameters included the proportion of participants achieving seroconversion, the proportion achieving a seroresponse (defined as $\mu PRNT_{50} \geq 150$ in baseline seronegative participants), and fold-increase in antibody titres.

For note, the proportion of adult participants achieving CHIKV-specific neutralizing antibody titres of µPRNT50 ≥ 150 at Day 29 (seroresponders) was used as a surrogate endpoint to evaluate the efficacy of the vaccine, and was the basis for the approval of IXCHIQ. The threshold of 150 µPRNT50 was defined as reasonably likely to predict protection. Please refer to EPAR of MAA for further justification of this threshold and its relevance.

As an exploratory objective, the efficacy of VLA1553 was assessed in CHIKV-endemic areas, with onset starting 15 days after vaccination.

Resulting questions:

None.

Sample size

At least 300 healthy children aged 1 to 11 years of either gender will be invited to participate in the study.

The total number of 240 children aged 1 to 11 years exposed to VLA1553 in this trial has been selected to provide a sufficient number of participants for proper safety evaluation. With 240 participants exposed, the trial will provide 95% confidence that an AE does not occur at a frequency of 1.24% or higher, if not observed in the trial.

In terms of immunogenicity, up to 240 participants exposed to VLA1553 and assuming 10% seropositive participants and among seronegatives an expected rate of 10% of participants to be excluded due to drop-outs/major protocol deviations would leave 194 participants in the analysis and would allow determination of the GMT with meaningful accuracy. Ie., with an assumed Log10-SD of 0.45 and an expected GMT of 2954 (based on pooled data from Phase 3 results in adults), the 95%CI for the GMT would be [2551, 3421] for combined VLA1553 groups and [2397, 3640] for one dose group. Furthermore, these 97 participants per dose group would allow for the detection of a difference in GMTs of 2954 vs. 1943 between the groups with a two-sided significance level of 5% and a statistical power of 80%.

Assessment

The planned total sample size was 300 participants. Of these, 240 participants were assigned to receive the investigational vaccine VLA1553, with 120 participants allocated to each dose group, while 60 participants were assigned to receive the control vaccine (Nimenrix).

Resulting questions:

None.

Randomisation and blinding (masking)

At least 300 male and female healthy children aged 1 to 11 years will be enrolled and will be randomized in a 2:2:1 ratio to VLA1553 half dose formulation, VLA1553 full dose or control group.

In order to minimize/avoid bias, assignment into one of these trial arms will be blinded for the participants and the site staff performing the safety assessments as well as the biostatistician (i.e. double-blind).

Each participant will have a unique participant number obtained via the randomization and trial supply management system (RTSM) and assigned at the screening visit. The Investigator will keep a record (i.e. the participant screening log) of participants who entered screening.

Randomization will be performed via the RTSM. At Day 1 (Visit 1, Day of vaccination) eligible participants will be assigned to VLA1553 or control. Participants will be allocated to trial arms according to the randomization code.

The IMP will be prepared by unblinded trial staff in accordance with the information obtained from the RTSM.

Assessment

Participants are randomised in a 2:2:1 ratio to receive VLA1553 at the nominal half-dose level, VLA1553 at the full-dose level, or the control vaccine.

The study is conducted in a double-blind manner, whereby participants, site personnel involved in safety assessment, and statisticians remained blinded to treatment allocation.

Resulting questions:

None.

Statistical Methods

Datasets and Analysis Cohorts

In terms of immunogenicity, up to 240 participants exposed to VLA1553, assuming 10% seropositive subjects and among seronegatives an expected rate of 10% of drop-outs/major protocol deviations would leave 194 subjects in the analysis and would allow determination of the GMT with meaningful accuracy. I.e., with an assumed Log10-SD of 0.45 and an expected GMT of 2954 (based on pooled data from Phase 3 results in adults), the 95% CI for the GMT would be [2551, 3421] for combined VLA1553 groups and [2397, 3640] for one dose group. Furthermore, these 97 subjects per dose group would allow for the detection of a difference in GMTs of 2954 vs. 1943 between the groups with a two-sided significance level of 5% and a statistical power of 80%.

The safety analysis population contains all participants who entered into the study and received one vaccination.

Statistical analyses for immunogenicity will be based on µPRNT serostatus. Detection of anti-CHIKV antibodies at screening will be used for enrollment at the sites only. The immunogenicity analysis population (IMM) is defined to include all vaccinated participants who have evaluable µPRNT antibody titer results at baseline and at least one post-baseline titer measurement after vaccination. The baseline seronegative immunogenicity analysis set (seronegative IMM) includes all IMM participants, who are seronegative (µPRNT50 $\leq$ 40) at baseline (Day 1). The baseline seropositive immunogenicity analysis set (seropositive IMM) includes all IMM participants, who are seropositive (µPRNT50 >40) at baseline (Day 1).

The per protocol analysis population (PP) contains all seronegative IMM participants who have no major protocol violations that could impact immune response. Examples that may lead to exclusion from the PP are provided here, further criteria may be defined in the SAP:

- Participant has a known or suspected defect of the immune system that can be expected to influence the immune response to the vaccine, such as participants with congenital or acquired immunodeficiency, status post organ transplantation or immuno-suppressive therapy within 4 weeks prior to Visit 1. Immuno-suppressive therapy is defined as administration of chronic (longer than 14 days) prednisone or equivalent ≥0.05 mg/kg/day within 4 weeks prior to study entry, radiation therapy or immunosuppressive cytotoxic drugs/ monoclonal antibodies in the previous 3 years; topical and inhaled steroids are allowed;
- Subject has a history of immune-mediated or clinically relevant arthritis/arthralgia;
- Subject has received the wrong (not according to randomization) or no IMP.

These criteria for protocol violations are identified at the time of planning the study. However, during the course of the trial unforeseen events may occur or new scientific knowledge may become available, therefore final decisions on whether any protocol violation could impact immune response and thus lead to exclusion from the PP will be made by the sponsor on a case by case basis. Sample testing issues may also lead to exclusion from the PP for particular time points.

Handling of Missing, Unused and Spurious Data

All statistical analysis will generally be based on observed values, missing values will not be imputed.

Safety Analysis

All participants entered into the study, who receive the vaccination, will be included in the safety analysis.

The primary safety analysis will be the number and percentage of participants with solicited injection site reactions and solicited systemic reactions, by term and overall, up to 14 days after vaccination and will be presented by treatment group and overall. Groups will be compared using Fisher's exact test (Fisher- Freeman-Halton test).

For the secondary safety analyses tabulations will generally be provided separately for solicited AEs and unsolicited AEs, and for both types of AEs combined. 95% confidence intervals according to Altman (Wilson score interval) will generally be provided for all AE rates. Further details in addition to the outline below will be provided in the SAP.

The number and percentage of participants with any AE, any related solicited AE, any unsolicited AE, any related unsolicited AE, any related severe AE, any SAE, any related SAE, any medically attended AE, any AE leading to withdrawal from study, and any AE occurring at a frequency of at least 10% up to Day 29, and up to Day 180, and any AESI (i.e. early and late onset AESI) and any related AESI up to Day 22, will be presented for treatment group overall and by system organ class (SOC) and preferred term (PT). Selected frequencies will be compared using Fisher's exact test (Fisher-Freeman-Halton test) as will be pre-defined in the analysis plan.

The occurrence of solicited local and systemic AEs will also be tabulated by participant diary day and mean duration of symptoms will be presented (for participants with symptoms).

Changes in any laboratory values from study entry will be analyzed descriptively for sentinel participants and will be part of the unsolicited AE evaluation only in case of clinically relevant deviations. The rates of participants with laboratory assessments outside the normal range, and with abnormal laboratory parameters falling into the grade 0 vs. 1 through 3 will be calculated for treatment group overall, by visit and overall. The rate of participants with urinalysis results according to the test manufacturer's results categories will be calculated.

Selected safety analysis will be repeated stratified by baseline serostatus, these will be defined in the SAP.

Immunogenicity Analysis

All analyses for Part A, Part B and Part C of immunogenicity data will be performed primarily on the PP and secondarily on the IMM.

The secondary immunogenicity analysis will be a comparison of the GMTs in the per-protocol analysis set between the VLA1553 Study Arms and control at Day 15, Day 29, Day 85, Day 180 and Month 12 post-vaccination by ANOVA (factor Study Arm, age stratum and baseline serostatus), including pair-wise comparisons (Tukey's HSD test) between VLA1553 Study Arms. The models will be applied on logarithmic values and estimates and two-sided 95% confidence intervals for GMTs and GMT ratios will be obtained by back-transformation.

GMFI's will be analyzed at various time points analogously. The seroresponse rates and seroconversion for various study days will be compared between the study arms by Fisher-Freeman-Halton test, amended by Fisher' s exact test for pairwise comparisons, and two-sided 95% confidence intervals will be calculated according to Altman (Wilson score interval). Select immunogenicity analyses will also be stratified by age stratum and by baseline serostatus (based on μPRNT), these will be defined in the SAP.

Planned Data Analysis of the Study

The following data analyses will be performed:

- Part A includes safety and immunogenicity data after all participants have completed Visit 5 (Day 29).
- Part B includes safety and immunogenicity data after all participants have completed Visit 7 (Day 180).
- Part C includes safety and immunogenicity data after all participants have completed Visit 8 (Month 12).

Individual study parts will be analyzed sequentially.

Part A analysis will be performed unblinded (blind will be maintained for study sites) and a clinical study report will be compiled. For the Part B analysis another clinical study report will be compiled (integrated Clinical Study Report of Part A+B). For the Part C analysis a final clinical study report will be compiled (integrated Clinical Study Report of Part A+B+C).

Assessment

Analysis populations include a safety set (all vaccinated participants), an immunogenicity analysis set (IMM) (all vaccinated participants who have evaluable µPRNT antibody titer results at baseline and at least one measurement after vaccination), and a per-protocol (PP) population restricted to baseline seronegative participants without major protocol deviations impacting immune response.

Participants with a CHIKV neutralising antibody titre of µPRNT50 ≤ 40 were classified as seronegative, while those with an antibody titres µPRNT50 >40 were classified as seropositive at baseline. A threshold of µPRNT50 < 20 for defining seronegativity at baseline was used in the pivotal trial supporting the MA (VLA1553-301 trial). This threshold was considered more appropriate to define a negative serostatus at baseline. Based on the results (Table 10), the cut-off used is acceptable (no/few participants have a CHIKV neutralizing antibody titre between 20 and 40 µPRNT50).

Safety and immunogenicity analyses are all descriptive in nature.

Immunogenicity analyses are conducted primarily on the PP population and secondarily on the IMM. Selected immunogenicity analyses are further stratified by age group and by baseline serostatus (based on µPRNT).

Analyses are performed in stages: Part A includes safety and immunogenicity data after completion of the Day 29 visit, Part B after completion of the Day 180 visit, and Part C after completion of the Month 12 visit. The submitted final clinical study report presents the integrated analysis of all study parts.

Resulting questions:

None.

Results

Results summarised below are from Part C (Month 12) CSR version 1.0 (final), dated 23 Feb 2026, with a database closure date of 23 Oct 2025.

Participant flow

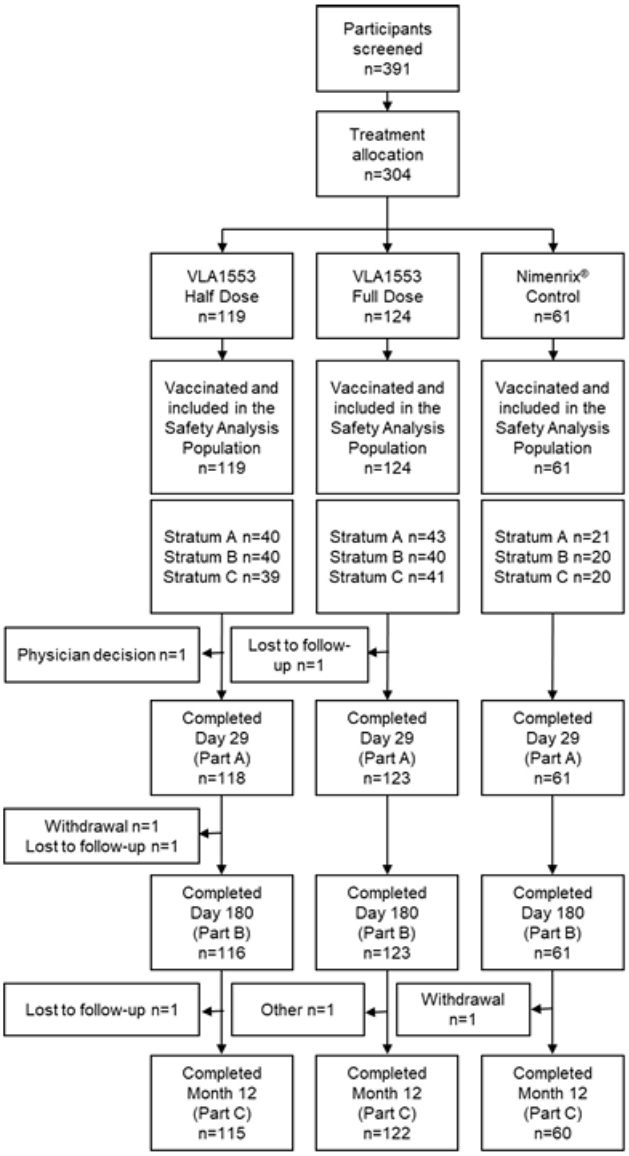
The disposition of participants is provided by trial arm and age group in Table 5.

Participant disposition to Day 29 (Part A), Day 180 (Part B), and Month 12 (Part C) is summarized in Figure 3.

Table 5. Participant Enrollment and Disposition (All Participants)

		7 - 11 years			3 - 6 years			1 - 2 years				
	Statistic	Half Dose (N=40)	Full Dose (N=43)	Control (N=21)	Half Dose (N=40)	Full Dose (N=40)	Control (N=20)	Half Dose (N=39)	Full Dose (N=41)	Control (N=20)	Not treatment allocated (N=87)	Total Population (N=391)
Screened	n	40	43	21	40	40	20	39	41	20	87	391
Re-screened	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.9)	1 (5.0)	0 (0.0)	3 (0.8)
Sentinels	n (%)	5 (12.5)	5 (11.6)	0 (0.0)	5 (12.5)	5 (12.5)	0 (0.0)	5 (12.8)	5 (12.2)	0 (0.0)	1 (1.1)	31 (7.9)
Randomized	n (%)	35 (87.5)	38 (88.4)	21 (100)	35 (87.5)	35 (87.5)	20 (100)	34 (87.2)	36 (87.8)	20 (100)	0 (0.0)	274 (70.1)
Treatment allocated	n (%)	40 (100)	43 (100)	21 (100)	40 (100)	40 (100)	20 (100)	39 (100)	41 (100)	20 (100)	0 (0.0)	304 (77.7)
Vaccinated*	n (%)	40 (100)	43 (100)	21 (100)	40 (100)	40 (100)	20 (100)	39 (100)	41 (100)	20 (100)	0 (NC)	304 (100)
Treatment allocated but not vaccinated*	n (%)	0 (NC)	0 (NC)	0 (NC)	0 (NC)	0 (NC)	0 (NC)	0 (NC)	0 (NC)	0 (NC)	0 (NC)	0 (NC)
Safety Analysis Population	n (%)	40 (100)	43 (100)	21 (100)	40 (100)	40 (100)	20 (100)	39 (100)	41 (100)	20 (100)	0 (0.0)	304 (77.7)
Reason not in Safety Analysis Population												
Not vaccinated	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	87 (100)	87 (22.3)
Immunogenicity Analysis Population	n (%)	40 (100)	43 (100)	21 (100)	40 (100)	39 (97.5)	20 (100)	38 (97.4)	41 (100)	20 (100)	0 (0.0)	302 (77.2)
Reason not in Immunogenicity Analysis Population												
No immunogenicity sample after baseline	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
No immunogenicity sample at baseline	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Baseline Seronegative Immunogenicity Analysis Set	n (%)	31 (77.5)	36 (83.7)	13 (61.9)	40 (100)	39 (97.5)	20 (100)	38 (97.4)	41 (100)	20 (100)	0 (0.0)	278 (71.1)
Baseline Seropositive Immunogenicity Analysis Set	n (%)	9 (22.5)	7 (16.3)	8 (38.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	24 (6.1)
Per-Protocol Analysis Population	n (%)	29 (72.5)	36 (83.7)	13 (61.9)	40 (100)	39 (97.5)	20 (100)	38 (97.4)	40 (97.6)	20 (100)	0 (0.0)	275 (70.3)
Reason not in Per-Protocol Analysis Population												
Participant is baseline seropositive	n (%)	8 (20.0)	7 (16.3)	8 (38.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	23 (5.9)
											allocated (N=87)	n (N=391)
Exclusionary protocol deviation**	n (%)	2 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	3 (0.8)
Participant is baseline seropositive and has an exclusionary protocol deviation**	n (%)	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

n=number of participants, percentages are based on N; NC=not calculable.
The column 'Not treatment allocated' counts all participants who were not allocated to a trial arm due to screening failure, withdrawal of consent or any other reason.
*Percentages are based on the number of treatment allocated participants.
**Participants with a protocol deviation classified as 'major' in the Data Review Meeting were excluded from the Per-Protocol Population entirely.



n=number of participants.. ET information is presented for participants who had ET, while the corresponding ET visits are assigned to respective analysis visits according to visit windowing rules as defined in the SAP. Lost to follow-up means participant has been vaccinated, but parent(s)/LAR(s) could not be contacted 3 times.

Figure 2. Participant Disposition (Safety Analysis Population)

Of the 3 centers involved in the trial, participants were evenly distributed across the trial sites.

According to windowed visits, all 304 (100%) participants completed Visit 0 (Screening) and Visit 1 (Day 1). Visit 2 (Day 4) and Visit 3 (Day 8) were completed by 301/304 (99.0%) participants, Visit 4 (Day 15), Visit 5 (Day 29), and Visit 6 (Day 85) were completed by 302/304 (99.3%) participants, Visit 7 (Day 180) was completed by 300/304 (98.7%) participants, and Visit 8 (Month 12) was completed by 299/304 (98.4%).

Protocol deviations (PD) for the Safety Analysis Population are presented by age group and trial arm in Table 6.

Table 6. Protocol deviations by age group and trial arm (Safety Analysis Population)

		7 - 11 years			3 - 6 years			1 - 2 years			
	Statistic	Half Dose (N=40)	Full Dose (N=43)	Control (N=21)	Half Dose (N=40)	Full Dose (N=40)	Control (N=20)	Half Dose (N=39)	Full Dose (N=41)	Control (N=20)	Total Population (N=304)
Any PDs	n (%) Obs	39 (97.5) 66	28 (65.1) 39	16 (76.2) 25	24 (60.0) 34	25 (62.5) 38	10 (50.0) 19	22 (56.4) 47	30 (73.2) 50	13 (65.0) 27	207 (68.1) 345
Major PDs (impact on immunogenicity)*	n (%) Obs	3 (7.5) 3	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (2.4) 1	0 (0.0) 0	4 (1.3) 4
Major PDs by Deviation Type*											
ELIGIBILITY	n (%) Obs	3 (100) 3	0 (NC) 0	0 (NC) 0	0 (NC) 0	0 (NC) 0	0 (NC) 0	0 (NC) 0	0 (0.0) 0	0 (NC) 0	3 (75.0) 3
ELIGIBILITY AND LABORATORY	n (%) Obs	0 (0.0) 0	0 (NC) 0	0 (NC) 0	0 (NC) 0	0 (NC) 0	0 (NC) 0	0 (NC) 0	1 (100) 1	0 (NC) 0	1 (25.0) 1
Minor PDs (no impact on immunogenicity)	n (%) Obs	39 (97.5) 63	28 (65.1) 39	16 (76.2) 25	24 (60.0) 34	25 (62.5) 38	10 (50.0) 19	22 (56.4) 47	30 (73.2) 49	13 (65.0) 27	207 (68.1) 341
Minor PDs by Deviation Type											
CONCOMITANT MEDICATION	n (%) Obs	1 (2.6) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (0.5) 1
ELIGIBILITY	n (%) Obs	1 (2.6) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (0.5) 1
INFORMED CONSENT/ ASSENT	n (%) Obs	13 (33.3) 18	2 (7.1) 2	3 (18.8) 4	1 (4.2) 1	2 (8.0) 3	2 (20.0) 2	0 (0.0) 0	1 (3.3) 1	1 (7.7) 1	25 (12.1) 32
LABORATORY	n (%) Obs	4 (10.3) 4	1 (3.6) 1	2 (12.5) 2	3 (12.5) 4	2 (8.0) 2	0 (0.0) 0	1 (4.5) 3	14 (46.7) 20	4 (30.8) 12	31 (15.0) 48
OTHER	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (3.3) 1	0 (0.0) 0	1 (0.5) 1
SAFETY	n (%) Obs	27 (69.2) 32	26 (92.9) 33	11 (68.8) 17	21 (87.5) 25	18 (72.0) 22	5 (50.0) 7	17 (77.3) 25	16 (53.3) 20	4 (30.8) 6	145 (70.0) 187
TRIAL PROCEDURE	n (%) Obs	6 (15.4) 7	2 (7.1) 2	1 (6.3) 1	0 (0.0) 0	7 (28.0) 7	5 (50.0) 6	10 (45.5) 12	5 (16.7) 5	6 (46.2) 6	42 (20.3) 46
VISIT SCHEDULE	n (%) Obs	0 (0.0) 0	1 (3.6) 1	1 (6.3) 1	3 (12.5) 4	4 (16.0) 4	4 (40.0) 4	4 (18.2) 7	2 (6.7) 2	2 (15.4) 2	21 (10.1) 25
Important PDs according to Severity Classification of Sponsor	n (%) Obs	21 (52.5) 26	2 (4.7) 2	4 (19.0) 5	0 (0.0) 0	7 (17.5) 7	5 (25.0) 5	10 (25.6) 10	4 (9.8) 4	8 (40.0) 8	61 (20.1) 67
Important PDs by Deviation Type											
CONCOMITANT MEDICATION	n (%) Obs	1 (4.8) 1	0 (0.0) 0	0 (0.0) 0	0 (NC) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (1.6) 1
ELIGIBILITY	n (%) Obs	4 (19.0) 4	0 (0.0) 0	0 (0.0) 0	0 (NC) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	4 (6.6) 4
ELIGIBILITY AND LABORATORY	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (NC) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (25.0) 1	0 (0.0) 0	1 (1.6) 1
INFORMED CONSENT/ ASSENT	n (%) Obs	13 (61.9) 15	1 (50.0) 1	3 (75.0) 4	0 (NC) 0	1 (14.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (12.5) 1	19 (31.1) 22
LABORATORY	n (%) Obs	1 (4.8) 1	0 (0.0) 0	0 (0.0) 0	0 (NC) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (25.0) 1	1 (12.5) 1	3 (4.9) 3
SAFETY	n (%) Obs	0 (0.0) 0	0 (0.0) 0	1 (25.0) 1	0 (NC) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (1.6) 1
TRIAL PROCEDURE	n (%) Obs	5 (23.8) 5	0 (0.0) 0	0 (0.0) 0	0 (NC) 0	6 (85.7) 6	5 (100) 5	10 (100) 10	2 (50.0) 2	6 (75.0) 6	34 (55.7) 34
VISIT SCHEDULE	n (%) Obs	0 (0.0) 0	1 (50.0) 1	0 (0.0) 0	0 (NC) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (1.6) 1
Non-important PDs according to Severity Classification of Sponsor	n (%) Obs	28 (70.0) 40	27 (62.8) 37	14 (66.7) 20	24 (60.0) 34	24 (60.0) 31	8 (40.0) 14	20 (51.3) 37	29 (70.7) 46	9 (45.0) 19	183 (60.2) 278
Non-important PDs by Deviation Type											
INFORMED CONSENT/ ASSENT	n (%) Obs	3 (10.7) 3	1 (3.7) 1	0 (0.0) 0	1 (4.2) 1	1 (4.2) 2	2 (25.0) 2	0 (0.0) 0	1 (3.4) 1	0 (0.0) 0	9 (4.9) 10
LABORATORY	n (%) Obs	3 (10.7) 3	1 (3.7) 1	2 (14.3) 2	3 (12.5) 4	2 (8.3) 2	0 (0.0) 0	1 (5.0) 3	14 (48.3) 19	4 (44.4) 11	30 (16.4) 45
OTHER	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (3.4) 1	0 (0.0) 0	1 (0.5) 1
SAFETY	n (%) Obs	27 (96.4) 32	26 (96.3) 33	11 (78.6) 16	21 (87.5) 25	18 (75.0) 22	5 (62.5) 7	17 (85.0) 25	16 (55.2) 20	4 (44.4) 6	145 (79.2) 186
TRIAL PROCEDURE	n (%) Obs	2 (7.1) 2	2 (7.4) 2	1 (7.1) 1	0 (0.0) 0	1 (4.2) 1	1 (12.5) 1	2 (10.0) 2	3 (10.3) 3	0 (0.0) 0	12 (6.6) 12
VISIT SCHEDULE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	1 (7.1) 1	3 (12.5) 4	4 (16.7) 4	4 (50.0) 4	4 (20.0) 7	2 (6.9) 2	2 (22.2) 2	20 (10.9) 24

n=number of participants with event. Percentages are based on N, except for tabulations by deviation type where percentages are based on number of participants with respective PD classification; NC=not calculable; Obs=number of events.
*Major PDs lead to exclusion of the participants from the Per-Protocol Analysis Population according to the assessment made in the Data Review Meeting.
Table contains only PDs on participant level. PDs on site level are listed only. For details, please see Listing 16.2.1.8.
No PDs are documented in the DRM report of Part C, that lead to exclusions on time point level. PDs violating the per-protocol time window defined in SAP

Assessment

Participant disposition

A total of 391 participants were screened, of whom 304 (77.7%) were randomised and vaccinated, constituting the Safety Analysis Population. Participants were evenly distributed across the three study sites (n=125; n=129; n=137).

Among vaccinated participants, allocation to treatment arms was in line with the planned randomisation (VLA1553 full dose: n=124; VLA1553 half dose: n=119; control: n=61), and age stratification was well maintained across predefined strata (A: 7–11 years, B: 3–6 years, and C: 1–2 years). The immunogenicity analysis population (IMM) comprised 302 participants, with only two exclusions due to missing post-baseline samples.

Overall study completion was high, with 297/304 participants (97.7%) completing the Month 12 visit. Only seven participants (2.3%) discontinued prematurely, with reasons including loss to follow-up, withdrawal of consent, and other non-safety-related factors. No discontinuations were attributed to adverse events.

Protocol deviations

PDs were reported for 207/304 participants (68.1%) in the Safety Analysis Population.

Important PDs were reported in 61/304 participants (20.1%), mainly within the categories of trial procedures and informed consent/assent, while non-important PDs were observed in 183/304 participants (60.2%), predominantly related to safety assessments.

Major PDs, defined as having a potential impact on immunogenicity, were infrequent and identified in 4/304 participants (1.3%), primarily related to eligibility criteria. Minor PDs (no impact on immunogenicity) were more common (207/304; 68.1%), most frequently related to safety procedures, trial procedures, and laboratory assessments.

Protocol deviations were overall balanced across age strata and treatment arms.

To conclude, the vast majority of PD were minor and not considered to impact the primary immunogenicity endpoints. Overall, the pattern of deviations does not raise concerns regarding the integrity of the study results.

Resulting questions:

None.

Recruitment

Countries and sites

- Dominican Republic : 2 sites
    - Fundacion Dominicana de Perinatología Hospital Universitario Maternidad Nuestra Señora de La Altagracia Fundación PROBEBE
    - Instituto Dermatologico y Cirugia de la Piel "Dr Huberto Bogaert Diaz" IDCP
- Honduras: 1 site
    - Inversiones en Investigación Médica INVERIME

Trials dates:

First Participant In (informed consent form): 18-Dec-2023

First Participant First Vaccination: 09-Jan-2024

Last Participant Last Vaccination: 17-Jul-2024

Last Participant Last Visit: 02-Jul-2025

Part A Data Cut-off Date: 12-Nov-2024

Part B Data Cut-off Date: 15-Apr-2025

Part C Database Closure Date: 23-Oct-2025

Assessment

The trial was conducted at two sites in the Dominican Republic and one site in Honduras, countries considered endemic for chikungunya virus, irrespective of recent local transmission. All participants were vaccinated between 9 January and 17 July 2024.

Resulting questions:

None.

Baseline data

Demographic characteristics of the Safety Analysis Population by age group and trial arm are provided in Table 7.

Demographic characteristics for the IMM, µPRNT baseline serostatus, and PP populations were similar to those seen in the Safety Analysis Population.

Table 7. Demographic and Baseline Characteristics by Age Group and Trial Arm (Safety Analysis Population)

		7 - 11 years			3 - 6 years			1 - 2 years			
	Statistic	Half Dose (N=40)	Full Dose (N=43)	Control (N=21)	Half Dose (N=40)	Full Dose (N=40)	Control (N=20)	Half Dose (N=39)	Full Dose (N=41)	Control (N=20)	Total Population (N=304)
Gender											
Female	n (%)	19 (47.5)	23 (53.5)	8 (38.1)	15 (37.5)	22 (55.0)	12 (60.0)	18 (46.2)	20 (48.8)	9 (45.0)	146 (48.0)
Male	n (%)	21 (52.5)	20 (46.5)	13 (61.9)	25 (62.5)	18 (45.0)	8 (40.0)	21 (53.8)	21 (51.2)	11 (55.0)	158 (52.0)
	Total	40	43	21	40	40	20	39	41	20	304
Females with childbearing potential*											
Yes	n (%)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
No	n (%)	19 (100)	23 (100)	7 (87.5)	15 (100)	22 (100)	12 (100)	18 (100)	20 (100)	9 (100)	145 (99.3)
	Total	19	23	8	15	22	12	18	20	9	146
Race											
American Indian or Alaska Native	n (%)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)
Asian	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Black or African American	n (%)	13 (32.5)	16 (37.2)	5 (23.8)	14 (35.0)	13 (32.5)	3 (15.0)	15 (38.5)	5 (12.2)	4 (20.0)	88 (28.9)
White	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.3)
Other	n (%)	27 (67.5)	26 (60.5)	16 (76.2)	26 (65.0)	26 (65.0)	17 (85.0)	24 (61.5)	35 (85.4)	16 (80.0)	213 (70.1)
	Total	40	43	21	40	40	20	39	41	20	304
Specification other race											
Indigenous	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multiracial	n (%)	27 (100)	26 (100)	16 (100)	26 (100)	26 (100)	17 (100)	24 (100)	35 (100)	16 (100)	213 (100)
	Total	27	26	16	26	26	17	24	35	16	213
Ethnicity											
Hispanic or Latino	n (%)	40 (100)	43 (100)	21 (100)	40 (100)	40 (100)	20 (100)	39 (100)	41 (100)	20 (100)	304 (100)
Not Hispanic or Latino	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not Reported/Unknown	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	40	43	21	40	40	20	39	41	20	304
Age [years]											
	Mean	8.6	8.6	9.1	4.6	4.5	4.6	1.6	1.6	1.5	5.0
	SD	1.30	1.07	1.55	1.17	0.99	1.00	0.49	0.50	0.51	3.11
	Median	8.5	9.0	9.0	5.0	5.0	4.5	2.0	2.0	1.0	5.0

		7 - 11 years			3 - 6 years			1 - 2 years			
	Statistic	Half Dose (N=40)	Full Dose (N=43)	Control (N=21)	Half Dose (N=40)	Full Dose (N=40)	Control (N=20)	Half Dose (N=39)	Full Dose (N=41)	Control (N=20)	Total Population (N=304)
	Q1 / Q3	7.5 / 9.5	8.0 / 9.0	8.0 / 10.0	3.5 / 6.0	4.0 / 5.0	4.0 / 5.0	1.0 / 2.0	1.0 / 2.0	1.0 / 2.0	2.0 / 8.0
	Min / Max	7 / 11	7 / 11	7 / 11	3 / 6	3 / 6	3 / 6	1 / 2	1 / 2	1 / 2	1 / 11
	n	40	43	21	40	40	20	39	41	20	304
Body height [cm]											
	Mean	132.4	131.4	136.3	110.3	109.3	107.4	87.3	87.1	83.7	109.8
	SD	8.78	9.16	11.49	9.67	6.96	8.19	6.75	6.27	6.62	20.71
	Median	133.0	132.0	138.0	110.0	111.0	106.5	87.0	88.0	85.0	110.0
	Q1 / Q3	126.0 / 137.0	125.0 / 136.0	126.0 / 146.0	103.0 / 118.0	105.5 / 113.0	101.5 / 110.5	83.0 / 92.0	83.0 / 92.0	79.0 / 89.5	91.0 / 126.5
	Min / Max	118 / 156	113 / 158	117 / 154	90 / 130	94 / 124	94 / 124	75 / 101	75 / 99	71 / 92	71 / 158
	n	40	43	21	40	40	20	39	41	20	304
Body weight [kg]											
	Mean	29.3	29.3	33.9	18.7	18.0	18.2	12.4	12.7	11.4	20.4
	SD	7.55	7.01	8.71	4.91	2.72	3.66	2.19	2.11	1.64	9.10
	Median	26.7	28.0	34.1	18.0	18.1	18.1	12.3	12.4	11.4	18.1
	Q1 / Q3	24.5 / 32.4	24.0 / 31.8	27.7 / 42.5	15.3 / 20.5	16.5 / 19.8	15.6 / 19.5	10.5 / 14.3	11.0 / 14.1	10.4 / 12.9	13.2 / 25.0
	Min / Max	20 / 55	18 / 48	19 / 48	13 / 39	12 / 23	13 / 28	8 / 18	10 / 18	8 / 14	8 / 55
	n	40	43	21	40	40	20	39	41	20	304
BMI [kg/m^2]											
	Mean	16.5	16.7	18.0	15.2	15.0	15.7	16.2	16.8	16.4	16.2
	SD	2.65	2.17	3.07	2.14	1.44	1.96	1.93	2.20	2.09	2.30
	Median	15.8	16.2	17.6	15.2	15.0	15.5	15.8	16.6	16.0	15.7
	Q1 / Q3	15.3 / 17.4	15.2 / 18.0	15.9 / 20.0	14.1 / 15.7	14.3 / 15.7	14.8 / 16.2	14.8 / 18.0	15.6 / 17.3	15.3 / 17.1	14.8 / 17.1
	Min / Max	12 / 26	14 / 22	14 / 24	11 / 23	12 / 19	12 / 20	13 / 20	12 / 26	13 / 22	11 / 26
	n	40	43	21	40	40	20	39	41	20	304
BMI category**											
Underweight	n (%)	3 (7.5)	2 (4.7)	0 (0.0)	4 (10.0)	5 (12.5)	3 (15.0)	7 (17.9)	2 (4.9)	1 (5.0)	27 (8.9)
Healthy Weight	n (%)	33 (82.5)	33 (76.7)	15 (71.4)	33 (82.5)	31 (77.5)	14 (70.0)	21 (53.8)	29 (70.7)	15 (75.0)	224 (73.7)
Overweight	n (%)	2 (5.0)	6 (14.0)	3 (14.3)	1 (2.5)	3 (7.5)	1 (5.0)	5 (12.8)	5 (12.2)	0 (0.0)	26 (8.6)
Obesity	n (%)	2 (5.0)	2 (4.7)	3 (14.3)	2 (5.0)	1 (2.5)	2 (10.0)	6 (15.4)	5 (12.2)	4 (20.0)	27 (8.9)

		7 - 11 years			3 - 6 years			1 - 2 years			
	Statistic	Half Dose (N=40)	Full Dose (N=43)	Control (N=21)	Half Dose (N=40)	Full Dose (N=40)	Control (N=20)	Half Dose (N=39)	Full Dose (N=41)	Control (N=20)	Total Population (N=304)
	Total	40	43	21	40	40	20	39	41	20	304
Baseline serostatus according to µPRNT											
Seronegative (µPRNT<=40)	n (%)	31 (77.5)	36 (83.7)	13 (61.9)	40 (100)	40 (100)	20 (100)	39 (100)	41 (100)	20 (100)	280 (92.1)
Seropositive (µPRNT>40)	n (%)	9 (22.5)	7 (16.3)	8 (38.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	24 (7.9)
	Total	40	43	21	40	40	20	39	41	20	304

n=number of participants, percentages are based on Total.
*Percentages of childbearing potential are based on the number of female participants.
µPRNT = Micro Plaque Reduction Neutralization Test.
Baseline seronegative is defined as µPRNT50 ≤ 40. Baseline seropositive is defined as µPRNT50 > 40.
Race-reassessment performed for 27 participants (DRM Report Part C Appendix 3, ID A-STD-4-612) as initial race and ethnicity in Parts A and B were not self-reported.

In the Safety Analysis Population, 222/304 (73.0%) participants received concomitant medications. Analgesics were used by 161/304 of the participants (53.0%) while anti-inflammatory and antirheumatic products were used by 39/304 of the participants (12.8%).

Assessment

Baseline demographic characteristics are overall well balanced across treatment arms and age strata.

In the safety analysis population, the overall sex distribution is balanced (48% female, 52% male); however, some differences in sex proportions between treatment groups are noted within individual age strata.

All participants are of Hispanic or Latino ethnicity and predominantly of multiracial (70.1%) or Black/African American (28.9%) background, reflecting the geographic regions in which the study was conducted.

Age distribution is consistent with the predefined strata, with mean ages aligned within each age group. Baseline anthropometric parameters (weight, height, BMI) are overall comparable between treatment arms.

The majority of participants were seronegative at baseline (280/304; 92.1%), with all seropositive participants belonging to the oldest age group (7–11 years), which is considered plausible in an endemic setting. Within this age group, baseline seropositivity rates were 22.5% (9/40) in the half-dose group, 16.3% (7/43) in the full-dose group, and 38.1% (8/21) in the control group. This limited number of seropositive participants should be considered when interpreting immunogenicity results.

Half of the participants used analgesics but their use was evenly distributed across age categories and trail arms.

Of note, in the Safety Analysis Population, 3.9% participants received concomitant systemic steroids (9.3%, 2.5%, and 4.9% in the VLA1553 Full Dose arm of participants in the 7-11, 3-6, and 1-2 years strata, respectively, 2.5% and 7.7% in the VLA1553 Half Dose arm of participants in the 7-11 and 1-2 years strata, respectively, and 5.0% in the control arm of participants in the 3-6 years stratum).

Demographic characteristics of the immunogenicity and per-protocol populations are comparable to those of the Safety Analysis Population.

Resulting questions:

None.

Immunogenicity and Efficacy results

Immunogenicity assessment was a secondary objective. Efficacy was explored.

In the PP population, titres of CHIKV-specific neutralizing antibodies analysed at baseline (Day 1) were used to determine the serostatus. Seronegative participants were defined as µPRNT50 ≤40.

Seroresponse was defined as µPRNT50 ≥ 150 at the respective timepoint.

Proportion of baseline seronegative participants (PP population) with seroresponse post-vaccination

A summary of the seroresponse rate (SRR) for CHIKV-specific neutralizing antibody titres by visit pooled by trial arm for the PP population is provided in Table 8.

A summary of the SRR for CHIKV-specific neutralizing antibody titres by visit by age group and trial arm for the PP population is provided in Table 9.

Table 8. Seroresponse rate for CHIKV-specific neutralizing antibody titres by visit pooled by trial arm (PP analysis population)

	Statistic	Half Dose (N=107)	Full Dose (N=115)	Control (N=53)
Visit 4 – Day 15	n/Nm (%)	92/105 (87.6)	109/114 (95.6)	0/49 (0.0)
	[95% CI]	[79.8, 93.2]	[90.1, 98.6]	[0.0, 7.3]
Overall p-value		<.0001		
Pairwise comparisons	vs. Control	<.0001	<.0001	
	vs. Half Dose		0.0467	
Visit 5 – Day 29	n/Nm (%)	95/107 (88.8)	109/114 (95.6)	0/52 (0.0)
	[95% CI]	[81.2, 94.1]	[90.1, 98.6]	[0.0, 6.8]
Overall p-value		<.0001		
Pairwise comparisons	vs. Control	<.0001	<.0001	
	vs. Half Dose		0.0765	
Visit 6 – Day 85	n/Nm (%)	90/102 (88.2)	109/114 (95.6)	0/52 (0.0)
	[95% CI]	[80.4, 93.8]	[90.1, 98.6]	[0.0, 6.8]
Overall p-value		<.0001		
Pairwise comparisons	vs. Control	<.0001	<.0001	
	vs. Half Dose		0.0738	
Visit 7 – Day 180	n/Nm (%)	93/105 (88.6)	110/114 (96.5)	0/51 (0.0)
	[95% CI]	[80.9, 94.0]	[91.3, 99.0]	[0.0, 7.0]
Overall p-value		<.0001		
Pairwise comparisons	vs. Control	<.0001	<.0001	
	vs. Half Dose		0.0355	
Visit 8 – Day 365	n/Nm (%)	90/104 (86.5)	108/114 (94.7)	0/51 (0.0)
	[95% CI]	[78.4, 92.4]	[88.9, 98.0]	[0.0, 7.0]
Overall p-value		<.0001		
Pairwise comparisons	vs. Control	<.0001	<.0001	
	vs. Half Dose		0.0580	

N=number of participants of the respective population, trial arm and/or age group as described in the column header, n=number of participants, percentages are based on the number of non-missing observations within each trial arm (Nm).
Two-sided 95% confidence intervals are calculated using the Clopper-Pearson method.
Pairwise test (Fisher exact) performed in case of a significant overall p-value (Fisher-Freeman-Halton).
Seroresponse is defined as $\mu PRNT_{50} \geq 150$ at the respective time point.

Table 9. Seroresponse rate for CHIKV-specific neutralizing antibody titres by visit by age group and trial arm (PP analysis population)

		7 – 11 years			3 – 6 years			1 – 2 years		
	Statistic	Half Dose (N=29)	Full Dose (N=36)	Control (N=13)	Half Dose (N=40)	Full Dose (N=39)	Control (N=20)	Half Dose (N=38)	Full Dose (N=40)	Control (N=20)
Visit 4 – Day 15	n/Nm (%)	26/29 (89.7)	36/36 (100)	0/13 (0.0)	36/39 (92.3)	38/39 (97.4)	0/18 (0.0)	30/37 (81.1)	35/39 (89.7)	0/18 (0.0)
	[95% CI]	[72.6, 97.8]	[90.3, 100]	[0.0, 24.7]	[79.1, 98.4]	[86.5, 99.9]	[0.0, 18.5]	[64.8, 92.0]	[75.8, 97.1]	[0.0, 18.5]
Overall p-value		<.0001			<.0001			<.0001		
Pairwise comparisons	vs. Control	<.0001	<.0001		<.0001	<.0001		<.0001	<.0001	
	vs. Half Dose		0.0837			0.6151			0.3406	
Visit 5 – Day 29	n/Nm (%)	26/29 (89.7)	36/36 (100)	0/13 (0.0)	37/40 (92.5)	38/39 (97.4)	0/20 (0.0)	32/38 (84.2)	35/39 (89.7)	0/19 (0.0)
	[95% CI]	[72.6, 97.8]	[90.3, 100]	[0.0, 24.7]	[79.6, 98.4]	[86.5, 99.9]	[0.0, 16.8]	[68.7, 94.0]	[75.8, 97.1]	[0.0, 17.6]
Overall p-value		<.0001			<.0001			<.0001		
Pairwise comparisons	vs. Control	<.0001	<.0001		<.0001	<.0001		<.0001	<.0001	
	vs. Half Dose		0.0837			0.6153			0.5170	
Visit 6 – Day 85	n/Nm (%)	26/29 (89.7)	35/35 (100)	0/13 (0.0)	34/37 (91.9)	38/39 (97.4)	0/20 (0.0)	30/36 (83.3)	36/40 (90.0)	0/19 (0.0)
	[95% CI]	[72.6, 97.8]	[90.0, 100]	[0.0, 24.7]	[78.1, 98.3]	[86.5, 99.9]	[0.0, 16.8]	[67.2, 93.6]	[76.3, 97.2]	[0.0, 17.6]
Overall p-value		<.0001			<.0001			<.0001		
Pairwise comparisons	vs. Control	<.0001	<.0001		<.0001	<.0001		<.0001	<.0001	
	vs. Half Dose		0.0877			0.3518			0.5032	
Visit 7 – Day 180	n/Nm (%)	26/29 (89.7)	36/36 (100)	0/13 (0.0)	37/40 (92.5)	38/39 (97.4)	0/19 (0.0)	30/36 (83.3)	36/39 (92.3)	0/19 (0.0)
	[95% CI]	[72.6, 97.8]	[90.3, 100]	[0.0, 24.7]	[79.6, 98.4]	[86.5, 99.9]	[0.0, 17.6]	[67.2, 93.6]	[79.1, 98.4]	[0.0, 17.6]
Overall p-value		<.0001			<.0001			<.0001		
Pairwise comparisons	vs. Control	<.0001	<.0001		<.0001	<.0001		<.0001	<.0001	
	vs. Half Dose		0.0837			0.6153			0.2976	
Visit – Day 365	n/Nm (%)	26/29 (89.7)	35/36 (97.2)	0/13 (0.0)	36/40 (90.0)	38/39 (97.4)	0/19 (0.0)	28/35 (80.0)	35/39 (89.7)	0/19 (0.0)
	[95% CI]	[72.6, 97.8]	[85.5, 99.9]	[0.0, 24.7]	[76.3, 97.2]	[86.5, 99.9]	[0.0, 17.6]	[63.1, 91.6]	[75.8, 97.1]	[0.0, 17.6]
Overall p-value		<.0001			<.0001			<.0001		
Pairwise comparisons	vs. Control	<.0001	<.0001		<.0001	<.0001		<.0001	<.0001	
	vs. Half Dose		0.3164			0.3589			0.3303	

N=number of participants of the respective population, trial arm and/or age group as described in the column header; n=number of participants, percentages are based on the number of non-missing observations within each trial arm (Nm).
Two-sided 95% confidence intervals are calculated using the Clopper-Pearson method.
Pairwise test (Fisher exact) performed in case of a significant overall p-value (Fisher-Freeman-Halton).
Seroresponse is defined as $\mu PRNT_{50} \geq 150$ at the respective time point.

Assessment

A total of 95/107 (88.8%, 95% CI: 81.2-94.1) and of 109/114 (95.6%, 95% CI: 90.1-98.6) CHIKV-baseline seronegative participants had an antibody titre above the defined threshold reasonably likely to predict protection (µPRNT50 ≥150) at 28 days post-vaccination with the half dose and full dose, respectively (PP population). Proportion of adult participants with a threshold of at least 150 µPRNT50 at 28 days post-vaccination in the VLA1553 arm (full dose) of the pivotal trial VLA1553-301 supporting the MA was 98.9% (263/266, 95% CI: 96.7-99.8) (PP population). This proportion was 98.8% (248/251, 95% CI: 95.6-99.8) in the VLA1553-321 trial (PP population), that supported the extension of indication to adolescents.

Proportion of seroresponders was already high at 14 days post-vaccination, being 87.6 % (92/105, 95% CI: 79.8-93.2) and 95.6% (109/114, 95% CI: 90.1-98.6) for the half and full dose respectively. This timepoint was not assessed in adults. Only 1.6% (95% CI: 0.4-4.0, n=4/251) and 5.7% (95% CI: 3.2-9.4, n=14/251) of the adult and adolescent participants vaccinated with VLA1553 (PP population) had antibody level ≥150 µPRNT50 at Day 8.

Proportion of seroresponders was sustained up to one year post-vaccination. A total of 90/104 (86.5%, 95% CI: 78.4-92.4) and of 108/114 (94.7%, 95% CI: 88.9-98.0) children had still an antibody titre above the defined threshold reasonably likely to predict protection (µPRNT50 ≥150) with the half dose and full dose, respectively (PP population). At one year post-vaccination, similarly to the children, the proportion of adult and adolescent seroresponders was comparable to the proportion observed at 1 month post-vaccination, i.e. 99.5% (183/184, 95% CI: 97.0-100.0) (PP population, VLA1553-303 trial) and 98.3% (232/236, 95% CI: 39.8-100.0) (PP population, VLA1553-321 trial), respectively.

None of the control group participants had a CHIKV-specific neutralising antibody titre µPRNT50 ≥150 at any timepoint post-vaccination with Nimenrix.

A consistent trend for slightly lower proportion of seroresponders was observed for the half dose as compared to the full dose, at each timepoint post-vaccination. However, 95% CI largely overlapped.

Results stratified by age group (7-11, 3-6 and 1-2 years) were overall comparable, although interpretation is constrained by the limited number of participants in each age group (n ranging between 29 and 40 for the vaccinated groups).

Resulting questions:

None.

Immune response in baseline seronegative participants (PP population) as measured by CHIKV-specific neutralizing antibody titres up to Month 12 post-vaccination

Summaries of GMTs for CHIKV-specific neutralizing antibodies by visit pooled by trial arm and by visit and age group are provided in Table 10 and Table 11, respectively.

CHIKV-specific neutralizing antibodies after vaccination by trial visit pooled by trial arm in the PP population are presented in Figure 4 by overlaying scatter plot over boxplots.

Reverse cumulative distribution curves for CHIKV-specific neutralizing antibodies by visit and by trial arm and age group for the PP population are presented in Figure 5.

Table 10. GMTs for CHIKV-specific titres by visit pooled by trial arm (PP analysis population)

	Statistic	Half Dose (N=107)	Full Dose (N=115)	Control (N=53)
Visit 1 - Day 1				
	n	107	115	53
	GM	10.1	10.0	10.3
	[95% CI]	[9.9, 10.3]	[10.0, 10.0]	[9.9, 10.7]
	SD(log10)	0.04	0.00	0.06
	Mean	10.2	10.0	10.4
	SD	1.74	0.00	2.23
	Median	10.0	10.0	10.0
	Q1 / Q3	10.0 / 10.0	10.0 / 10.0	10.0 / 10.0
	Min / Max	10.0 / 28.0	10.0 / 10.0	10.0 / 23.0
Visit 4 - Day 15				
	n	105	114	49
	GM	1073.6	1944.8	10.2
	[95% CI]	[748.1, 1540.7]	[1506.5, 2510.8]	[9.8, 10.8]
	SD(log10)	0.81	0.60	0.07
	Mean	2463.8	3184.4	10.5
	SD	2423.65	2998.31	3.29
	Median	1693.0	2459.0	10.0
	Q1 / Q3	782.0 / 3822.0	1322.0 / 4363.0	10.0 / 10.0
	Min / Max	10.0 / 14137	10.0 / 22122	10.0 / 33.0
Visit 5 - Day 29				
	n	107	114	52
	GM	1829.3	2843.6	10.3
	[95% CI]	[1280.8, 2612.8]	[2247.1, 3598.5]	[9.9, 10.8]
	SD(log10)	0.81	0.55	0.07
	Mean	3613.1	4353.4	10.5
	SD	2696.60	4588.51	2.78
	Median	3302.0	3547.0	10.0
	Q1 / Q3	1941.0 / 4980.0	2122.0 / 5324.0	10.0 / 10.0
	Min / Max	10.0 / 16016	10.0 / 40725	10.0 / 27.0
Visit 6 - Day 85				
	n	102	114	52
	GM	631.4	1025.9	10.0
	[95% CI]	[463.5, 860.2]	[824.8, 1276.2]	[10.0, 10.0]
	SD(log10)	0.68	0.51	0.00
	Mean	1157.3	1462.6	10.0
	SD	928.61	973.13	0.00
	Median	972.0	1330.0	10.0
	Q1 / Q3	564.0 / 1621.0	793.0 / 2048.0	10.0 / 10.0
	Min / Max	10.0 / 5294	10.0 / 6170	10.0 / 10.0
Visit 7 - Day 180				
	n	105	114	51
	GM	508.5	842.5	10.0
	[95% CI]	[377.1, 685.8]	[689.1, 1030.1]	[10.0, 10.0]
	SD(log10)	0.67	0.47	0.00
	Mean	982.0	1198.6	10.0
	SD	888.98	906.22	0.00
	Median	684.0	944.0	10.0
	Q1 / Q3	366.0 / 1607.0	598.0 / 1496.0	10.0 / 10.0
	Min / Max	10.0 / 4097	10.0 / 4798	10.0 / 10.0

Visit 8 - Day 365				
	n	104	114	51
	GM	794.5	1353.4	10.5
	[95% CI]	[566.8, 1113.7]	[1067.5, 1715.8]	[9.9, 11.0]
	SD(log10)	0.75	0.56	0.08
	Mean	1697.4	2066.4	10.7
	SD	1496.28	1502.15	2.87
	Median	1134.5	1595.5	10.0
	Q1 / Q3	525.0 / 2713.0	961.0 / 3123.0	10.0 / 10.0
	Min / Max	10.0 / 6011	10.0 / 5979	10.0 / 23.0

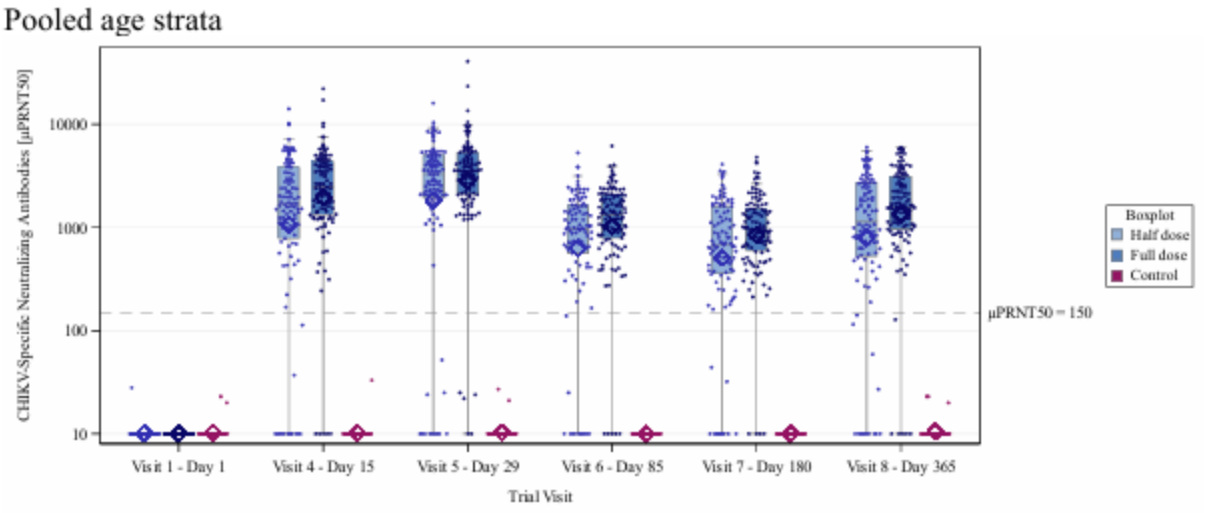
N=number of participants of the respective population, trial arm and/or age group as described in the column header, n=number of participants with valid results.
GM = geometric mean, CI = confidence interval, SD = standard deviation
Titers below the quantitation limit of $\mu PRNT_{50} < 20$ were imputed as 10 for the analysis.

Table 11. GMTs for CHIKV-specific titres by visit by age group and trial arm (PP analysis population)

		7 - 11 years			3 - 6 years			1 - 2 years		
	Statistic	**Half Dose (N=29)**	**Full Dose (N=36)**	**Control (N=13)**	**Half Dose (N=40)**	**Full Dose (N=39)**	**Control (N=20)**	**Half Dose (N=38)**	**Full Dose (N=40)**	**Control (N=20)**
Visit 1 - Day 1										
	n	29	36	13	40	39	20	38	40	20
	GM	10.0	10.0	10.7	10.3	10.0	10.0	10.0	10.0	10.4
	[95% CI]	[10.0, 10.0]	[10.0, 10.0]	[9.3, 12.3]	[9.7, 10.8]	[10.0, 10.0]	[10.0, 10.0]	[10.0, 10.0]	[10.0, 10.0]	[9.6, 11.1]
	SD(log10)	0.00	0.00	0.10	0.07	0.00	0.00	0.00	0.00	0.07
	Mean	10.0	10.0	11.0	10.5	10.0	10.0	10.0	10.0	10.5
	SD	0.00	0.00	3.61	2.85	0.00	0.00	0.00	0.00	2.24
	Median	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
	Q1 / Q3	10.0 / 10.0	10.0 / 10.0	10.0 / 10.0	10.0 / 10.0	10.0 / 10.0	10.0 / 10.0	10.0 / 10.0	10.0 / 10.0	10.0 / 10.0
	Min / Max	10.0 / 10.0	10.0 / 10.0	10.0 / 23.0	10.0 / 28.0	10.0 / 10.0	10.0 / 10.0	10.0 / 10.0	10.0 / 10.0	10.0 / 20.0
Visit 4 - Day 15										
	n	29	36	13	39	39	18	37	39	18
	GM	836.0	2214.5	10.0	1437.4	2275.4	10.0	960.3	1474.5	10.7
	[95% CI]	[443.2, 1576.7]	[1716.3, 2857.2]	[10.0, 10.0]	[836.1, 2471.1]	[1518.3, 3410.3]	[10.0, 10.0]	[462.7, 1993.1]	[808.7, 2688.8]	[9.3, 12.3]
	SD(log10)	0.72	0.33	0.00	0.73	0.54	0.00	0.95	0.80	0.12
	Mean	1570.7	2789.4	10.0	2784.6	3630.1	10.0	2825.7	3103.4	11.3
	SD	1288.85	1710.92	0.00	2638.32	3727.51	0.00	2727.93	3127.96	5.42
	Median	1432.0	2358.5	10.0	1745.0	2649.0	10.0	2126.0	2362.0	10.0
	Q1 / Q3	660.0 / 1979.0	1340.0 / 4168.5	10.0 / 10.0	1115.0 / 4311.0	1259.0 / 4585.0	10.0 / 10.0	728.0 / 4639.0	1322.0 / 4069.0	10.0 / 10.0
	Min / Max	10.0 / 5572	313.0 / 6169	10.0 / 10.0	10.0 / 14137	10.0 / 22122	10.0 / 10.0	10.0 / 10251	10.0 / 17198	10.0 / 33.0
Visit 5 - Day 29										
	n	29	36	13	40	39	20	38	39	19
	GM	1979.1	3443.6	10.0	2170.2	3134.8	10.0	1439.2	2161.7	11.0
	[95% CI]	[941.9, 4158.4]	[2957.0, 4010.3]	[10.0, 10.0]	[1304.9, 3609.2]	[2108.4, 4660.7]	[10.0, 10.0]	[730.0, 2837.1]	[1235.0, 3783.7]	[9.6, 12.5]
	SD(log10)	0.85	0.20	0.00	0.69	0.53	0.00	0.90	0.75	0.12
	Mean	4087.4	3770.2	10.0	3656.9	5234.7	10.0	3204.9	4010.4	11.5
	SD	3375.12	1551.84	0.00	2563.47	7064.22	0.00	2221.61	3041.02	4.53
	Median	3831.0	3557.5	10.0	3166.5	3304.0	10.0	3110.0	3460.0	10.0
	Q1 / Q3	2085.0 / 5055.0	2663.5 / 4511.0	10.0 / 10.0	1908.0 / 5191.5	1872.0 / 5417.0	10.0 / 10.0	1742.0 / 4362.0	1896.0 / 5552.0	10.0 / 10.0
	Min / Max	10.0 / 16016	1224 / 7772	10.0 / 10.0	10.0 / 10426	10.0 / 40725	10.0 / 10.0	10.0 / 8518	10.0 / 13558	10.0 / 27.0

		7 - 11 years			3 - 6 years			1 - 2 years		
	Statistic	Half Dose (N=29)	Full Dose (N=36)	Control (N=13)	Half Dose (N=40)	Full Dose (N=39)	Control (N=20)	Half Dose (N=38)	Full Dose (N=40)	Control (N=20)
Visit 6 - Day 85										
	n	29	35	13	37	39	20	36	40	19
	GM	634.5	1240.8	10.0	763.4	1073.7	10.0	517.5	831.1	10.0
	[95% CI]	[347.7, 1157.7]	[1003.9, 1533.6]	[10.0, 10.0]	[497.7, 1170.9]	[763.8, 1509.2]	[10.0, 10.0]	[277.9, 963.8]	[500.1, 1381.1]	[10.0, 10.0]
	SD(log10)	0.69	0.27	0.00	0.56	0.46	0.00	0.80	0.69	0.00
	Mean	1177.2	1468.0	10.0	1182.8	1477.7	10.0	1115.0	1443.3	10.0
	SD	1116.31	823.65	0.00	884.67	953.63	0.00	826.82	1125.03	0.00
	Median	977.0	1392.0	10.0	946.0	1379.0	10.0	1028.0	1259.0	10.0
	Q1 / Q3	645.0 / 1380.0	916.0 / 2039.0	10.0 / 10.0	607.0 / 1619.0	698.0 / 2107.0	10.0 / 10.0	453.0 / 1858.5	803.5 / 1743.0	10.0 / 10.0
	Min / Max	10.0 / 5294	344.0 / 3580	10.0 / 10.0	10.0 / 3881	10.0 / 4050	10.0 / 10.0	10.0 / 2775	10.0 / 6170	10.0 / 10.0
Visit 7 - Day 180										
	n	29	36	13	40	39	19	36	39	19
	GM	573.8	835.4	10.0	468.0	872.4	10.0	506.0	820.1	10.0
	[95% CI]	[315.9, 1042.1]	[648.3, 1076.7]	[10.0, 10.0]	[313.2, 699.4]	[635.4, 1197.8]	[10.0, 10.0]	[272.4, 940.0]	[517.8, 1298.9]	[10.0, 10.0]
	SD(log10)	0.68	0.33	0.00	0.55	0.42	0.00	0.79	0.62	0.00
	Mean	1041.8	1075.0	10.0	796.8	1180.5	10.0	1139.5	1330.8	10.0
	SD	812.46	765.34	0.00	814.70	872.07	0.00	1006.45	1053.25	0.00
	Median	796.0	909.0	10.0	514.0	920.0	10.0	874.0	1017.0	10.0
	Q1 / Q3	526.0 / 1681.0	431.5 / 1491.0	10.0 / 10.0	309.0 / 964.5	598.0 / 1392.0	10.0 / 10.0	383.5 / 1686.0	665.0 / 1698.0	10.0 / 10.0
	Min / Max	10.0 / 3309	212.0 / 3435	10.0 / 10.0	10.0 / 3547	10.0 / 4202	10.0 / 10.0	10.0 / 4097	10.0 / 4798	10.0 / 10.0
Visit 8 - Day 365										
	n	29	36	13	40	39	19	35	39	19
	GM	693.3	1451.0	10.7	858.6	1382.2	10.0	814.0	1242.6	10.8
	[95% CI]	[376.4, 1277.2]	[1102.4, 1909.9]	[9.3, 12.3]	[524.5, 1405.4]	[975.0, 1959.5]	[10.0, 10.0]	[400.4, 1654.7]	[703.3, 2195.8]	[9.6, 12.2]
	SD(log10)	0.70	0.35	0.10	0.67	0.47	0.00	0.90	0.76	0.10
	Mean	1277.3	1929.0	11.0	1691.6	1956.8	10.0	2052.0	2302.7	11.2
	SD	1060.49	1480.31	3.61	1544.95	1479.97	0.00	1684.74	1553.63	3.66
	Median	930.0	1434.0	10.0	1047.5	1591.0	10.0	1911.0	2011.0	10.0
	Q1 / Q3	539.0 / 1647.0	908.5 / 2453.5	10.0 / 10.0	410.0 / 2747.5	949.0 / 2593.0	10.0 / 10.0	629.0 / 3219.0	1077.0 / 3404.0	10.0 / 10.0
	Min / Max	10.0 / 4442	128.0 / 5792	10.0 / 23.0	10.0 / 5559	10.0 / 5979	10.0 / 10.0	10.0 / 6011	10.0 / 5593	10.0 / 23.0

N=number of participants of the respective population, trial arm and/or age group as described in the column header; n=number of participants with valid results.
GM = geometric mean, CI = confidence interval, SD = standard deviation
Titers below the quantitation limit of $\mu PRNT_{50} < 20$ were imputed as 10 for the analysis.



Note: Circles represent participants' results, diamonds represent the geometric mean. The upper, center and lower line of the box represent the corresponding 75th percentile (Q3), median (Q2) and 25th percentile titer (Q1), respectively. The lower whisker is generally defined as Q1 - 1.5 x IQR, but in case this is lower than the minimum value 10, it is set to 10. The upper whisker is generally defined as Q3 + 1.5 x IQR, but in case it is higher than the maximum value, it is set to the maximum value. IQR = Q3 – Q1 denotes the interquartile range.
µPRNT = Micro Plaque Reduction Neutralization Test.

Figure 3. Overlaying scatter plot over boxplots: CHIKV-specific neutralizing after vaccination by visit pooled by trial arm (PP analysis population)

Assessment

Baseline seronegative participants (PP population)

GMTs for CHIKV-specific neutralising antibody titres at baseline were 10.1 (95% CI: 9.9-10.3) and 10.0 (95% CI: 10.0-10.0) in the VLA1553 half and full dose groups, respectively, i.e. comparable to the GMT observed in the control group (10.3, 95% CI: 9.9-10.7).

GMTs were high at 14 days post-half and -full VLA1553 dose (1073.6 [95%CI: 748.1-1540.7] and 1944.8 [95% CI: 1506.5-2510.8], respectively) and further increase up to 28 days post-vaccination (1829.3 [95% CI: 1280.8-2612.8] and 2843.6 [95% CI: 2247.1-3598.5], respectively).

At 3 month (Day 85) and 6 month (Day 180) post-vaccination, GMTs were decreased in both the half dose group with GMTs of 631.4 (95% CI: 463.5-860.2) and 508.5 (95% CI: 377.1-685.8) respectively and the full dose group with GMTs of 1025.9 (95% CI: 824.8-1276.2) and 842.5 (95% CI: 689.1-1030.1). At one year post-vaccination, GMTs were slightly increased but still with 95% CI overlapping with those of previous Day 85 and Day 180 timepoints (Month 12-GMTs of 794.5 [95% CI: 566.8-1113.7] and 1353.4 [95%CI: 1067.5-1715.8] for the half and the full dose respectively).

A trend for lower immune response is observed after the half dose as compared to the full dose. However, antibody titres still largely overlapped as illustrated in Figure 4.

The kinetics of the response is similar than the kinetics observed for adult participants (PP population, VLA1553-301 trial) and for adolescent population (PP population, VLA1553-321 trial), with a peak of the neutralising antibody response at 28 days post-vaccination followed by a decrease. GMTs observed in adults were overall comparable to those observed in children after the full dose administration, i.e. 3361.6 (95% CI: 2993.8-3774.4) at Day 29, 1083.6 (95% CI: 968.3-1212.6) at Day 85 and 752.1 (95% CI: 665.9-849.5) at Day 180 while GMTs post-half dose tended to be lower at each timepoint. GMTs post-full dose observed in children were also similar to those observed in adolescents with GMTs of 3855.9 (95% CI: 3432.1-4332.0) at Day 29, 1701.8 (95% CI: 1544.8-1874.7) at Day 85 and 1399.0 (95% CI: 1257.0-1557.0) at Day 180.

GMTs in the control group were stable overtime.

The limited number of participants per age group and trial arms preclude any conclusion on potential difference of GMTs between age groups.

Baseline seropositive participants

As indicated earlier, there were a total of 24 participants aged 7- 11 years who were CHIKV seropositive at baseline (n=9 and n=7 in the VLA1553 half- and full- dose, n=8 in the control group). Baseline GMTs were not provided for the whole age group, only data by trial arm are presented. GMTs range from 529.0 to 6837 (min-max) at baseline. No significant increase was noted following VLA1553 vaccination.

No conclusion on GMT comparability can be drawn between baseline GMTs of baseline seropositive 7-11 years children and Day 29 GMTs of baseline seronegative 7-11 years of age children .

Resulting questions:

None.

Fold Increase of CHIKV-Specific Neutralizing Antibody Titers Determined by µPRNT Assay Post-vaccination

A summary of fold increase of CHIKV specific neutralizing antibody titres by visit by age group and trial arm for the PP population is provided in Table 10.

Table 12. Fold increase for CHIKV-specific neutralizing antibody titres by visit by age group and trial arm (PP analysis population)

		7 – 11 years			3 – 6 years			1 – 2 years		
	Statistic	Half Dose (N=29)	Full Dose (N=36)	Control (N=13)	Half Dose (N=40)	Full Dose (N=39)	Control (N=20)	Half Dose (N=38)	Full Dose (N=40)	Control (N=20)
Visit 4 – Day 15										
	n	29	36	13	39	39	18	37	39	18
	GM	83.6	221.4	0.9	140.0	227.5	1.0	96.0	147.5	1.0
	[95% CI]	[44.3, 157.7]	[171.6, 285.7]	[0.8, 1.1]	[80.9, 242.2]	[151.8, 341.0]	[1.0, 1.0]	[46.3, 199.3]	[80.9, 268.9]	[0.9, 1.2]
	SD(log10)	0.72	0.33	0.10	0.73	0.54	0.00	0.95	0.80	0.14
	Mean	157.1	278.9	1.0	277.3	363.0	1.0	282.6	310.3	1.1
	SD	128.89	171.09	0.16	264.86	372.75	0.00	272.79	312.80	0.56
	Median	143.2	235.9	1.0	174.5	264.9	1.0	212.6	236.2	1.0
	Q1 / Q3	66.0 / 197.9	134.0 / 416.9	1.0 / 1.0	111.5 / 431.1	125.9 / 458.5	1.0 / 1.0	72.8 / 463.9	132.2 / 406.9	1.0 / 1.0
	Min / Max	1.0 / 557.2	31.3 / 616.9	0.4 / 1.0	1.0 / 1414	1.0 / 2212	1.0 / 1.0	1.0 / 1025	1.0 / 1720	0.5 / 3.3
Visit 5 – Day 29										
	n	29	36	13	40	39	20	38	39	19
	GM	197.9	344.4	0.9	211.5	313.5	1.0	143.9	216.2	1.1
	[95% CI]	[94.2, 415.8]	[295.7, 401.0]	[0.8, 1.1]	[126.3, 354.2]	[210.8, 466.1]	[1.0, 1.0]	[73.0, 283.7]	[123.5, 378.4]	[0.9, 1.2]
	SD(log10)	0.85	0.20	0.10	0.70	0.53	0.00	0.90	0.75	0.14
	Mean	408.7	377.0	1.0	364.2	523.5	1.0	320.5	401.0	1.1
	SD	337.51	155.18	0.16	258.17	706.42	0.00	222.16	304.10	0.48
	Median	383.1	355.8	1.0	316.7	330.4	1.0	311.0	346.0	1.0
	Q1 / Q3	208.5 / 505.5	266.4 / 451.1	1.0 / 1.0	190.8 / 519.2	187.2 / 541.7	1.0 / 1.0	174.2 / 436.2	189.6 / 555.2	1.0 / 1.0
	Min / Max	1.0 / 1602	122.4 / 777.2	0.4 / 1.0	1.0 / 1043	1.0 / 4073	1.0 / 1.0	1.0 / 851.8	1.0 / 1356	0.5 / 2.7
Visit 6 – Day 85										
	n	29	35	13	37	39	20	36	40	19
	GM	63.4	124.1	0.9	74.2	107.4	1.0	51.7	83.1	1.0
	[95% CI]	[34.8, 115.8]	[100.4, 153.4]	[0.8, 1.1]	[48.3, 114.2]	[76.4, 150.9]	[1.0, 1.0]	[27.8, 96.4]	[50.0, 138.1]	[0.9, 1.0]
	SD(log10)	0.69	0.27	0.10	0.56	0.46	0.00	0.80	0.69	0.07
	Mean	117.7	146.8	1.0	116.7	147.8	1.0	111.5	144.3	1.0
	SD	111.63	82.36	0.16	89.49	95.36	0.00	82.68	112.50	0.11
	Median	97.7	139.2	1.0	94.6	137.9	1.0	102.8	125.9	1.0
	Q1 / Q3	64.5 / 138.0	91.6 / 203.9	1.0 / 1.0	46.3 / 161.9	69.8 / 210.7	1.0 / 1.0	45.3 / 185.9	80.4 / 174.3	1.0 / 1.0
	Min / Max	1.0 / 529.4	34.4 / 358.0	0.4 / 1.0	1.0 / 388.1	1.0 / 405.0	1.0 / 1.0	1.0 / 277.5	1.0 / 617.0	0.5 / 1.0
Visit 7 – Day 180										
	n	29	36	13	40	39	19	36	39	19
	GM	57.4	83.5	0.9	45.6	87.2	1.0	50.6	82.0	1.0
	[95% CI]	[31.6, 104.2]	[64.8, 107.7]	[0.8, 1.1]	[30.4, 68.4]	[63.5, 119.8]	[1.0, 1.0]	[27.2, 94.0]	[51.8, 129.9]	[0.9, 1.0]
	SD(log10)	0.68	0.33	0.10	0.55	0.42	0.00	0.79	0.62	0.07
	Mean	104.2	107.5	1.0	79.0	118.0	1.0	113.9	133.1	1.0
	SD	81.25	76.53	0.16	81.91	87.21	0.00	100.65	105.32	0.11
	Median	79.6	90.9	1.0	51.4	92.0	1.0	87.4	101.7	1.0
	Q1 / Q3	52.6 / 168.1	43.2 / 149.1	1.0 / 1.0	25.0 / 96.5	59.8 / 139.2	1.0 / 1.0	38.4 / 168.6	66.5 / 169.8	1.0 / 1.0
	Min / Max	1.0 / 330.9	21.2 / 343.5	0.4 / 1.0	1.0 / 354.7	1.0 / 420.2	1.0 / 1.0	1.0 / 409.7	1.0 / 479.8	0.5 / 1.0
Visit 8 – Day 365										
	n	29	36	13	40	39	19	35	39	19
	GM	69.3	145.1	1.0	83.7	138.2	1.0	81.4	124.3	1.0
	[95% CI]	[37.6, 127.7]	[110.2, 191.0]	[0.8, 1.2]	[50.8, 137.9]	[97.5, 195.9]	[1.0, 1.0]	[40.0, 165.5]	[70.3, 219.6]	[0.9, 1.2]
	SD(log10)	0.70	0.35	0.15	0.68	0.47	0.00	0.90	0.76	0.13
	Mean	127.7	192.9	1.1	168.5	195.7	1.0	205.2	230.3	1.1
	SD	106.05	148.03	0.40	155.12	148.00	0.00	168.47	155.36	0.39
	Median	93.0	143.4	1.0	104.8	159.1	1.0	191.1	201.1	1.0
	Q1 / Q3	53.9 / 164.7	90.9 / 245.4	1.0 / 1.0	38.9 / 274.8	94.9 / 259.3	1.0 / 1.0	62.9 / 321.9	107.7 / 340.4	1.0 / 1.0
	Min / Max	1.0 / 444.2	12.8 / 579.2	0.4 / 2.3	1.0 / 555.9	1.0 / 597.9	1.0 / 1.0	1.0 / 601.1	1.0 / 559.3	0.5 / 2.3

N=number of participants of the respective population, trial arm and/or age group as described in the column header; n=number of participants with valid results. NC=Not calculable.
GM = geometric mean, CI = confidence interval, SD = standard deviation
Titers below the quantitation limit of $\mu PRNT_{50} < 20$ were imputed as 10 for the analysis.

Assessment

Consistent with GMTs, GM increases peak at 28 days post-vaccination in all 3 age groups, and for both the half- and the full- dose. The fold increases tend to be higher for the full dose as compared to the half dose.

Resulting questions:

None.

Exploratory analysis of natural CHIKV Infections

No indication of natural CHIKV infection was identified in the trial based on the absence of CHIKV-like symptoms in the majority of participants.

A total of 39 participants in VLA1553 arms were identified with >4-fold increase of µPRNT50 from Day 85 post-vaccination. Two participants in the control treatment arm, seropositive at baseline were also identified: 1 participant with >4-fold increase of µPRNT50 from Day 85, and 1 participant at Day 180 against baseline.

Of 41 participants with seroconversion, only one experienced CHIKV-like symptoms accompanied by fever. However, this was considered not representative of a natural CHIKV infection due to the discrepancy between the timing of seroconversion (at Day 180 against baseline; no >4-fold increase between Day 29 and Day 85/180) and symptom onset (headache and fever at Day 52).

Assessment

According to the MAH, most of the participants did not present any CHIK-like symptom during the trial. As a consequence, no PCR was performed to detect wild-type CHIKV and confirmed any infection. Indeed, AESIs (protocol definition) were only reported in 5/119 (4.2%) participants. However, CHIK-Like ARs (regulatory agencies definition) were identified in 7/119 (5.9%) participants in the VLA1553 Half Dose arm and 10/124 (8.1%) participants in the VLA1553 Full Dose arm (see safety section). These participants could have been checked (issue not pursued).

A total of 41 participants seroconverted from Day 85 (n=40) or Day 180 (n=1). In the absence of laboratory confirmation, these participants cannot be considered has having had a natural CHIK infection.

Resulting questions:

None.

Safety results

<u>Overall summary pooled by trial arms</u>

Table 13. Overall Summary of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest (Safety Analysis Population) to Month 12

	Statistic	Half Dose (N=119)	Full Dose (N=124)	Control (N=61)	Total Population (N=304)
Any AE	n (%) Obs	93 (78.2) 352	98 (79.0) 389	48 (78.7) 169	239 (78.6) 910
	[95% CI]	[69.6, 85.2]	[70.8, 85.8]	[66.3, 88.1]	[73.6, 83.1]
Overall p-value		0.9830			
Any related AE	n (%) Obs	35 (29.4) 67	39 (31.5) 72	13 (21.3) 25	87 (28.6) 164
	[95% CI]	[21.4, 38.5]	[23.4, 40.4]	[11.9, 33.7]	[23.6, 34.1]
Overall p-value		0.3544			
Any severe AE	n (%) Obs	6 (5.0) 9	10 (8.1) 11	2 (3.3) 2	18 (5.9) 22
	[95% CI]	[1.9, 10.7]	[3.9, 14.3]	[0.4, 11.3]	[3.5, 9.2]
Overall p-value		0.4146			
Any related severe AE	n (%) Obs	1 (0.8) 1	1 (0.8) 1	0 (0.0) 0	2 (0.7) 2
	[95% CI]	[0.0, 4.6]	[0.0, 4.4]	[0.0, 5.9]	[0.1, 2.4]
Overall p-value		1.0000			
Any serious AE	n (%) Obs	2 (1.7) 2	4 (3.2) 4	1 (1.6) 1	7 (2.3) 7
	[95% CI]	[0.2, 5.9]	[0.9, 8.1]	[0.0, 8.8]	[0.9, 4.7]
Overall p-value		0.8834			
Any related serious AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.0, 3.1]	[0.0, 2.9]	[0.0, 5.9]	[0.0, 1.2]
Overall p-value		NC			
Any AESI (protocol definition)	n (%) Obs	5 (4.2) 12	0 (0.0) 0	0 (0.0) 0	5 (1.6) 12
	[95% CI]	[1.4, 9.5]	[0.0, 2.9]	[0.0, 5.9]	[0.5, 3.8]
Overall p-value		0.0151			
Pairwise comparisons	vs. Control	0.1684	NC		
	vs. Half Dose		0.0270		
Any early onset AESI (protocol definition)	n (%) Obs	3 (2.5) 6	0 (0.0) 0	0 (0.0) 0	3 (1.0) 6
	[95% CI]	[0.5, 7.2]	[0.0, 2.9]	[0.0, 5.9]	[0.2, 2.9]
Overall p-value		0.1627			
Any late onset AESI (protocol definition)	n (%) Obs	2 (1.7) 6	0 (0.0) 0	0 (0.0) 0	2 (0.7) 6
	[95% CI]	[0.2, 5.9]	[0.0, 2.9]	[0.0, 5.9]	[0.1, 2.4]
Overall p-value		0.1922			
Any AESI (protocol definition) adjudicated	n (%)	5 (4.2)	0 (0.0)	0 (0.0)	5 (1.6)
	[95% CI]	[1.4, 9.5]	[0.0, 2.9]	[0.0, 5.9]	[0.5, 3.8]
Overall p-value		0.0151			
Pairwise comparisons	vs. Control	0.1684	NC		
	vs. Half Dose		0.0270		
Any CLAR (AESI by regulatory agencies definition)	n (%) Obs	7 (5.9) 17	10 (8.1) 23	0 (0.0) 0	17 (5.6) 40
	[95% CI]	[2.4, 11.7]	[3.9, 14.3]	[0.0, 5.9]	[3.3, 8.8]
Overall p-value		0.0572			
Any prolonged CLAR (AESI by regulatory agencies definition)	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.0, 3.1]	[0.0, 2.9]	[0.0, 5.9]	[0.0, 1.2]
Overall p-value		NC			

CI=confidence interval; n=number of participants with event, percentages are based on N; NC=Not calculable; Obs=number of events.
AEs are counted as related if causality is 'probably related' or 'possibly related' or missing. AEs are counted as severe if standard toxicity grade is 'Grade 3' or 'Grade 4' or missing.
Obs for AESI contribute to the symptom count of the AESI case.

Early onset AESI are AESI that started 2 to 21 days post-vaccination with a duration of >=3 days. Late onset AESI are AESI that started after 22 days post-vaccination with a duration of >=3 days.
Two-sided 95% confidence intervals are calculated using the Clopper-Pearson method. Pairwise test (Fisher exact) performed in case of a significant overall p-value (Fisher-Freeman-Halton).

Table 14. Overall Summary of Solicited Adverse Events (Safety Analysis Population)

	Statistic	Half Dose (N=119)	Full Dose (N=124)	Control (N=61)	Total Population (N=304)
Any solicited AE	n (%) Obs	41 (34.5) 91	47 (37.9) 99	16 (26.2) 28	104 (34.2) 218
	[95% CI]	[26.0, 43.7]	[29.3, 47.1]	[15.8, 39.1]	[28.9, 39.8]
Overall p-value		0.2931			
Any related solicited AE	n (%) Obs	34 (28.6) 66	39 (31.5) 72	13 (21.3) 24	86 (28.3) 162
	[95% CI]	[20.7, 37.6]	[23.4, 40.4]	[11.9, 33.7]	[23.3, 33.7]
Overall p-value		0.3611			
Any severe solicited AE	n (%) Obs	2 (1.7) 2	4 (3.2) 4	0 (0.0) 0	6 (2.0) 6
	[95% CI]	[0.2, 5.9]	[0.9, 8.1]	[0.0, 5.9]	[0.7, 4.2]
Overall p-value		0.4452			
Any related severe solicited AE	n (%) Obs	1 (0.8) 1	1 (0.8) 1	0 (0.0) 0	2 (0.7) 2
	[95% CI]	[0.0, 4.6]	[0.0, 4.4]	[0.0, 5.9]	[0.1, 2.4]
Overall p-value		1.0000			
Any serious solicited AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.0, 3.1]	[0.0, 2.9]	[0.0, 5.9]	[0.0, 1.2]
Overall p-value		NC			
Any related serious solicited AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.0, 3.1]	[0.0, 2.9]	[0.0, 5.9]	[0.0, 1.2]
Overall p-value		NC			
Any solicited injection site AE	n (%) Obs	21 (17.6) 32	16 (12.9) 25	8 (13.1) 15	45 (14.8) 72
	[95% CI]	[11.3, 25.7]	[7.6, 20.1]	[5.8, 24.2]	[11.0, 19.3]
Overall p-value		0.5751			
Any related solicited injection site AE	n (%) Obs	21 (17.6) 32	16 (12.9) 25	8 (13.1) 15	45 (14.8) 72
	[95% CI]	[11.3, 25.7]	[7.6, 20.1]	[5.8, 24.2]	[11.0, 19.3]
Overall p-value		0.5751			
Any severe solicited injection site AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.0, 3.1]	[0.0, 2.9]	[0.0, 5.9]	[0.0, 1.2]
Overall p-value		NC			
Any related severe solicited injection site AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.0, 3.1]	[0.0, 2.9]	[0.0, 5.9]	[0.0, 1.2]
Overall p-value		NC			
Any solicited systemic AE	n (%) Obs	30 (25.2) 59	42 (33.9) 74	10 (16.4) 13	82 (27.0) 146
	[95% CI]	[17.7, 34.0]	[25.6, 42.9]	[8.2, 28.1]	[22.1, 32.3]
Overall p-value		0.0352			
Pairwise comparisons	vs. Control	0.1916	0.0148		
	vs. Half Dose		0.1607		
Any related solicited systemic AE	n (%) Obs	22 (18.5) 34	31 (25.0) 47	7 (11.5) 9	60 (19.7) 90
	[95% CI]	[12.0, 26.6]	[17.7, 33.6]	[4.7, 22.2]	[15.4, 24.7]
Overall p-value		0.0923			
Any severe solicited systemic AE	n (%) Obs	2 (1.7) 2	4 (3.2) 4	0 (0.0) 0	6 (2.0) 6
	[95% CI]	[0.2, 5.9]	[0.9, 8.1]	[0.0, 5.9]	[0.7, 4.2]
Overall p-value		0.4452			
Any related severe solicited systemic AE	n (%) Obs	1 (0.8) 1	1 (0.8) 1	0 (0.0) 0	2 (0.7) 2
	[95% CI]	[0.0, 4.6]	[0.0, 4.4]	[0.0, 5.9]	[0.1, 2.4]
Overall p-value		1.0000			
Any solicited AE ongoing after Day 15	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.0, 3.1]	[0.0, 2.9]	[0.0, 5.9]	[0.0, 1.2]
Overall p-value		NC			

CI=confidence interval; n=number of participants with event, percentages are based on N; NC=Not calculable; Obs=number of events.
This table includes all solicited AEs documented in the database.
AEs are counted as related if causality is 'probably related' or 'possibly related' or missing. AEs are counted as severe if standard toxicity grade is 'Grade 3' or 'Grade 4' or missing.
Two-sided 95% confidence intervals are calculated using the Clopper-Pearson method. Pairwise test (Fisher exact) performed in case of a significant overall p-value (Fisher-Freeman-Halton).

Table 15. Overall Summary of Unsolicited Adverse Events to Month 12 (Safety Analysis Population)

	Statistic	Half Dose (N=119)	Full Dose (N=124)	Control (N=61)	Total Population (N=304)
Any unsolicited AE	n (%) Obs	84 (70.6) 261	88 (71.0) 290	45 (73.8) 141	217 (71.4) 692
	[95% CI]	[61.5, 78.6]	[62.1, 78.8]	[60.9, 84.2]	[65.9, 76.4]
Overall p-value		0.9184			
Any related unsolicited AE	n (%) Obs	1 (0.8) 1	0 (0.0) 0	1 (1.6) 1	2 (0.7) 2
	[95% CI]	[0.0, 4.6]	[0.0, 2.9]	[0.0, 8.8]	[0.1, 2.4]
Overall p-value		0.3498			
Any severe unsolicited AE	n (%) Obs	6 (5.0) 7	6 (4.8) 7	2 (3.3) 2	14 (4.6) 16
	[95% CI]	[1.9, 10.7]	[1.8, 10.2]	[0.4, 11.3]	[2.5, 7.6]
Overall p-value		0.9398			
Any related severe unsolicited AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.0, 3.1]	[0.0, 2.9]	[0.0, 5.9]	[0.0, 1.2]
Overall p-value		NC			
Any serious unsolicited AE	n (%) Obs	2 (1.7) 2	4 (3.2) 4	1 (1.6) 1	7 (2.3) 7
	[95% CI]	[0.2, 5.9]	[0.9, 8.1]	[0.0, 8.8]	[0.9, 4.7]
Overall p-value		0.8834			
Any related serious unsolicited AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.0, 3.1]	[0.0, 2.9]	[0.0, 5.9]	[0.0, 1.2]
Overall p-value		NC			

CI=confidence interval; n=number of participants with event, percentages are based on N; NC=Not calculable; Obs=number of events.
This table includes all unsolicited AEs documented in the database.
AEs are counted as related if causality is 'probably related' or 'possibly related' or missing. AEs are counted as severe if standard toxicity grade is 'Grade 3' or 'Grade 4' or missing.
Two-sided 95% confidence intervals are calculated using the Clopper-Pearson method. Pairwise test (Fisher exact) performed in case of a significant overall p-value (Fisher-Freeman-Halton).

Assessment

Within 14 days of vaccination, solicited AEs were reported at a higher frequency in the VLA1553 arms than in the control arm (41/119 [34.5%] participants in the VLA1553 Half Dose, 47/124 [37.9%] participants in the VLA1553 Full Dose, and 16/61 [26.2%] participants in the control, difference not significant). There were no serious solicited AE.

Solicited injection site AEs were reported more frequently in the VLA1553 Half Dose arm (17.6%) than in the VLA1553 Full Dose (12.9%) and control arms (13.1%) (not statistically different) (all considered related). None were severe.

Solicited systemic AEs were more reported in the VLA1553 full dose (33.9%), vs. the half dose (25.2%), vs. the control (16.4%) (difference vs. control significant). Similarly, related solicited systemic AEs were more reported in the VLA1553 full dose (25%), vs. the half dose (18.5%), vs. the control (11.5%) (not statistically significant). Two and 4 participants in the VLA1553 Half Dose and Full Dose arms, respectively, experienced at least one severe solicited systemic AE (vs. none in the control). Of these, one case in each VLA1553 arm (0.8% each) was considered related to the vaccination by the Investigator, both being brief AEs of fever that were severe for 1 day.

Up to Month 12, unsolicited AEs were reported at a similar frequency in the three trial arms (70.6%, 71.0%, and 73.8% participants in the VLA1553 Half Dose, Full Dose, and control arms, respectively). One participant in the VLA1553 Half Dose and one participant in the control arm experienced at least one unsolicited AE that was considered related to the vaccination (events of miliaria and dermatitis, respectively). Most unsolicited AEs after vaccination were graded as mild or moderate. In total, 6/119 (5.0%), 6/124 (4.8%), and 2/61 (3.3%) participants in the VLA1553 Half Dose, VLA1553 Full Dose and control arms, respectively, experienced at least one severe unsolicited AE (see below for details).

There were 2/119 (1.7%), 4/124 (3.2%), and 1/61 (1.6%) participants in the VLA1553 Half Dose, VLA1553 Full Dose and control arms, respectively, who experienced at least one serious unsolicited AE (see below for details).

No related unsolicited severe AEs or SAEs were reported.

AESI (protocol definition) were reported in 5/119 (4.2%) participants in the VLA1553 Half Dose arm (reporting 12 AESI symptoms), including 3 participants reporting 6 early onset AESI symptoms starting within 2 to 21 days post-vaccination (i.e. Day 3 – Day 22) and 2 participants reporting 6 late onset AESI symptoms starting 22 days post-vaccination (i.e. from Day 23). Each case included symptoms that were considered related to VLA1553 (see below for details). Up to Month 12, all protocol definition AESI were resolved. No AESI were reported in the VLA1553 Full Dose and control arms.

CLAR (regulatory agencies definition) were identified in 7/119 (5.9%) participants in the VLA1553 Half Dose arm (reporting 17 CLAR symptoms) and 10/124 (8.1%) participants in the VLA1553 Full Dose arm (reporting 23 CLAR symptoms) (see below for details). No CLAR were identified in the control arm.

Resulting questions:

None.

Analysis per age category

2.3.2.1.1. Solicited AEs

Table 16. Overall Summary of Solicited Adverse Events by Age Group and Trial Arm (Safety Analysis Population)

		7 - 11 years			3 - 6 years			1 - 2 years			
	Statistic	Half Dose (N=40)	Full Dose (N=43)	Control (N=21)	Half Dose (N=40)	Full Dose (N=40)	Control (N=20)	Half Dose (N=39)	Full Dose (N=41)	Control (N=20)	Total Population (N=304)
Any solicited AE	n (%) Obs	17 (42.5) 44	20 (46.5) 41	9 (42.9) 17	14 (35.0) 27	12 (30.0) 31	4 (20.0) 6	10 (25.6) 20	15 (36.6) 27	3 (15.0) 5	104 (34.2) 218
	[95% CI]	[27.0, 59.1]	[31.2, 62.3]	[21.8, 66.0]	[20.6, 51.7]	[16.6, 46.5]	[5.7, 43.7]	[13.0, 42.1]	[22.1, 53.1]	[3.2, 37.9]	[28.9, 39.8]
Overall p-value		0.9665			0.5370			0.2161			
Any related solicited AE	n (%) Obs	15 (37.5) 37	15 (34.9) 33	9 (42.9) 17	12 (30.0) 20	12 (30.0) 24	3 (15.0) 4	7 (17.9) 9	12 (29.3) 15	1 (5.0) 3	86 (28.3) 162
	[95% CI]	[22.7, 54.2]	[21.0, 50.9]	[21.8, 66.0]	[16.6, 46.5]	[16.6, 46.5]	[3.2, 37.9]	[7.5, 33.5]	[16.1, 45.5]	[0.1, 24.9]	[23.3, 33.7]
Overall p-value		0.8070			0.4516			0.0758			
Any severe solicited AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	3 (7.5) 3	0 (0.0) 0	2 (5.1) 2	1 (2.4) 1	0 (0.0) 0	6 (2.0) 6
	[95% CI]	[0.0, 8.8]	[0.0, 8.2]	[0.0, 16.1]	[0.0, 8.8]	[1.6, 20.4]	[0.0, 16.8]	[0.6, 17.3]	[0.1, 12.9]	[0.0, 16.8]	[0.7, 4.2]
Overall p-value		NC			0.2233			0.6045			
Any related severe solicited AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (2.6) 1	1 (2.4) 1	0 (0.0) 0	2 (0.7) 2
	[95% CI]	[0.0, 8.8]	[0.0, 8.2]	[0.0, 16.1]	[0.0, 8.8]	[0.0, 8.8]	[0.0, 16.8]	[0.1, 13.5]	[0.1, 12.9]	[0.0, 16.8]	[0.1, 2.4]
Overall p-value		NC			NC			1.0000			
Any serious solicited AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.0, 8.8]	[0.0, 8.2]	[0.0, 16.1]	[0.0, 8.8]	[0.0, 8.8]	[0.0, 16.8]	[0.0, 9.0]	[0.0, 8.6]	[0.0, 16.8]	[0.0, 1.2]
Overall p-value		NC			NC			NC			
Any related serious solicited AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.0, 8.8]	[0.0, 8.2]	[0.0, 16.1]	[0.0, 8.8]	[0.0, 8.8]	[0.0, 16.8]	[0.0, 9.0]	[0.0, 8.6]	[0.0, 16.8]	[0.0, 1.2]
Overall p-value		NC			NC			NC			
Any solicited injection site AE	n (%) Obs	12 (30.0) 21	8 (18.6) 13	7 (33.3) 13	6 (15.0) 8	7 (17.5) 11	0 (0.0) 0	3 (7.7) 3	1 (2.4) 1	1 (5.0) 2	45 (14.8) 72
	[95% CI]	[16.6, 46.5]	[8.4, 33.4]	[14.6, 57.0]	[5.7, 29.8]	[7.3, 32.8]	[0.0, 16.8]	[1.6, 20.9]	[0.1, 12.9]	[0.1, 24.9]	[11.0, 19.3]
Overall p-value		0.3375			0.1622			0.6232			
Any related solicited injection site AE	n (%) Obs	12 (30.0) 21	8 (18.6) 13	7 (33.3) 13	6 (15.0) 8	7 (17.5) 11	0 (0.0) 0	3 (7.7) 3	1 (2.4) 1	1 (5.0) 2	45 (14.8) 72
	[95% CI]	[16.6, 46.5]	[8.4, 33.4]	[14.6, 57.0]	[5.7, 29.8]	[7.3, 32.8]	[0.0, 16.8]	[1.6, 20.9]	[0.1, 12.9]	[0.1, 24.9]	[11.0, 19.3]
Overall p-value		0.3375			0.1622			0.6232			
Any severe solicited injection site AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.0, 8.8]	[0.0, 8.2]	[0.0, 16.1]	[0.0, 8.8]	[0.0, 8.8]	[0.0, 16.8]	[0.0, 9.0]	[0.0, 8.6]	[0.0, 16.8]	[0.0, 1.2]
Overall p-value		NC			NC			NC			
Any related severe solicited injection site AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.0, 8.8]	[0.0, 8.2]	[0.0, 16.1]	[0.0, 8.8]	[0.0, 8.8]	[0.0, 16.8]	[0.0, 9.0]	[0.0, 8.6]	[0.0, 16.8]	[0.0, 1.2]
Overall p-value		NC			NC			NC			

Any solicited systemic AE Overall p-value	n (%) Obs [95% CI]	11 (27.5) 23 [14.6, 43.9] 0.1200	17 (39.5) 28 [25.0, 55.6]	3 (14.3) 4 [3.0, 36.3]	10 (25.0) 19 [12.7, 41.2] 0.9099	10 (25.0) 20 [12.7, 41.2]	4 (20.0) 6 [5.7, 43.7]	9 (23.1) 17 [11.1, 39.3] 0.1985	15 (36.6) 26 [22.1, 53.1]	3 (15.0) 3 [3.2, 37.9]	82 (27.0) 146 [22.1, 32.3]
Any related solicited systemic AE Overall p-value	n (%) Obs [95% CI]	9 (22.5) 16 [10.8, 38.5] 0.7428	10 (23.3) 20 [11.8, 38.6]	3 (14.3) 4 [3.0, 36.3]	8 (20.0) 12 [9.1, 35.6] 0.8544	9 (22.5) 13 [10.8, 38.5]	3 (15.0) 4 [3.2, 37.9]	5 (12.8) 6 [4.3, 27.4] 0.0523	12 (29.3) 14 [16.1, 45.5]	1 (5.0) 1 [0.1, 24.9]	60 (19.7) 90 [15.4, 24.7]
Any severe solicited systemic AE Overall p-value	n (%) Obs [95% CI]	0 (0.0) 0 [0.0, 8.8] NC	0 (0.0) 0 [0.0, 8.2]	0 (0.0) 0 [0.0, 16.1]	0 (0.0) 0 [0.0, 8.8] 0.2233	3 (7.5) 3 [1.6, 20.4]	0 (0.0) 0 [0.0, 16.8]	2 (5.1) 2 [0.6, 17.3] 0.6045	1 (2.4) 1 [0.1, 12.9]	0 (0.0) 0 [0.0, 16.8]	6 (2.0) 6 [0.7, 4.2]
Any related severe solicited systemic AE Overall p-value	n (%) Obs [95% CI]	0 (0.0) 0 [0.0, 8.8] NC	0 (0.0) 0 [0.0, 8.2]	0 (0.0) 0 [0.0, 16.1]	0 (0.0) 0 [0.0, 8.8] NC	0 (0.0) 0 [0.0, 8.8]	0 (0.0) 0 [0.0, 16.8]	1 (2.6) 1 [0.1, 13.5] 1.0000	1 (2.4) 1 [0.1, 12.9]	0 (0.0) 0 [0.0, 16.8]	2 (0.7) 2 [0.1, 2.4]
Any solicited AE ongoing after Day 15 Overall p-value	n (%) Obs [95% CI]	0 (0.0) 0 [0.0, 8.8] NC	0 (0.0) 0 [0.0, 8.2]	0 (0.0) 0 [0.0, 16.1]	0 (0.0) 0 [0.0, 8.8] NC	0 (0.0) 0 [0.0, 8.8]	0 (0.0) 0 [0.0, 16.8]	0 (0.0) 0 [0.0, 9.0] NC	0 (0.0) 0 [0.0, 8.6]	0 (0.0) 0 [0.0, 16.8]	0 (0.0) 0 [0.0, 1.2]

CI=confidence interval; n=number of participants with event, percentages are based on N; NC=Not calculable; Obs=number of events.
This table includes all solicited AEs documented in the database.
AEs are counted as related if causality is 'probably related' or 'possibly related' or missing. AEs are counted as severe if standard toxicity grade is 'Grade 3' or 'Grade 4' or missing.
Two-sided 95% confidence intervals are calculated using the Clopper-Pearson method. Pairwise test (Fisher exact) performed in case of a significant overall p-value (Fisher-Freeman-Halton).

Assessment

Within 14 days of vaccination, solicited AEs were reported at a higher frequency in the VLA1553 arms than in the control arm (41/119 [34.5%] participants in the VLA1553 Half Dose, 47/124 [37.9%] participants in the VLA1553 Full Dose, and 16/61 [26.2%] participants in the control, without statistically significant differences between trial arms and age groups:

- 7-11 years: VLA1553 Half Dose 17/40 [42.5%], VLA1553 Full Dose 20/43 [46.5%], control 9/21 [42.9%];

- 3-6 years: VLA1553 Half Dose 14/40 [35.0%], VLA1553 Full Dose 12/40 [30.0%], control 4/20 [20.0%];

- 1-2 years: VLA1553 Half Dose 10/39 [25.6%], VLA1553 Full Dose 15/41 [36.6%], control 3/20 [15.0%]).

No statistically significant differences on AEs distribution across trial arms (Half Dose, Full Dose, and control) were observed depending of the baseline serostatus:

- Solicited AEs in participants who were µPRNT seronegative at baseline (7-11 years only) were as follows: VLA1553 Half Dose 13/31 (41.9%), VLA1553 Full Dose 16/36 (44.4%), and control 7/13 (53.8%).

- Solicited AEs in participants who were µPRNT seropositive at baseline (7-11 years only) were reported as follows: VLA1553 Half Dose 4/9 (44.4%), VLA1553 Full Dose 4/7 (57.1%), and control 2/8 (25.0%).

Resulting questions:

None.

2.3.2.1.1.1. Solicited injection site AEs

Table 17. Solicited Injection Site Adverse Events Overall and by Symptom (Safety Analysis Population)

		7 - 11 years			3 - 6 years			1 - 2 years			
	Statistic	Half Dose (N=40)	Full Dose (N=43)	Control (N=21)	Half Dose (N=40)	Full Dose (N=40)	Control (N=20)	Half Dose (N=39)	Full Dose (N=41)	Control (N=20)	Total Population (N=304)
Any injection site AE											
	n (%) Obs	12 (30.0) 21	8 (18.6) 13	7 (33.3) 13	6 (15.0) 8	7 (17.5) 11	0 (0.0) 0	3 (7.7) 3	1 (2.4) 1	1 (5.0) 2	45 (14.8) 72
	[95% CI]	[16.6, 46.5]	[8.4, 33.4]	[14.6, 57.0]	[5.7, 29.8]	[7.3, 32.8]	[0.0, 16.8]	[1.6, 20.9]	[0.1, 12.9]	[0.1, 24.9]	[11.0, 19.3]
Overall p-value		0.3375			0.1622			0.6232			
Injection Site Pain	n (%)	9 (22.5)	3 (7.0)	5 (23.8)	2 (5.0)	5 (12.5)	0 (0.0)	2 (5.1)	0 (0.0)	0 (0.0)	26 (8.6)
	[95% CI]	[10.8, 38.5]	[1.5, 19.1]	[8.2, 47.2]	[0.6, 16.9]	[4.2, 26.8]	[0.0, 16.8]	[0.6, 17.3]	[0.0, 8.6]	[0.0, 16.8]	[5.7, 12.3]
Injection Site Tenderness	n (%)	9 (22.5)	8 (18.6)	5 (23.8)	4 (10.0)	5 (12.5)	0 (0.0)	0 (0.0)	1 (2.4)	1 (5.0)	33 (10.9)
	[95% CI]	[10.8, 38.5]	[8.4, 33.4]	[8.2, 47.2]	[2.8, 23.7]	[4.2, 26.8]	[0.0, 16.8]	[0.0, 9.0]	[0.1, 12.9]	[0.1, 24.9]	[7.6, 14.9]
Injection Site Pain/Tenderness Pooled	n (%)	12 (30.0)	8 (18.6)	6 (28.6)	5 (12.5)	7 (17.5)	0 (0.0)	2 (5.1)	1 (2.4)	1 (5.0)	42 (13.8)
	[95% CI]	[16.6, 46.5]	[8.4, 33.4]	[11.3, 52.2]	[4.2, 26.8]	[7.3, 32.8]	[0.0, 16.8]	[0.6, 17.3]	[0.1, 12.9]	[0.1, 24.9]	[10.1, 18.2]
Injection Site Erythema/Redness	n (%)	0 (0.0)	0 (0.0)	2 (9.5)	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)
	[95% CI]	[0.0, 8.8]	[0.0, 8.2]	[1.2, 30.4]	[0.1, 13.2]	[0.0, 8.8]	[0.0, 16.8]	[0.0, 9.0]	[0.0, 8.6]	[0.0, 16.8]	[0.2, 2.9]
Injection Site Swelling	n (%)	2 (5.0)	2 (4.7)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	6 (2.0)
	[95% CI]	[0.6, 16.9]	[0.6, 15.8]	[0.1, 23.8]	[0.0, 8.8]	[0.0, 8.8]	[0.0, 16.8]	[0.1, 13.5]	[0.0, 8.6]	[0.0, 16.8]	[0.7, 4.2]
Injection Site Induration/Hardening	n (%)	1 (2.5)	0 (0.0)	0 (0.0)	1 (2.5)	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	4 (1.3)
	[95% CI]	[0.1, 13.2]	[0.0, 8.2]	[0.0, 16.1]	[0.1, 13.2]	[0.1, 13.2]	[0.0, 16.8]	[0.0, 9.0]	[0.0, 8.6]	[0.1, 24.9]	[0.4, 3.3]

CI=confidence interval; n=number of participants with event, percentages are based on N; NC=Not calculable; Obs=number of events.
Solicited AEs are documented within 14 days after vaccination. Symptoms injection site pain and tenderness pooled in accordance with US FDA.
Two-sided 95% confidence intervals are calculated using the Clopper-Pearson method. Pairwise test (Fisher exact) performed in case of a significant overall p-value

Assessment

Solicited injection site AEs were reported more frequently in the VLA1553 Half Dose arm (21/119 [17.6%] participants) than in the VLA1553 Full Dose (16/124 [12.9%] participants) and control arms (8/61 [13.1%] participants) (not statistically different).

Although there were no statistically significant differences, the older age group had numerically higher frequencies of solicited injection site AEs in each arm (7-11 years: VLA1553 Half Dose 12/40 [30.0%], VLA1553 Full Dose 8/43 [18.6%], and control 7/21 [33.3%]; 3-6 years: VLA1553 Half Dose 6/40 [15.0%], VLA1553 Full Dose 7/40 [17.5%], and control 0/20 [0.0%]; 1-2 years: VLA1553 Half Dose 3/39 [7.7%], VLA1553 Full Dose 1/41 [2.4%], and control 1/20 [5.0%]).

All solicited injection site AEs were considered related to trial treatment (per protocol). Regarding severity, all solicited injection site AEs were mild (40/304 [13.2%] participants) or moderate (8/304 [2.6%] participants).

Overall, the most common solicited injection site AEs were pain combined with tenderness (42/304 [13.8%]), tenderness (33/304 [10.9%]), pain (26/304 [8.6%]), swelling (6/304 [2.0%]), induration/hardening (4/304 [1.3%]), and erythema/redness (3/304 [1.0%]).

Solicited injection site AEs were transient and resolved within a few days. Mean duration of solicited injection site AEs ranged from 1.0 day (erythema/redness) to 1.7 days (tenderness).

No statistically significant differences on solicited injection site AE distribution across trial arms (Half Dose, Full Dose, and control) were observed depending of baseline serostatus:

- Solicited injection site AEs in participants who were µPRNT seronegative at baseline (7-11 years only) were as follows: VLA1553 Half Dose 8/31 (25.8%), VLA1553 Full Dose 6/36 (16.7%), and control 6/13 (46.2%).

- Solicited injection site AEs in participants who were µPRNT seropositive at baseline (7-11 years only) were reported as follows: VLA1553 Half Dose 4/9 (44.4%), VLA1553 Full Dose 2/7 (28.6%), and control 1/8 (12.5%).

Resulting questions:

None.

2.3.2.1.1.2. Solicited systemic AEs

Table 18. Solicited Systemic Adverse Events Overall and by Symptom (Safety Analysis Population)

		7 - 11 years			3 - 6 years			1 - 2 years			
	Statistic	Half Dose (N=40)	Full Dose (N=43)	Control (N=21)	Half Dose (N=40)	Full Dose (N=40)	Control (N=20)	Half Dose (N=39)	Full Dose (N=41)	Control (N=20)	Total Population (N=304)
Any systemic AE											
	n (%) Obs [95% CI]	11 (27.5) 23 [14.6, 43.9]	17 (39.5) 28 [25.0, 55.6]	3 (14.3) 4 [3.0, 36.3]	10 (25.0) 19 [12.7, 41.2]	10 (25.0) 20 [12.7, 41.2]	4 (20.0) 6 [5.7, 43.7]	9 (23.1) 17 [11.1, 39.3]	15 (36.6) 26 [22.1, 53.1]	3 (15.0) 3 [3.2, 37.9]	82 (27.0) 146 [22.1, 32.3]
Overall p-value		0.1200			0.9099			0.1985			
Fever	n (%) [95% CI]	5 (12.5) [4.2, 26.8]	5 (11.6) [3.9, 25.1]	0 (0.0) [0.0, 16.1]	5 (12.5) [4.2, 26.8]	6 (15.0) [5.7, 29.8]	1 (5.0) [0.1, 24.9]	8 (20.5) [9.3, 36.5]	7 (17.1) [7.2, 32.1]	1 (5.0) [0.1, 24.9]	38 (12.5) [9.0, 16.8]
Nausea	n (%) [95% CI]	3 (7.5) [1.6, 20.4]	2 (4.7) [0.6, 15.8]	0 (0.0) [0.0, 16.1]	3 (7.5) [1.6, 20.4]	0 (0.0) [0.0, 8.8]	0 (0.0) [0.0, 16.8]	2 (5.1) [0.6, 17.3]	0 (0.0) [0.0, 8.6]	0 (0.0) [0.0, 16.8]	10 (3.3) [1.6, 6.0]
Vomiting	n (%) [95% CI]	0 (0.0) [0.0, 8.8]	3 (7.0) [1.5, 19.1]	0 (0.0) [0.0, 16.1]	2 (5.0) [0.6, 16.9]	4 (10.0) [2.8, 23.7]	0 (0.0) [0.0, 16.8]	3 (7.7) [1.6, 20.9]	2 (4.9) [0.6, 16.5]	1 (5.0) [0.1, 24.9]	15 (4.9) [2.8, 8.0]
Headache	n (%) [95% CI]	8 (20.0) [9.1, 35.6]	12 (27.9) [15.3, 43.7]	3 (14.3) [3.0, 36.3]	3 (7.5) [1.6, 20.4]	6 (15.0) [5.7, 29.8]	3 (15.0) [3.2, 37.9]	N/A	N/A	N/A	35 (11.5) [8.2, 15.6]
Fatigue	n (%) [95% CI]	1 (2.5) [0.1, 13.2]	0 (0.0) [0.0, 8.2]	1 (4.8) [0.1, 23.8]	2 (5.0) [0.6, 16.9]	2 (5.0) [0.6, 16.9]	0 (0.0) [0.0, 16.8]	N/A	N/A	N/A	6 (2.0) [0.7, 4.2]
Muscle Pain	n (%) [95% CI]	4 (10.0) [2.8, 23.7]	4 (9.3) [2.6, 22.1]	0 (0.0) [0.0, 16.1]	2 (5.0) [0.6, 16.9]	0 (0.0) [0.0, 8.8]	1 (5.0) [0.1, 24.9]	N/A	N/A	N/A	11 (3.6) [1.8, 6.4]
Joint Pain	n (%) [95% CI]	2 (5.0) [0.6, 16.9]	1 (2.3) [0.1, 12.3]	0 (0.0) [0.0, 16.1]	0 (0.0) [0.0, 8.8]	2 (5.0) [0.6, 16.9]	0 (0.0) [0.0, 16.8]	N/A	N/A	N/A	5 (1.6) [0.5, 3.8]
Inconsolable or excessive crying	n (%) [95% CI]	N/A	N/A	N/A	N/A	N/A	N/A	1 (2.6) [0.1, 13.5]	4 (9.8) [2.7, 23.1]	0 (0.0) [0.0, 16.8]	5 (1.6) [0.5, 3.8]
Disturbed sleep	n (%) [95% CI]	N/A	N/A	N/A	N/A	N/A	N/A	0 (0.0) [0.0, 9.0]	2 (4.9) [0.6, 16.5]	0 (0.0) [0.0, 16.8]	2 (0.7) [0.1, 2.4]
Loss of appetite	n (%) [95% CI]	N/A	N/A	N/A	N/A	N/A	N/A	3 (7.7) [1.6, 20.9]	9 (22.0) [10.6, 37.6]	1 (5.0) [0.1, 24.9]	13 (4.3) [2.3, 7.2]
Drowsiness	n (%) [95% CI]	N/A	N/A	N/A	N/A	N/A	N/A	0 (0.0) [0.0, 9.0]	1 (2.4) [0.1, 12.9]	0 (0.0) [0.0, 16.8]	1 (0.3) [0.0, 1.8]
Rash	n (%) [95% CI]	0 (0.0) [0.0, 8.8]	1 (2.3) [0.1, 12.3]	0 (0.0) [0.0, 16.1]	2 (5.0) [0.6, 16.9]	0 (0.0) [0.0, 8.8]	1 (5.0) [0.1, 24.9]	0 (0.0) [0.0, 9.0]	1 (2.4) [0.1, 12.9]	0 (0.0) [0.0, 16.8]	5 (1.6) [0.5, 3.8]

CI=confidence interval; n=number of participants with event, percentages are based on N; N/A=Not applicable (data for these AEs were not collected in these age groups); NC=Not calculable; Obs=number of events.
Solicited AEs are documented within 14 days after vaccination.
Two-sided 95% confidence intervals are calculated using the Clopper-Pearson method. Pairwise test (Fisher exact) performed in case of a significant overall p-value

Assessment

Solicited systemic AEs were more reported in the VLA1553 full dose (42/124 [33.9%] participants), vs. the half dose (30/119 [25.2%] participants), vs. the control (16.4%) (10/61 [16.4%] participants) (difference vs. control significant). There were no clear differences between age groups (7-11 years: VLA1553 Half Dose 11/40 [27.5%], VLA1553 Full Dose 17/43 [39.5%], control 3/21 [14.3%]; 3-6 years: VLA1553 Half Dose 10/40 [25.0%], VLA1553 Full Dose 10/40 [25.0%], control 4/20 [20.0%]; 1-2 years: VLA1553 Half Dose 9/39 [23.1%], VLA1553 Full Dose 15/41 [36.6%], control 3/20 [15.0%]).

Five participants reported severe (Grade 3) fever (3-6 years: VLA1553 Full Dose 3/40 [7.5%]; 1-2 years: VLA1553 Half Dose 1/39 [2.6%], VLA1553 Full Dose 1/41 [2.4%]). Of them, 3 were considered unrelated to vaccination since they were associated with the occurrence of unsolicited events of infections such as amoebiasis, nasopharyngitis, and pharyngotonsillitis. Two participants 1-2 years experienced at least one related severe solicited systemic AE, in both cases fever, which was severe for 1 day and resolved:

- VLA1553 Half Dose 1/39 [2.6%] severe fever on Day 6 (with previous mild fever on Day 5)

- VLA1553 Full Dose 1/41 [2.4%] severe fever on Day 11 (with previous intermittent mild fever on Day 1 and Day 4 after vaccination overlapping with the occurrence of an unsolicited AE of gastrointestinal disorder).

Moreover, 1 participant had potentially life-threatening grade 4 fever (1-2 years: VLA1553 Half Dose 1/39 [2.6%]). This event occurred on Day 5 after vaccination, resolved after 1 day, and was considered unrelated, since the event occurred in the context of an unsolicited event of viral infection.

The most common solicited systemic AEs were:

- 7-11 years: headache (8/40 [20.0%]) with VLA1553 Half Dose; 12/43 [27.9%] with VLA1553 Full Dose, 3/21 [14.3%] with control) and fever (5/40 [12.5%]) with VLA1553 Half Dose; 5/43 [11.6%] with VLA1553 Full Dose, 0/21 [0%] with control)

- 3-6 years: headache (3/40 [7.5%]) with VLA1553 Half Dose; 6/40 [15.0%] with VLA1553 Full Dose, 3/20 [15.0%] with control) and fever (5/40 [12.5%]) with VLA1553 Half Dose; 6/40 [15.0%] with VLA1553 Full Dose, 1/20 [5.0%] with control)

- 1-2 years: fever (8/39 [20.5%]) with VLA1553 Half Dose; 7/41 [17.1%] with VLA1553 Full Dose, 1/20 [5.0%] with control) and loss of appetite (3/39 [7.7%]) with VLA1553 Half Dose; 9/41 [22.0%] with VLA1553 Full Dose, 1/20 [5.0%] with control)

Solicited systemic AEs were transient and resolved within a few days. Mean duration of solicited systemic AEs ranged from 1.0 day (disturbed sleep, drowsiness) to 3.2 days (joint pain).

No statistically significant differences in solicited systemic AE distribution across trial arms (Half Dose, Full Dose, and control) were observed regardless of previous CHIKV infection:

- Solicited systemic AEs in participants who were µPRNT seronegative at baseline (7-11 years only) were as follows: VLA1553 Half Dose 10/31 (32.3%), VLA1553 Full Dose 14/36 (38.9%), and control 2/13 (15.4).

- Solicited systemic AEs in participants who were µPRNT seropositive at baseline (7-11 years only) were reported as follows: VLA1553 Half Dose 1/9 (11.1%), VLA1553 Full Dose 3/7 (42.9%), and control 1/8 (12.5%).

Resulting questions:

None.

Table 19. Related Solicited Systemic Adverse Events Overall and by Symptom (Safety Analysis Population)

		7 - 11 years			3 - 6 years			1 - 2 years			
	Statistic	Half Dose (N=40)	Full Dose (N=43)	Control (N=21)	Half Dose (N=40)	Full Dose (N=40)	Control (N=20)	Half Dose (N=39)	Full Dose (N=41)	Control (N=20)	Total Population (N=304)
Any related systemic AE											
	n (%) Obs [95% CI]	9 (22.5) 16 [10.8, 38.5]	10 (23.3) 20 [11.8, 38.6]	3 (14.3) 4 [3.0, 36.3]	8 (20.0) 12 [9.1, 35.6]	9 (22.5) 13 [10.8, 38.5]	3 (15.0) 4 [3.2, 37.9]	5 (12.8) 6 [4.3, 27.4]	12 (29.3) 14 [16.1, 45.5]	1 (5.0) 1 [0.1, 24.9]	60 (19.7) 90 [15.4, 24.7]
Overall p-value		0.7428			0.8544			0.0523			
Fever	n (%) [95% CI]	5 (12.5) [4.2, 26.8]	2 (4.7) [0.6, 15.8]	0 (0.0) [0.0, 16.1]	4 (10.0) [2.8, 23.7]	3 (7.5) [1.6, 20.4]	1 (5.0) [0.1, 24.9]	3 (7.7) [1.6, 20.9]	6 (14.6) [5.6, 29.2]	0 (0.0) [0.0, 16.8]	24 (7.9) [5.1, 11.5]
Nausea	n (%) [95% CI]	1 (2.5) [0.1, 13.2]	2 (4.7) [0.6, 15.8]	0 (0.0) [0.0, 16.1]	1 (2.5) [0.1, 13.2]	0 (0.0) [0.0, 8.8]	0 (0.0) [0.0, 16.8]	1 (2.6) [0.1, 13.5]	0 (0.0) [0.0, 8.6]	0 (0.0) [0.0, 16.8]	5 (1.6) [0.5, 3.8]
Vomiting	n (%) [95% CI]	0 (0.0) [0.0, 8.8]	2 (4.7) [0.6, 15.8]	0 (0.0) [0.0, 16.1]	0 (0.0) [0.0, 8.8]	2 (5.0) [0.6, 16.9]	0 (0.0) [0.0, 16.8]	1 (2.6) [0.1, 13.5]	1 (2.4) [0.1, 12.9]	0 (0.0) [0.0, 16.8]	6 (2.0) [0.7, 4.2]
Headache	n (%) [95% CI]	6 (15.0) [5.7, 29.8]	9 (20.9) [10.0, 36.0]	3 (14.3) [3.0, 36.3]	2 (5.0) [0.6, 16.9]	5 (12.5) [4.2, 26.8]	2 (10.0) [1.2, 31.7]	N/A	N/A	N/A	27 (8.9) [5.9, 12.7]
Fatigue	n (%) [95% CI]	0 (0.0) [0.0, 8.8]	0 (0.0) [0.0, 8.2]	1 (4.8) [0.1, 23.8]	1 (2.5) [0.1, 13.2]	1 (2.5) [0.1, 13.2]	0 (0.0) [0.0, 16.8]	N/A	N/A	N/A	3 (1.0) [0.2, 2.9]
Muscle Pain	n (%) [95% CI]	3 (7.5) [1.6, 20.4]	4 (9.3) [2.6, 22.1]	0 (0.0) [0.0, 16.1]	2 (5.0) [0.6, 16.9]	0 (0.0) [0.0, 8.8]	1 (5.0) [0.1, 24.9]	N/A	N/A	N/A	10 (3.3) [1.6, 6.0]
Joint Pain	n (%) [95% CI]	1 (2.5) [0.1, 13.2]	1 (2.3) [0.1, 12.3]	0 (0.0) [0.0, 16.1]	0 (0.0) [0.0, 8.8]	2 (5.0) [0.6, 16.9]	0 (0.0) [0.0, 16.8]	N/A	N/A	N/A	4 (1.3) [0.4, 3.3]
Inconsolable or excessive crying	n (%) [95% CI]	N/A	N/A	N/A	N/A	N/A	N/A	0 (0.0) [0.0, 9.0]	0 (0.0) [0.0, 8.6]	0 (0.0) [0.0, 16.8]	0 (0.0) [0.0, 1.2]
Disturbed sleep	n (%) [95% CI]	N/A	N/A	N/A	N/A	N/A	N/A	0 (0.0) [0.0, 9.0]	0 (0.0) [0.0, 8.6]	0 (0.0) [0.0, 16.8]	0 (0.0) [0.0, 1.2]
Loss of appetite	n (%) [95% CI]	N/A	N/A	N/A	N/A	N/A	N/A	1 (2.6) [0.1, 13.5]	5 (12.2) [4.1, 26.2]	1 (5.0) [0.1, 24.9]	7 (2.3) [0.9, 4.7]
Drowsiness	n (%) [95% CI]	N/A	N/A	N/A	N/A	N/A	N/A	0 (0.0) [0.0, 9.0]	1 (2.4) [0.1, 12.9]	0 (0.0) [0.0, 16.8]	1 (0.3) [0.0, 1.8]
Rash	n (%) [95% CI]	0 (0.0) [0.0, 8.8]	0 (0.0) [0.0, 8.2]	0 (0.0) [0.0, 16.1]	2 (5.0) [0.6, 16.9]	0 (0.0) [0.0, 8.8]	0 (0.0) [0.0, 16.8]	0 (0.0) [0.0, 9.0]	1 (2.4) [0.1, 12.9]	0 (0.0) [0.0, 16.8]	3 (1.0) [0.2, 2.9]

CI=confidence interval; n=number of participants with event, percentages are based on N; N/A=Not applicable (data for these AEs were not collected in these age groups); NC=Not calculable; Obs=number of events.
Solicited AEs are documented within 14 days after vaccination.
AEs are counted as related if causality is 'probably related' or 'possibly related' or missing.
Two-sided 95% confidence intervals are calculated using the Clopper-Pearson method. Pairwise test (Fisher exact) performed in case of a significant overall p-value

Assessment

Similarly to solicited systemic AEs, related solicited systemic AEs were more reported in the VLA1553 full dose (25%), vs. the half dose (18.5%), vs. the control (11.5%) (not statistically significant). When stratified by age group, similar not statistically significant differences were observed:

- 7-11 years: related solicited systemic AEs were reported by 9/40 (22.5%) in VLA1553 Half Dose, 10/43 (23.3%) in VLA1553 Full Dose, and 3/21 (14.3%) in control.

- 3-6 years: related solicited systemic AEs were reported by 8/40 (20.0%) in VLA1553 Half Dose, 9/40 (22.5%) in VLA1553 Full Dose, and 3/20 (15.0%) in control.

- 1-2 years: related solicited systemic AEs were reported by 5/39 (12.8%) in VLA1553 Half Dose, 12/41 (29.3%) in VLA1553 Full Dose, and 1/20 (5.0%) in control.

Resulting questions:

None.

2.3.2.1.2. Unsolicited AEs

Frequency and severity of unsolicited AEs to Month 12

Table 20. Overall Summary of Unsolicited Adverse Events by Age Group and Trial Arm to Month 12 (Safety Analysis Population)

		7 - 11 years			3 - 6 years			1 - 2 years			
	Statistic	Half Dose (N=40)	Full Dose (N=43)	Control (N=21)	Half Dose (N=40)	Full Dose (N=40)	Control (N=20)	Half Dose (N=39)	Full Dose (N=41)	Control (N=20)	Total Population (N=304)
Any unsolicited AE	n (%) Obs	25 (62.5) 79	31 (72.1) 78	12 (57.1) 37	30 (75.0) 84	24 (60.0) 71	16 (80.0) 42	29 (74.4) 98	33 (80.5) 141	17 (85.0) 62	217 (71.4) 692
	[95% CI]	[45.8, 77.3]	[56.3, 84.7]	[34.0, 78.2]	[58.8, 87.3]	[43.3, 75.1]	[56.3, 94.3]	[57.9, 87.0]	[65.1, 91.2]	[62.1, 96.8]	[65.9, 76.4]
Overall p-value		0.4446			0.2340			0.6582			
Any related unsolicited AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (5.0) 1	1 (2.6) 1	0 (0.0) 0	0 (0.0) 0	2 (0.7) 2
	[95% CI]	[0.0, 8.8]	[0.0, 8.2]	[0.0, 16.1]	[0.0, 8.8]	[0.0, 8.8]	[0.1, 24.9]	[0.1, 13.5]	[0.0, 8.6]	[0.0, 16.8]	[0.1, 2.4]
Overall p-value		NC			0.2000			0.5900			
Any severe unsolicited AE	n (%) Obs	1 (2.5) 1	4 (9.3) 4	1 (4.8) 1	2 (5.0) 2	0 (0.0) 0	0 (0.0) 0	3 (7.7) 4	2 (4.9) 3	1 (5.0) 1	14 (4.6) 16
	[95% CI]	[0.1, 13.2]	[2.6, 22.1]	[0.1, 23.8]	[0.6, 16.9]	[0.0, 8.8]	[0.0, 16.8]	[1.6, 20.9]	[0.6, 16.5]	[0.1, 24.9]	[2.5, 7.6]
Overall p-value		0.5655			0.3535			0.8675			
Any related severe unsolicited AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.0, 8.8]	[0.0, 8.2]	[0.0, 16.1]	[0.0, 8.8]	[0.0, 8.8]	[0.0, 16.8]	[0.0, 9.0]	[0.0, 8.6]	[0.0, 16.8]	[0.0, 1.2]
Overall p-value		NC			NC			NC			
Any serious unsolicited AE	n (%) Obs	1 (2.5) 1	2 (4.7) 2	0 (0.0) 0	1 (2.5) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	2 (4.9) 2	1 (5.0) 1	7 (2.3) 7
	[95% CI]	[0.1, 13.2]	[0.6, 15.8]	[0.0, 16.1]	[0.1, 13.2]	[0.0, 8.8]	[0.0, 16.8]	[0.0, 9.0]	[0.6, 16.5]	[0.1, 24.9]	[0.9, 4.7]
Overall p-value		1.0000			1.0000			0.4166			
Any related serious unsolicited AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.0, 8.8]	[0.0, 8.2]	[0.0, 16.1]	[0.0, 8.8]	[0.0, 8.8]	[0.0, 16.8]	[0.0, 9.0]	[0.0, 8.6]	[0.0, 16.8]	[0.0, 1.2]
Overall p-value		NC			NC			NC			

CI=confidence interval; n=number of participants with event, percentages are based on N; NC=Not calculable; Obs=number of events.
This table includes all solicited and unsolicited AEs documented in the database.
AEs are counted as related if causality is 'probably related' or 'possibly related' or missing. AEs are counted as severe if standard toxicity grade is 'Grade 3' or 'Grade 4' or missing.
Two-sided 95% confidence intervals are calculated using the Clopper-Pearson method. Pairwise test (Fisher exact) performed in case of a significant overall p-value (Fisher-Freeman-Halton).

Table 21. Part C Unsolicited Adverse Events up to Month 12 by System Organ Class and Preferred Term by Age Group and Trial Arm With an Overall Frequency ≥2% (Safety Analysis Population)

		7 - 11 years			3 - 6 years			1 - 2 years			
	Statistic	Half Dose (N=40)	Full Dose (N=43)	Control (N=21)	Half Dose (N=40)	Full Dose (N=40)	Control (N=20)	Half Dose (N=39)	Full Dose (N=41)	Control (N=20)	Total Population (N=304)
Any unsolicited AE	n (%) Obs [95% CI]	25 (62.5) 79 [45.8, 77.3]	31 (72.1) 78 [56.3, 84.7]	12 (57.1) 37 [34.0, 78.2]	30 (75.0) 84 [58.8, 87.3]	24 (60.0) 71 [43.3, 75.1]	16 (80.0) 42 [56.3, 94.3]	29 (74.4) 98 [57.9, 87.0]	33 (80.5) 141 [65.1, 91.2]	17 (85.0) 62 [62.1, 96.8]	217 (71.4) 692 [65.9, 76.4]
Overall p-value		0.4446			0.2340			0.6582			
Infections and infestations	n (%) Obs	22 (55.0) 46	21 (48.8) 43	9 (42.9) 21	25 (62.5) 47	21 (52.5) 51	12 (60.0) 25	28 (71.8) 73	29 (70.7) 92	14 (70.0) 33	181 (59.5) 431
Nasopharyngitis	n (%) Obs	17 (42.5) 27	18 (41.9) 29	6 (28.6) 10	19 (47.5) 28	14 (35.0) 29	10 (50.0) 17	24 (61.5) 48	27 (65.9) 68	11 (55.0) 25	146 (48.0) 281
Viral infection	n (%) Obs	0 (0.0) 0	1 (2.3) 1	5 (23.8) 7	3 (7.5) 5	3 (7.5) 4	3 (15.0) 3	3 (7.7) 5	4 (9.8) 4	1 (5.0) 1	23 (7.6) 30
Gastroenteritis	n (%) Obs	1 (2.5) 1	2 (4.7) 2	0 (0.0) 0	1 (2.5) 1	3 (7.5) 3	1 (5.0) 1	0 (0.0) 0	3 (7.3) 3	1 (5.0) 1	12 (3.9) 12
Pharyngotonsillitis	n (%) Obs	2 (5.0) 3	1 (2.3) 1	1 (4.8) 1	0 (0.0) 0	1 (2.5) 1	1 (5.0) 1	2 (5.1) 2	3 (7.3) 4	1 (5.0) 1	12 (3.9) 14
Tonsillitis	n (%) Obs	2 (5.0) 2	0 (0.0) 0	1 (4.8) 1	1 (2.5) 1	1 (2.5) 1	0 (0.0) 0	3 (7.7) 3	3 (7.3) 3	0 (0.0) 0	11 (3.6) 11
Dengue fever	n (%) Obs	0 (0.0) 0	2 (4.7) 2	1 (4.8) 1	2 (5.0) 2	1 (2.5) 1	0 (0.0) 0	0 (0.0) 0	1 (2.4) 1	0 (0.0) 0	7 (2.3) 7
Conjunctivitis	n (%) Obs	0 (0.0) 0	2 (4.7) 2	0 (0.0) 0	0 (0.0) 0	1 (2.5) 1	0 (0.0) 0	3 (7.7) 3	0 (0.0) 0	0 (0.0) 0	6 (2.0) 6
Varicella	n (%) Obs	1 (2.5) 1	2 (4.7) 2	0 (0.0) 0	2 (5.0) 2	1 (2.5) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	6 (2.0) 6
Respiratory, thoracic and mediastinal disorders	n (%) Obs	4 (10.0) 6	6 (14.0) 11	3 (14.3) 5	8 (20.0) 12	5 (12.5) 10	3 (15.0) 5	6 (15.4) 7	11 (26.8) 18	6 (30.0) 10	52 (17.1) 84
Rhinitis allergic	n (%) Obs	4 (10.0) 4	3 (7.0) 4	1 (4.8) 1	2 (5.0) 5	2 (5.0) 3	3 (15.0) 5	5 (12.8) 5	8 (19.5) 8	4 (20.0) 7	32 (10.5) 42
Allergic cough	n (%) Obs	1 (2.5) 2	1 (2.3) 1	2 (9.5) 2	2 (5.0) 2	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	2 (10.0) 2	8 (2.6) 9
Cough	n (%) Obs	0 (0.0) 0	1 (2.3) 1	0 (0.0) 0	1 (2.5) 1	3 (7.5) 4	0 (0.0) 0	0 (0.0) 0	1 (2.4) 1	1 (5.0) 1	7 (2.3) 8
Gastrointestinal disorders	n (%) Obs	3 (7.5) 4	8 (18.6) 9	3 (14.3) 3	5 (12.5) 6	2 (5.0) 2	4 (20.0) 6	6 (15.4) 6	11 (26.8) 17	7 (35.0) 10	49 (16.1) 63
Diarrhea	n (%) Obs	1 (2.5) 1	3 (7.0) 3	0 (0.0) 0	2 (5.0) 2	1 (2.5) 1	2 (10.0) 2	3 (7.7) 3	7 (17.1) 11	5 (25.0) 7	24 (7.9) 30
Vomiting	n (%) Obs	1 (2.5) 1	1 (2.3) 1	0 (0.0) 0	2 (5.0) 2	0 (0.0) 0	2 (10.0) 2	0 (0.0) 0	3 (7.3) 3	1 (5.0) 1	10 (3.3) 10
Skin and subcutaneous tissue disorders	n (%) Obs	2 (5.0) 2	4 (9.3) 5	0 (0.0) 0	2 (5.0) 2	2 (5.0) 2	2 (10.0) 2	6 (15.4) 8	3 (7.3) 7	3 (15.0) 3	24 (7.9) 31
Injury, poisoning and procedural complications	n (%) Obs	1 (2.5) 1	3 (7.0) 3	2 (9.5) 2	4 (10.0) 4	2 (5.0) 2	1 (5.0) 1	2 (5.1) 2	3 (7.3) 3	1 (5.0) 1	19 (6.3) 19
Nervous system disorders	n (%) Obs	9 (22.5) 11	3 (7.0) 5	2 (9.5) 4	2 (5.0) 2	1 (2.5) 1	0 (0.0) 0	1 (2.6) 1	0 (0.0) 0	1 (5.0) 1	19 (6.3) 25
Headache	n (%) Obs	9 (22.5) 10	3 (7.0) 5	2 (9.5) 3	2 (5.0) 2	1 (2.5) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	17 (5.6) 21
General disorders and administration site conditions	n (%) Obs	3 (7.5) 3	1 (2.3) 1	1 (4.8) 1	4 (10.0) 4	0 (0.0) 0	3 (15.0) 3	1 (2.6) 1	1 (2.4) 1	0 (0.0) 0	14 (4.6) 14
Pyrexia	n (%) Obs	3 (7.5) 3	1 (2.3) 1	1 (4.8) 1	4 (10.0) 4	0 (0.0) 0	3 (15.0) 3	1 (2.6) 1	1 (2.4) 1	0 (0.0) 0	14 (4.6) 14
Musculoskeletal and connective tissue disorders	n (%) Obs	3 (7.5) 3	0 (0.0) 0	1 (4.8) 1	1 (2.5) 1	1 (2.5) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (5.0) 1	7 (2.3) 7

CI=confidence interval; n=number of participants with event, percentages are based on N; NC=Not calculable; Obs=number of events.
This table includes all unsolicited AEs documented in the database.
Two-sided 95% confidence intervals are calculated using the Clopper-Pearson method. Pairwise test (Fisher exact) performed in case of a significant overall p-value (Fisher-Freeman-Halton). For details, please see Listing 16.2.4.12.1 and Listing 16.2.4.12.2.

Assessment

Up to Month 12, unsolicited AEs were reported at a similar frequency in the three trial arms (70.6%, 71.0%, and 73.8% participants in the VLA1553 Half Dose, Full Dose, and control arms, respectively).

The proportion of participants who experienced unsolicited AEs was similar when stratified by age group (7-11 years: VLA1553 Half Dose 25/40 [62.5%], VLA1553 Full Dose 31/43 [72.1%], and control 12/21 [57.1%]; 3-6 years: VLA1553 Half Dose 30/40 [75.0%], VLA1553 Full Dose 24/40 [60.0%], and control 16/20 [80.0%]; 1-2 years: VLA1553 Half Dose 29/39 [74.4%], VLA1553 Full Dose 33/41 [80.5%], and control 17/20 [85.0%]).

The most common unsolicited AEs overall were nasopharyngitis (146/304 [48.0%]), rhinitis allergic (32/304 [10.5%]), diarrhoea (24/304 [7.9%]), viral infection (23/304 [7.6%]), headache (17/304 [5.6%]), and pyrexia (14/304 [4.6%]). When stratifying per age group and trial arm, viral infection, diarrhoea, and allergic rhinitis were mainly reported in the younger age groups, and headache was mainly reported in the 7-11 years age group in the VLA1553 trial arms.

Most unsolicited AEs were graded as mild or moderate. In total, 6/119 (5.0%), 6/124 (4.8%), and 2/61 (3.3%) participants in the VLA1553 Half Dose, VLA1553 Full Dose and control arms, respectively, experienced at least one severe unsolicited AE.

Overall up to Day 180, 9 participants (5/119 [4.2%] in the VLA1553 Half Dose and 4/124 [3.2%] in the VLA1553 Full Dose arms) experienced at least one unsolicited AE that was graded severe (Grade 3):

- 7-11 years: dengue fever: VLA1553 Full Dose 2/43 [4.7%]; cellulitis: VLA1553 Half Dose 1/40 [2.5%]

- 3-6 years: viral infection: VLA1553 Half Dose 1/40 [2.5%]

- 1-2 years: nasopharyngitis: VLA1553 Half Dose 2/39 [5.1%] and VLA1553 Full Dose 1/41 [2.4%]; viral infection: VLA1553 Half Dose 1/39 [2.6%]; dengue fever: VLA1553 Full Dose 1/41 [2.4%].

In addition, 5 further participants experienced at least one unsolicited AE that was graded severe up to month 12:

- 7-11 years: faecaloma: VLA1553 Full Dose 1/43 [2.3%]; asthmatic crisis: VLA1553 Full Dose 1/43 [2.3%]; viral infection: control 1/21 [4.8%]

- 3-6 years: appendicitis perforated: VLA1553 Half Dose 1/40 [2.5%]

- 1-2 years: drug hypersensitivity: VLA1553 Full Dose 1/41 [2.4%] (this participant also reported dengue fever up to Day 180).

All severe unsolicited AEs resolved and were considered unrelated to vaccination.

Only 2/304 (0.7%) possibly related unsolicited AEs were reported up to Day 29. These included mild dermatitis that resolved in 1 day in a participant in the 3-6 years age group who received control and a mild event of miliaria that resolved in 4 days in a participant in the 1-2 years age group who received VLA1553 Half Dose. No additional unsolicited AEs considered treatment-related were reported up to Month 12.

Resulting questions:

None.

2.3.2.1.3. Deaths, SAEs and other significant AEs

Frequency and severity of any SAE

Table 22. Participants with any Serious Adverse Events by System Organ Class and Preferred Term by Age Group and Trial Arm (Safety Analysis Population)

	Statistic	7 - 11 years			3 - 6 years			1 - 2 years			Total Population (N=304)
		Half Dose (N=40)	Full Dose (N=43)	Control (N=21)	Half Dose (N=40)	Full Dose (N=40)	Control (N=20)	Half Dose (N=39)	Full Dose (N=41)	Control (N=20)	
Any serious AE	n (%) Obs [95% CI]	1 (2.5) 1 [0.1, 13.2]	2 (4.7) 2 [0.6, 15.8]	0 (0.0) 0 [0.0, 16.1]	1 (2.5) 1 [0.1, 13.2]	0 (0.0) 0 [0.0, 8.8]	0 (0.0) 0 [0.0, 16.8]	0 (0.0) 0 [0.0, 9.0]	2 (4.9) 2 [0.6, 16.5]	1 (5.0) 1 [0.1, 24.9]	7 (2.3) 7 [0.9, 4.7]
Overall p-value		1.0000			1.0000			0.4166			
Infections and infestations	n (%) Obs	1 (2.5) 1	0 (0.0) 0	0 (0.0) 0	1 (2.5) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (5.0) 1	3 (1.0) 3
Appendicitis perforated	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (2.5) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (0.3) 1
Cellulitis	n (%) Obs	1 (2.5) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (0.3) 1
Pneumonia	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (5.0) 1	1 (0.3) 1
Respiratory, thoracic and mediastinal disorders	n (%) Obs	0 (0.0) 0	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (2.4) 1	0 (0.0) 0	2 (0.7) 2
Asthmatic crisis	n (%) Obs	0 (0.0) 0	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (2.4) 1	0 (0.0) 0	2 (0.7) 2
Gastrointestinal disorders	n (%) Obs	0 (0.0) 0	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (0.3) 1
Faecaloma	n (%) Obs	0 (0.0) 0	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (0.3) 1
Immune system disorders	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (2.4) 1	0 (0.0) 0	1 (0.3) 1
Drug hypersensitivity	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (2.4) 1	0 (0.0) 0	1 (0.3) 1

n=number of participants with event, percentages are based on N, Obs=number of events.
NC=Not calculable.
This table includes all solicited and unsolicited AEs documented in the database.
Two-sided 95% confidence intervals are calculated using the Clopper-Pearson method. Pairwise test (Fisher exact) performed in case of a significant overall p-

Assessment

There were 2/119 (1.7%), 4/124 (3.2%), and 1/61 (1.6%) participants in the VLA1553 Half Dose, VLA1553 Full Dose and control arms, respectively, who experienced at least one serious unsolicited AE.

Up to Day 29, one SAE was reported (cellulitis) in a participant who received VLA1553 Half Dose (7-11 years).

Up to Day 180, one additional SAE was reported (asthmatic crisis) in a participant who received VLA1553 Full Dose (1-2 years).

Up to Month 12, five additional SAEs were reported: 1 SAE of appendicitis perforated in the VLA1553 Half Dose arm (3-6 years group), 3 SAEs in the VLA1553 Full Dose arm (one SAE of asthmatic crisis and one SAE of faecaloma (7-11 years group); one SAE of drug hypersensitivity (1-2 years group), and 1 SAE of pneumonia in the control arm (1-2 years group).

None of the reported SAEs was considered related to treatment.

Resulting questions:

None.

Medically attended adverse events

Table 23. Overall Summary of Medically Attended Adverse Events by Age Group and Trial Arm to Month 12 (Safety Analysis Population)

		7 - 11 years			3 - 6 years			1 - 2 years			
	Statistic	Half Dose (N=40)	Full Dose (N=43)	Control (N=21)	Half Dose (N=40)	Full Dose (N=40)	Control (N=20)	Half Dose (N=39)	Full Dose (N=41)	Control (N=20)	Total Population (N=304)
Any medically attended AE	n (%) Obs	10 (25.0) 27	13 (30.2) 22	5 (23.8) 7	12 (30.0) 30	9 (22.5) 18	6 (30.0) 8	13 (33.3) 31	21 (51.2) 51	6 (30.0) 16	95 (31.3) 210
	[95% CI]	[12.7, 41.2]	[17.2, 46.1]	[8.2, 47.2]	[16.6, 46.5]	[10.8, 38.5]	[11.9, 54.3]	[19.1, 50.2]	[35.1, 67.1]	[11.9, 54.3]	[26.1, 36.8]
Overall p-value		0.8436			0.7357			0.1717			
Any related medically attended AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (2.5) 1	0 (0.0) 0	0 (0.0) 0	2 (4.9) 2	0 (0.0) 0	3 (1.0) 3
	[95% CI]	[0.0, 8.8]	[0.0, 8.2]	[0.0, 16.1]	[0.0, 8.8]	[0.1, 13.2]	[0.0, 16.8]	[0.0, 9.0]	[0.6, 16.5]	[0.0, 16.8]	[0.2, 2.9]
Overall p-value		NC			1.0000			0.6770			
Any medically attended unsolicited AE	n (%) Obs	10 (25.0) 27	13 (30.2) 22	5 (23.8) 7	12 (30.0) 25	9 (22.5) 12	6 (30.0) 8	13 (33.3) 24	21 (51.2) 46	6 (30.0) 16	95 (31.3) 187
	[95% CI]	[12.7, 41.2]	[17.2, 46.1]	[8.2, 47.2]	[16.6, 46.5]	[10.8, 38.5]	[11.9, 54.3]	[19.1, 50.2]	[35.1, 67.1]	[11.9, 54.3]	[26.1, 36.8]
Overall p-value		0.8436			0.7357			0.1717			
Any related medically attended unsolicited AE	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
	[95% CI]	[0.0, 8.8]	[0.0, 8.2]	[0.0, 16.1]	[0.0, 8.8]	[0.0, 8.8]	[0.0, 16.8]	[0.0, 9.0]	[0.0, 8.6]	[0.0, 16.8]	[0.0, 1.2]
Overall p-value		NC			NC			NC			

CI=confidence interval; n=number of participants with event, percentages are based on N; NC=Not calculable; Obs=number of events.
This table includes all solicited and unsolicited AEs documented in the database.
AEs are counted as related if causality is 'probably related' or 'possibly related' or missing. AEs are counted as severe if standard toxicity grade is 'Grade 3' or 'Grade 4' or missing.
Two-sided 95% confidence intervals are calculated using the Clopper-Pearson method. Pairwise test (Fisher exact) performed in case of a significant overall p-value (Fisher-Freeman-Halton).

Assessment

Up to Month 12, the frequency of participants who reported medically attended AEs was similar between each arm: 35/119 [29.4%], 43/124 [34.7%], and 17/61 [27.9%] participants in the VLA1553 Half Dose, Full Dose, and control arms, respectively.

When stratified by age group, similar not statistically significant differences were observed: 7-11 years: VLA1553 Half Dose 10/40 [25.0%], VLA1553 Full Dose 13/43 [30.2%], control 5/21 [23.8%]; 3-6 years: VLA1553 Half Dose 12/40 [30.0%], VLA1553 Full Dose 9/40 [22.5%], control 6/20 [30.0%]; 1-2 years: VLA1553 Half Dose 13/39 [33.3%], VLA1553 Full Dose 21/41 [51.2%], control 6/20 [30.0%]). There were no related medically attended unsolicited AEs.

The most common medically attended AEs were nasopharyngitis (39/304 [12.8%] participants), pharyngotonsillitis (11/304 [3.6%] participants), pyrexia (10/304 [3.3%] participants), vomiting and viral infection (each 9/304 [3.0%] participants), headache (7/304 [2.3%] participants), tonsillitis (6/304 [2.0%] participants), dengue fever (5/304 [1.6%] participants), dental caries, wound, asthmatic crisis, and decreased appetite (each 4/304 [1.3%] participants).

Three medically attended AEs were considered related to treatment, all in participants who received VLA1553 Full Dose, including pyrexia in 2/41 (4.9%) participants aged 1-2 years and headache in 1/40 (2.5%) participant aged 3-6 years.

With the exception of five participants who experienced (unrelated) nasopharyngitis, otitis externa, dengue fever, toothache and upper limb fracture, all medically attended AEs occurred in participants who were µPRNT seronegative at baseline.

No AEs leading to trial withdrawal or deaths were reported during the study.

Resulting questions:

None.

2.3.2.1.4. AESIs (protocol definition)

Table 24. Overall Summary of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest by Age Group and Trial Arm to Month 12 (Safety Analysis Population) (Safety Analysis Population)

		7 - 11 years			3 - 6 years			1 - 2 years			
	Statistic	Half Dose (N=40)	Full Dose (N=43)	Control (N=21)	Half Dose (N=40)	Full Dose (N=40)	Control (N=20)	Half Dose (N=39)	Full Dose (N=41)	Control (N=20)	Total Population (N=304)
Any AE	n (%) Obs [95% CI]	29 (72.5) 123 [56.1, 85.4]	36 (83.7) 119 [69.3, 93.2]	15 (71.4) 54 [47.8, 88.7]	34 (85.0) 111 [70.2, 94.3]	28 (70.0) 102 [53.5, 83.4]	16 (80.0) 48 [56.3, 94.3]	30 (76.9) 118 [60.7, 88.9]	34 (82.9) 168 [67.9, 92.8]	17 (85.0) 67 [62.1, 96.8]	239 (78.6) 910 [73.6, 83.1]
Overall p-value		0.3542			0.2532			0.7567			
Any related AE	n (%) Obs [95% CI]	15 (37.5) 37 [22.7, 54.2]	15 (34.9) 33 [21.0, 50.9]	9 (42.9) 17 [21.8, 66.0]	12 (30.0) 20 [16.6, 46.5]	12 (30.0) 24 [16.6, 46.5]	3 (15.0) 5 [3.2, 37.9]	8 (20.5) 10 [9.3, 36.5]	12 (29.3) 15 [16.1, 45.5]	1 (5.0) 3 [0.1, 24.9]	87 (28.6) 164 [23.6, 34.1]
Overall p-value		0.8070			0.4516			0.0852			
Any severe AE	n (%) Obs [95% CI]	1 (2.5) 1 [0.1, 13.2]	4 (9.3) 4 [2.6, 22.1]	1 (4.8) 1 [0.1, 23.8]	2 (5.0) 2 [0.6, 16.9]	3 (7.5) 3 [1.6, 20.4]	0 (0.0) 0 [0.0, 16.8]	3 (7.7) 6 [1.6, 20.9]	3 (7.3) 4 [1.5, 19.9]	1 (5.0) 1 [0.1, 24.9]	18 (5.9) 22 [3.5, 9.2]
Overall p-value		0.5655			0.6284			1.0000			
Any related severe AE	n (%) Obs [95% CI]	0 (0.0) 0 [0.0, 8.8]	0 (0.0) 0 [0.0, 8.2]	0 (0.0) 0 [0.0, 16.1]	0 (0.0) 0 [0.0, 8.8]	0 (0.0) 0 [0.0, 8.8]	0 (0.0) 0 [0.0, 16.8]	1 (2.6) 1 [0.1, 13.5]	1 (2.4) 1 [0.1, 12.9]	0 (0.0) 0 [0.0, 16.8]	2 (0.7) 2 [0.1, 2.4]
Overall p-value		NC			NC			1.0000			
Any serious AE	n (%) Obs [95% CI]	1 (2.5) 1 [0.1, 13.2]	2 (4.7) 2 [0.6, 15.8]	0 (0.0) 0 [0.0, 16.1]	1 (2.5) 1 [0.1, 13.2]	0 (0.0) 0 [0.0, 8.8]	0 (0.0) 0 [0.0, 16.8]	0 (0.0) 0 [0.0, 9.0]	2 (4.9) 2 [0.6, 16.5]	1 (5.0) 1 [0.1, 24.9]	7 (2.3) 7 [0.9, 4.7]
Overall p-value		1.0000			1.0000			0.4166			
Any related serious AE	n (%) Obs [95% CI]	0 (0.0) 0 [0.0, 8.8]	0 (0.0) 0 [0.0, 8.2]	0 (0.0) 0 [0.0, 16.1]	0 (0.0) 0 [0.0, 8.8]	0 (0.0) 0 [0.0, 8.8]	0 (0.0) 0 [0.0, 16.8]	0 (0.0) 0 [0.0, 9.0]	0 (0.0) 0 [0.0, 8.6]	0 (0.0) 0 [0.0, 16.8]	0 (0.0) 0 [0.0, 1.2]
Overall p-value		NC			NC			NC			
Any AESI (protocol definition)	n (%) Obs [95% CI]	3 (7.5) 6 [1.6, 20.4]	0 (0.0) 0 [0.0, 8.2]	0 (0.0) 0 [0.0, 16.1]	2 (5.0) 6 [0.6, 16.9]	0 (0.0) 0 [0.0, 8.8]	0 (0.0) 0 [0.0, 16.8]	0 (0.0) 0 [0.0, 9.0]	0 (0.0) 0 [0.0, 8.6]	0 (0.0) 0 [0.0, 16.8]	5 (1.6) 12 [0.5, 3.8]
Overall p-value		0.1573			0.3535			NC			
Any early onset AESI (protocol definition)	n (%) Obs [95% CI]	2 (5.0) 4 [0.6, 16.9]	0 (0.0) 0 [0.0, 8.2]	0 (0.0) 0 [0.0, 16.1]	1 (2.5) 2 [0.1, 13.2]	0 (0.0) 0 [0.0, 8.8]	0 (0.0) 0 [0.0, 16.8]	0 (0.0) 0 [0.0, 9.0]	0 (0.0) 0 [0.0, 8.6]	0 (0.0) 0 [0.0, 16.8]	3 (1.0) 6 [0.2, 2.9]
Overall p-value		0.1848			1.0000			NC			
Any late onset AESI (protocol definition)	n (%) Obs [95% CI]	1 (2.5) 2 [0.1, 13.2]	0 (0.0) 0 [0.0, 8.2]	0 (0.0) 0 [0.0, 16.1]	1 (2.5) 4 [0.1, 13.2]	0 (0.0) 0 [0.0, 8.8]	0 (0.0) 0 [0.0, 16.8]	0 (0.0) 0 [0.0, 9.0]	0 (0.0) 0 [0.0, 8.6]	0 (0.0) 0 [0.0, 16.8]	2 (0.7) 6 [0.1, 2.4]
Overall p-value		0.5865			1.0000			NC			
Any AESI (protocol definition) adjudicated	n (%) [95% CI]	3 (7.5) [1.6, 20.4]	0 (0.0) [0.0, 8.2]	0 (0.0) [0.0, 16.1]	2 (5.0) [0.6, 16.9]	0 (0.0) [0.0, 8.8]	0 (0.0) [0.0, 16.8]	0 (0.0) [0.0, 9.0]	0 (0.0) [0.0, 8.6]	0 (0.0) [0.0, 16.8]	5 (1.6) [0.5, 3.8]
Overall p-value		0.1573			0.3535			NC			
Any CLAR (AESI by regulatory agencies definition)	n (%) Obs [95% CI]	4 (10.0) 9 [2.8, 23.7]	3 (7.0) 7 [1.5, 19.1]	0 (0.0) 0 [0.0, 16.1]	2 (5.0) 6 [0.6, 16.9]	5 (12.5) 12 [4.2, 26.8]	0 (0.0) 0 [0.0, 16.8]	1 (2.6) 2 [0.1, 13.5]	2 (4.9) 4 [0.6, 16.5]	0 (0.0) 0 [0.0, 16.8]	17 (5.6) 40 [3.3, 8.8]
Overall p-value		0.4620			0.2083			1.0000			
Any prolonged CLAR (AESI by regulatory agencies definition)	n (%) Obs [95% CI]	0 (0.0) 0 [0.0, 8.8]	0 (0.0) 0 [0.0, 8.2]	0 (0.0) 0 [0.0, 16.1]	0 (0.0) 0 [0.0, 8.8]	0 (0.0) 0 [0.0, 8.8]	0 (0.0) 0 [0.0, 16.8]	0 (0.0) 0 [0.0, 9.0]	0 (0.0) 0 [0.0, 8.6]	0 (0.0) 0 [0.0, 16.8]	0 (0.0) 0 [0.0, 1.2]
Overall p-value		NC			NC			NC			

CI=confidence interval; n=number of participants with event, percentages are based on N; NC=Not calculable; Obs=number of events.
This table includes all solicited and unsolicited AEs documented in the database.
AEs are counted as related if causality is 'probably related' or 'possibly related' or missing. AEs are counted as severe if standard toxicity grade is 'Grade 3' or 'Grade 4' or missing.
Obs for AESI contribute to the symptom count of the AESI case.
Early onset AESI are defined as AESI that started 2 to 21 days post-vaccination with a duration of >=3 days. Late onset AESI are defined as AESI that started after 22 days post-vaccination with a duration of >=3 days.
Two-sided 95% confidence intervals are calculated using the Clopper-Pearson method. Pairwise test (Fisher exact) performed in case of a significant overall p-value (Fisher-Freeman-Halton).

Assessment

In total, 5/304 (1.6%) participants met the criteria of AESI (protocol definition) (7-11 years: VLA1553 Half Dose 3/40 [7.5%]; 3-6 years: VLA1553 Half Dose 2/40 [5.0%]. Three AESI cases were early onset up to Day 29 and two of the AESI cases qualified as late onset AESI up to Month 12. All AESI were graded as mild or moderate (Table 14.4.52.1) and all symptoms were considered probably or possibly related to trial treatment in the early onset AESI and not related in the late onset AESI. No AESI were reported in the VLA1553 Full Dose and control arms. Up to Day 180, all AESI were resolved. No additional AESI was reported up to Month 12. None of the AESI met seriousness criteria.

The 3 participants in the 7-11 years age group experienced a combination of pyrexia and headache and the 2 participants in the 3-6 years age group experienced pyrexia/macular rash, and pyrexia/headache/rash/myalgia. All AESI were nonserious, and resolved in less than one week.

Resulting questions:

None.

2.3.2.1.5. CHIK-like AEs (CLAR; regulatory agencies definitions)

Table 25. Adverse Event of Special Interest (Regulatory Agencies Definition – CLAR) by System Organ Class and Preferred Term by Age Group and Trial Arm (Safety Analysis Population)

		7 - 11 years			3 - 6 years			1 - 2 years			
	Statistic	Half Dose (N=40)	Full Dose (N=43)	Control (N=21)	Half Dose (N=40)	Full Dose (N=40)	Control (N=20)	Half Dose (N=39)	Full Dose (N=41)	Control (N=20)	Total Population (N=304)
Any CLAR case	n (%) Obs [95% CI]	4 (10.0) 4 [2.8, 23.7]	3 (7.0) 3 [1.5, 19.1]	0 (0.0) 0 [0.0, 16.1]	2 (5.0) 2 [0.6, 16.9]	5 (12.5) 5 [4.2, 26.8]	0 (0.0) 0 [0.0, 16.8]	1 (2.6) 1 [0.1, 13.5]	2 (4.9) 2 [0.6, 16.5]	0 (0.0) 0 [0.0, 16.8]	17 (5.6) 17 [3.3, 8.8]
Overall p-value		0.4620			0.2083			1.0000			
Any CLAR symptom	n (%) Obs [95% CI]	4 (10.0) 9 [2.8, 23.7]	3 (7.0) 7 [1.5, 19.1]	0 (0.0) 0 [0.0, 16.1]	2 (5.0) 6 [0.6, 16.9]	5 (12.5) 12 [4.2, 26.8]	0 (0.0) 0 [0.0, 16.8]	1 (2.6) 2 [0.1, 13.5]	2 (4.9) 4 [0.6, 16.5]	0 (0.0) 0 [0.0, 16.8]	17 (5.6) 40 [3.3, 8.8]
Overall p-value		0.4620			0.2083			1.0000			
General disorders and administration site conditions	n (%) Obs	4 (10.0) 4	3 (7.0) 3	0 (0.0) 0	2 (5.0) 4	5 (12.5) 6	0 (0.0) 0	1 (2.6) 2	2 (4.9) 4	0 (0.0) 0	17 (5.6) 23
Pyrexia	n (%) Obs	4 (10.0) 4	3 (7.0) 3	0 (0.0) 0	2 (5.0) 2	5 (12.5) 5	0 (0.0) 0	1 (2.6) 1	2 (4.9) 2	0 (0.0) 0	17 (5.6) 17
Crying	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (2.6) 1	2 (4.9) 2	0 (0.0) 0	3 (1.0) 3
Fatigue	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	2 (5.0) 2	1 (2.5) 1	0 (0.0) 0	N/A	N/A	N/A	3 (1.0) 3
Nervous system disorders	n (%) Obs	3 (7.5) 3	3 (7.0) 3	0 (0.0) 0	1 (2.5) 1	5 (12.5) 5	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	12 (3.9) 12
Headache	n (%) Obs	3 (7.5) 3	3 (7.0) 3	0 (0.0) 0	1 (2.5) 1	5 (12.5) 5	0 (0.0) 0	N/A	N/A	N/A	12 (3.9) 12
Musculoskeletal and connective tissue disorders	n (%) Obs	2 (5.0) 2	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0	1 (2.5) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	4 (1.3) 4
Myalgia	n (%) Obs	2 (5.0) 2	1 (2.3) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	N/A	N/A	N/A	3 (1.0) 3
Arthralgia	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (2.5) 1	0 (0.0) 0	N/A	N/A	N/A	1 (0.3) 1
Skin and subcutaneous tissue disorders	n (%) Obs	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (2.5) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (0.3) 1

CI=confidence interval; n=number of participants with event, percentages are based on N; N/A=Not applicable (data for these AEs were not collected in these age groups); NC=Not calculable; Obs=number of events.
This table includes all CLAR documented in the database.
Obs for CLAR symptom count includes a count of all symptoms contributing to the CLAR case. System Organ class and Preferred Terms are presented by individual symptoms.
Two-sided 95% confidence intervals are calculated using the Clopper-Pearson method. Pairwise test (Fisher exact) performed in case of a significant overall p-value (Fisher-Freeman-Halton). For details, please see Listing 16.2.4.16.

Table 26. Chikungunya-like Adverse Reactions (AESI as defined by Regulatory Agencies) and Relatedness of Symptoms (Vaccinated Participants)

Participant Identifier	Trial Arm	Age Group	CLAR Symptoms accompanied with fever	CLAR Number of symptoms	CLAR Severity (worst symptom)	CLAR Longest symptom duration [days]	Includes related symptom
1553-2-01-012	Full dose	7-11 years	Headache	2	1	2	probably related
1553-2-01-031	Full dose	3-6 years	Headache	2	1	1	probably related
1553-2-02-002	Half dose	7-11 years	Muscle Pain	2	1	2	not related
1553-2-02-015	Half dose	7-11 years	Headache	2	2	6	possibly related
1553-2-02-029	Full dose	7-11 years	Headache, Muscle Pain	3	1	1	possibly related
1553-2-02-085*	Full dose	3-6 years	Headache	2	3	10	possibly related
1553-2-02-104	Full dose	3-6 years	Headache	2	2	2	possibly related
1553-2-21-003	Half dose	7-11 years	Headache	2	2	5	probably related
1553-2-21-008	Half dose	7-11 years	Headache, Muscle Pain	3	2	1	probably related
1553-2-21-038	Full dose	7-11 years	Headache	2	1	9	probably related
1553-2-21-042	Half dose	3-6 years	Fatigue, Headache	3	1	1	not related
1553-2-21-059	Half dose	3-6 years	Fatigue, Rash	3	1	5	probably related
1553-2-21-069*	Full dose	3-6 years	Joint Pain, Headache	3	3	1	possibly related
1553-2-21-070*	Full dose	3-6 years	Fatigue, Headache	3	3	2	not related
1553-2-21-081	Half dose	1-2 years	Inconsolable Or Excessive Crying	2	1	1	not related
1553-2-21-119	Full dose	1-2 years	Inconsolable Or Excessive Crying	2	2	1	not related
1553-2-21-126	Full dose	1-2 years	Inconsolable Or Excessive Crying	2	1	5	possibly related

*Cases in which a severe symptom of fever occurred.
AESI=adverse event of special interest; CLAR=Chikungunya-like Adverse Reactions.

Assessment

CLAR (regulatory agencies definition) were identified in 7/119 (5.9%) participants in the VLA1553 Half Dose arm (reporting 17 CLAR symptoms) and 10/124 (8.1%) participants in the VLA1553 Full Dose arm (reporting 23 CLAR symptoms). No CLAR were identified in the control arm.

When stratified by age group, no significant differences between groups were observed:

- 7-11 years: VLA1553 Half Dose 4/40 [10.0%], VLA1553 Full Dose 3/43 [7.0%];

- 3-6 years: VLA1553 Half Dose 2/40 [5.0%], VLA1553 Full Dose 5/40 [12.5%];

- 1-2 years: VLA1553 Half Dose 1/39 [2.6%], VLA1553 Full Dose 2/41 [4.9%]).

The most common CLAR symptoms overall were pyrexia and headache in 17/304 (5.6%) and 12 (3.9%) of participants, respectively. The most common combinations of CLAR symptoms were pyrexia with headache, followed by pyrexia with inconsolable or excessive crying, pyrexia with headache and myalgia, or pyrexia with headache and fatigue. When stratified by age group, the 7-11 years age group experienced pyrexia with headache or myalgia alone, or pyrexia with both headache and myalgia. Fatigue

in combination with pyrexia was only experienced by participants in the 3-6 years age group, and pyrexia with inconsolable or excessive crying was only reported in the 1-2 years age group.

Three of 304 (1.0%) participants in the 3-6 years age group who received VLA1553 Full Dose (3/40 [7.5%]) experienced a CLAR that was graded severe (Grade 3), meaning that at least one symptom of the CLAR case was graded severe.

Although CLAR per definition are considered related, each symptom was assessed for causality by the Investigator:

- Six out of 17 CLAR cases were considered probably related to treatment, meaning that at least one symptom of the CLAR case was assessed probably related to vaccination by the Investigator: 7-11 years: VLA1553 Half Dose 2/40 (5.0%), VLA1553 Full Dose 2/43 (4.7%); 3-6 years: VLA1553 Half Dose 1/40 (2.5%), VLA1553 Full Dose 1/40 (2.5%).

- Six out of 17 cases were considered possibly related to treatment, meaning that at least one symptom of the CLAR case was assessed possibly related to vaccination by the Investigator: 7-11 years: VLA1553 Half Dose 1/40 (2.5%), VLA1553 Full Dose 1/43 (2.3%); 3-6 years: VLA1553 Full Dose 3/40 (7.5%); 1-2 years: VLA1553 Full Dose 1/41 (2.4%).

Resulting questions:

None.

2.3.2.1.6. Clinical laboratory evaluation, vital signs and physical findings

Evaluation of Haematology Parameters

The following mean changes from screening to Day 29 were observed in the Safety Analysis Population:

- Haemoglobin decrease: -1.47 g/L
- Erythrocytes decrease: -0.10 x 10^{12}/L
- Leukocytes increase: 0.46 x 10^{9}/L
- Basophils/Leukocytes decrease: -0.002 (-0.2%)
- Lymphocytes/leukocytes decrease: -0.03 (-3.0%)
- Neutrophils/leukocytes increase: 0.04 (4.0%)
- Platelets increase: 4.57 x 10^{9}/L
- Erythrocyte sedimentation rate (ESR) increase: 0.45 mm/h

At Day 29, the proportions of participants with haematology parameters within the normal range were as follows:

- Haemoglobin: 83.3%
- Hematocrit: 73.3%
- Erythrocytes: 86.7%
- Leukocytes: 86.7%
- Basophils/Leukocytes: 100%
- Eosinophils/leukocytes: 66.7%

- Lymphocytes/leukocytes: 53.3%
- Monocytes/leukocytes: 96.7%
- Neutrophils/leukocytes: 63.3%
- Platelets: 56.7%
- ESR: 53.3%

At Day 29, one Grade 2 neutropenia ("neutrophils decrease") was observed in the VLA1553 Half Dose arm, in 1/40 [2.5%] participant aged 7-11 years. This participant had Grade 4 neutropenia at screening, prior to vaccination; both values were considered not clinically significant by the Investigator. All other hematology parameters on Day 29 were Grade 0. Hematology parameters by severity grading by visit are provided.

Evaluation of Coagulation Parameters

The following mean changes from screening to Day 29 were observed in the Safety Analysis Population:

- Prothrombin time (PTT) increase: 0.18 s
- Activated partial thromboplastin time increase: 0.10 s
- Fibrinogen increase: 0.09 g/L

At Day 29, the proportions of participants with coagulation parameters within the normal range were as follows :

- Prothrombin time: 93.3%
- Activated partial thromboplastin time: 65.5%
- Fibrinogen: 86.7%

No severe coagulation parameters were observed.

Evaluation of Urine Laboratory Results

Few clinically relevant changes from baseline to Month 12 were observed for urine laboratory parameters. One participant from each age group had abnormal analysis values that were listed as clinically significant. According to the Investigator's interpretation, the results were linked in one case to an unsolicited AE of proteinuria and in two cases linked to unsolicited AEs of urinary tract infection. Urinalysis results by visit for the Safety Analysis Population are provided. The proportion of participants with abnormal urinalysis results at Month 12 is listed below:

- pH: 0.4%
- Urine leukocytes: 3.7%
- Protein: 7.8%
- Ketones: 1.5%
- Urine erythrocytes: 2.2%

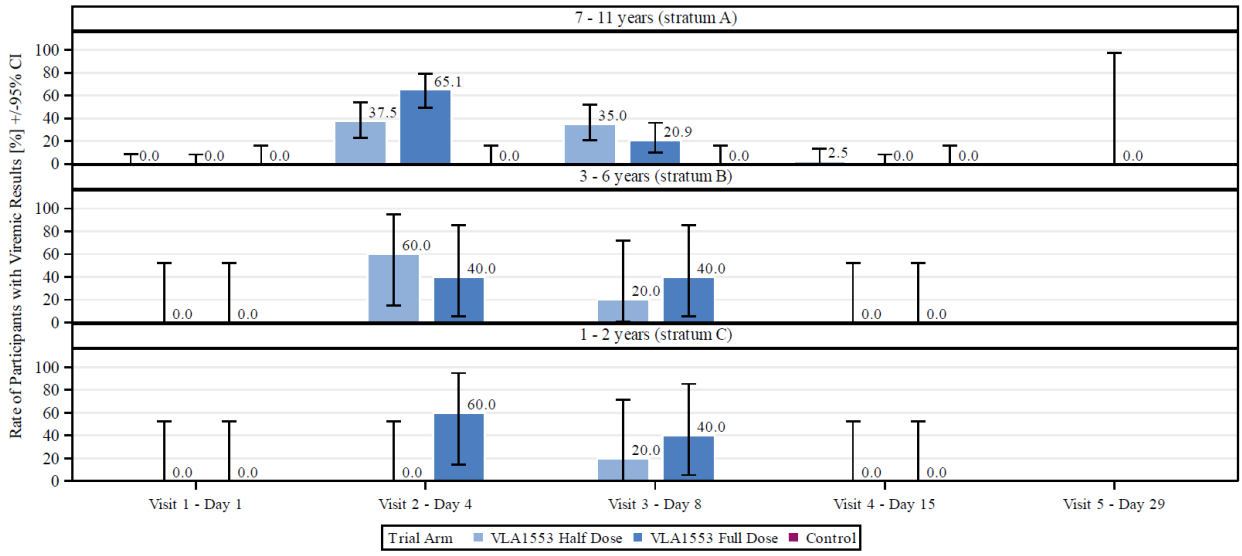
2.3.2.1.7. Vital signs, physical findings, and other observation related to safety

No significant changes from baseline to Day 1 post-dose were observed for any vital signs in either age group or trial arm.

No significant changes from screening to Month 12 were observed for physical examination results.

2.3.2.1.8. Viremia

The presence of CHIKV RNA in plasma from participants included in the viremia subset of the Safety Analysis Population (N=124) is summarized in Figure 4 by visit, trial arm, and age group, and viremia results (GCE/mL) by visit is presented in Figure 4.



CI=confidence interval; LLOQ=lower limit of quantification
Viremic results are all samples with numeric results and with <LLOQ. Note: For exact values, see Table 14.5.12.
Visit 5 (Day 29) not applicable for participants aged 1-6 years, since no participant tested positive for viremia at Visit 4 (Day 15).
Viremia samples were taken from all participants of Stratum A and only taken from sentinel participants from Stratum B and C.

Figure 4. Participants with Viremia Results by Trial Visit and Trial Arm panelled by Age Group (Safety Analysis Population, Viremia Subset)

Assessment

Vaccine-induced viremia was assessed by detection of CHIKV RNA (amplified by RT-qPCR targeting the nsP1 region within the viral genome). CHIKV RNA was detected in a proportion of vaccinated individuals between Day 4 and Day 15 post-vaccination. Overall, the highest proportion of quantifiable viremia was observed on Day 4 (35/124; 28.2%), with an additional 12.9% (16/124) below LLOQ and above LOD. By Day 8, the proportion with quantifiable viremia decreased to 14.5% (18/124), and further to 0.8% (1/124) by Day 15. In this single participant with quantifiable viremia on Day 15, had undetectable CHIKV RNA by Day 29. Viremia ranged from 536 to 413.236 genome copy equivalents per millilitre (GCE/mL).

Due to the small sample size, no meaningful comparisons can be made between the full- and half-dose groups or across age groups (1–2, 3–6, and 7–11 years) with respect to the proportion of participants with viremia or viremia levels (GCE/mL).

Vaccine-induced viremia was not detected in any of the baseline seropositive participants at all time points.

Overall, the pattern observed in children is consistent with adult data at the time of MAA, showing that vaccine viremia occurs within the first week following vaccination and resolves by approximately Day 14.

Resulting questions:

None.

2.3.3. Discussion on clinical aspects

VLA1553-221 is a randomized, observer-blinded, dose response phase 2 trial to assess the safety and immunogenicity of two different dose level of VLA1553, a live-attenuated chikungunya vaccine (commercialized as Ixchiq), in healthy children aged 1 to 11 years. The aim of this study is to support dose selection for further clinical development in this age group.

Ixchiq is authorized by EMA since 2024. The current indication is active immunisation for the prevention of disease caused by chikungunya virus (CHIKV) in individuals 12 years and older. The use of this vaccine should be in accordance with official recommendations. Posology comprises a single intramuscular administration of a dose containing not less than 3.0 log10 $TCID_{50}$ of live attenuated chikungunya virus.

In study VLA1553-221, participants were randomised in a 2:2:1 ratio to receive either a full dose (4.0 log_{10} $TCID_{50}$/0.5 mL) or a half dose (3.7 log_{10} $TCID_{50}$/0.5 mL) of the investigational vaccine VLA1553 (n=120 per group) or a control MenACWY vaccine (Nimenrix; n=60). However, the clinical relevance of comparing a half versus full dose is unclear, as the theoretical difference in potency falls within the variability of the assay and manufacturing process. It is therefore unlikely that the half dose will translate into a meaningful difference in the actual administered dose, reactogenicity/safety and immune response. Nevertheless, this concern was already raised during the initial PIP evaluation, where the MAH indicated that lower dose levels are not technically feasible.

The study enrolled generally healthy male and female paediatric participants aged 1 to 11 years at the time of vaccination. Participants were stratified into three age groups: Stratum A (7 to 11 years), Stratum B (3 to 6 years), and Stratum C (1 to 2 years).

Participants could be either seropositive for prior CHIKV exposure (defined as IgM+/IgG+ or IgM-/IgG+), seronegative (IgM-/IgG-), or present with indeterminate serological status (i.e. IgM?/IgG-, IgM+/IgG?, or IgM-/IgG?). Participants with an IgM+/IgG− serological profile, indicative of a recent CHIKV infection, were excluded from the study. The reason for including participants with a serostatus IgM?/IgG- or, IgM+/IgG? is unclear as those participants could have experienced a recent CHIKV infection.

The primary objective was to assess the tolerability of the full-dose and half-dose formulations of VLA1553. Solicited local reactions (injection site pain, tenderness, erythema/redness, induration, and swelling) and systemic reactions (nausea/vomiting, headache, fatigue, myalgia, arthralgia, and rash) were recorded within 14 days following vaccination.

Secondary objectives included further evaluation of safety and immunogenicity. Safety assessments comprised the recording of unsolicited adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) up to 12 months post-vaccination. Viraemia was assessed on Days 1, 4, 8, and 15, and beyond as applicable.

Immunogenicity endpoints included the evaluation of CHIKV-specific neutralising antibody titres measured by µPRNT assay at Day 1 (baseline), Day 15, Day 29, Day 85, Day 180, and Month 12. Additional parameters included the proportion of participants achieving seroconversion, the proportion achieving a sero-response (defined as $\mu PRNT_{50}$ ≥150 in baseline seronegative participants), and fold-increase in antibody titres.

As an exploratory objective, the efficacy of VLA1553 was assessed in CHIKV-endemic areas, with onset starting 15 days after vaccination. No PCR for testing wild-type CHIKV was performed precluding any conclusion regarding efficacy.

Analysis populations include a safety set (all vaccinated participants), an immunogenicity analysis set (IMM) (all vaccinated participants who have evaluable μPRNT antibody titre results at baseline and at least one measurement after vaccination), and a per-protocol (PP) population restricted to baseline seronegative participants without major protocol deviations (PD) impacting immune response.

Participants with a CHIKV neutralising antibody titre of μPRNT50 ≤ 40 were classified as seronegative, while those with an antibody titres μPRNT50 >40 were classified as seropositive at baseline.

A total of 304 participants were vaccinated (Safety analysis population), in line with the planned randomization. The immunogenicity analysis population (IMM) included 302 participants.

Protocol deviations were reported for 207/304 participants (68.1%) in the Safety Analysis Population, and were balanced across age strata and treatment arms. The vast majority of PD were minor and not considered to impact the primary immunogenicity endpoints. This resulted in 275 participants included in the PP population. There were also 24 seropositive participants included in the IMM.

The trial was conducted at two sites in the Dominican Republic and one site in Honduras, countries considered endemic for chikungunya virus, irrespective of recent local transmission. All participants were vaccinated between 9 January and 17 July 2024.

Baseline demographic characteristics are overall well balanced across treatment arms and age strata. The study population had a balanced sex distribution (48% female) and consisted predominantly of Hispanic/Latino participants of multiracial (70.1%) or Black/African American (28.9%) background. Most participants were seronegative at baseline (92.1%), with a small number of seropositive individuals limited to the oldest age group.

In line with observations in adults (VLA1553-301 trial) and adolescents (VLA1553-321 trial), most of the paediatric participants who were CHIKV- seronegative at baseline elicited a response ≥ 150 μPRNT50 at 28 days post-vaccination with VLA1553. This threshold of 150 μPRNT50 was defined as reasonably likely to predict protection (cfr EPAR MAA). GMTs were also within the same range as those observed in adults.

The kinetics of the immune response is similar to those observed in adults and adolescents, i.e. with a peak of the response at 28 days post-vaccination followed by a decrease in GMTs observed at 3 months post-VLA1553. Noteworthy, GMTs remained high at 12 months post-vaccination, resulting in a proportion of seroresponders comparable to that at 28 days post-vaccination.

No major differences in post-vaccination immune responses were observed between the half and the full dose, however a slight trend towards lower responses was noted with the half dose. This trend may not be observed in real-life settings as the theoretical difference in potency falls within the variability of the assay and manufacturing process. However, in this study an actual difference in potency between the half- and the full- doses cannot be excluded, given that the same lot was most probably used to administer either the half or the full dose. No information on lot numbers has been provided.

Within 14 days of vaccination, solicited injection site AEs were reported more frequently in the VLA1553 Half Dose arm (17.6%) than in the VLA1553 Full Dose (12.9%) and control arms (13.1%) (not statistically different) (all considered related). Although there were no statistically significant differences, the older age group had numerically higher frequencies of solicited injection site AEs in each arm.

Solicited systemic AEs were more frequently reported in the VLA1553 full dose (33.9%), vs. the half dose (25.2%), vs. the control (16.4%) (difference vs. control significant). There were no clear differences between age groups. Similarly, related solicited systemic AEs were more frequently reported in the VLA1553 full dose (25%), vs. the half dose (18.5%), vs. the control (11.5%) (not statistically significant).

Up to Month 12, unsolicited AEs were reported at a similar frequency in the three trial arms (70.6%, 71.0%, and 73.8% participants in the VLA1553 Half Dose, Full Dose, and control arms, respectively), and their frequencies were similar regardless of the age group.

AESI (protocol definition) were reported in 5/119 (4.2%) participants in the VLA1553 Half Dose arm: 3 participants in the 7-11 years age group experienced a combination of pyrexia and headache, and 2 participants in the 3-6 years age group experienced pyrexia/macular rash and pyrexia/headache/rash/myalgia. No AESI were reported in the VLA1553 Full Dose and control arms.

CLAR (regulatory agencies definition) were identified in 7/119 (5.9%) participants in the VLA1553 Half Dose arm (reporting 17 CLAR symptoms) and 10/124 (8.1%) participants in the VLA1553 Full Dose arm (reporting 23 CLAR symptoms), without significant differences between age groups. The most common combinations of CLAR symptoms were pyrexia with headache, followed by pyrexia with inconsolable or excessive crying, pyrexia with headache and myalgia, or pyrexia with headache and fatigue. No CLAR were identified in the control arm.

Transient vaccine-induced viremia was observed, with CHIKV RNA detectable from Day 4 to Day 15 post-vaccination. In the single participant with quantifiable viremia on Day 15, CHIKV RNA was undetectable by Day 29. This pattern is consistent with data at the time of MAA, showing that vaccine viraemia occurs within the first week following vaccination and resolves by approximately Day 14.

Data per age category and trial arm could not be interpreted due to the limited sample size. Moreover, the number of seropositive participants was too small to draw any definitive conclusions.

Conclusion

The MAH conclusion that "*The comparability of the VLA1553 doses tested in terms of safety and tolerability, along with the more pronounced immune response of the Full Dose observed for all age groups tested in children up to Day 180 post-vaccination, support the selection of the Full Dose for use in this population*", is not fully endorsed.

While no clear trend could be identified concerning the differences of safety profiles between the VLA1553 Full or Half Dose arms, or between the different age categories (1-2, 3-6 or 7-11 years), it is to be noted that only a trend, without meaningful differences, was observed in SRR and GMTs between the half and the full dose.

Evaluation of doses lower than the half dose would have been informative, since the theoretical difference in potency between the half and the full dose falls within the variability of the assay and manufacturing process. However, this concern was already raised during the initial PIP evaluation, where the MAH indicated that lower dose levels are not technically feasible. Furthermore, as the Phase 3 trial planned to be conducted in children 1-11 years of age (VLA1553-322) has been withdrawn according to ClinicalTrials.gov, this no longer has implications. Should a subsequent study in paediatric subjects aged 1–11 years at high risk of exposure nonetheless be conducted, the selected dose level should be carefully considered and justified, taking into account both safety considerations and immunogenicity data. In view of the known safety concerns associated with VLA1553, administration of a dose higher than necessary cannot be supported.

3. CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.