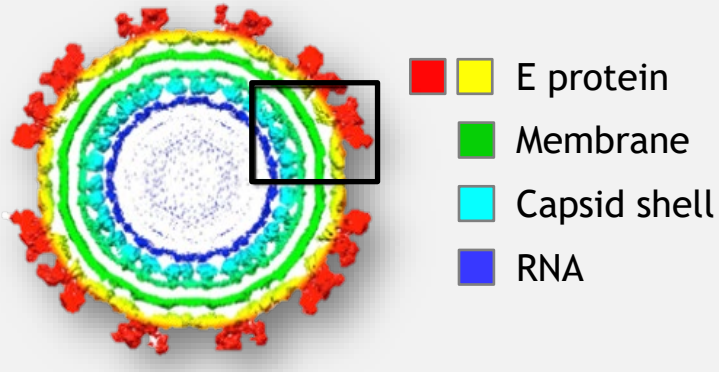
CHIKV VLP vaccine

Bavarian Nordic's chikungunya vaccine candidate

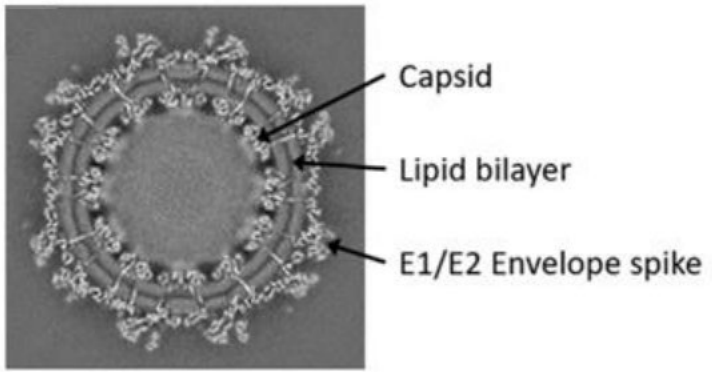
October 2024

Victoria Jenkins, PhD, MBA
VP Regulatory Affairs & CHIKV Program Lead
Bavarian Nordic
vije@bavarian-nordic.com

CHIKV virus-like particle vaccine (CHIKV VLP)[1]



Chikungunya virus[3]



CHIKV VLP vaccine

Cryo-electron microscopy reconstruction of CHIKV VLP[2]

- Comprised of 3 recombinant chikungunya virus (CHIKV) structural proteins that assemble into virus-like particles, which mimic the CHIKV but cannot replicate
- Adjuvanted with aluminum hydroxide; single 40 µg VLP dose (0.8 mL) in a pre-filled syringe; administered IM
- Priority Review for the BLA granted by FDA (PDUFA target action date: 14th Feb 2025)
  - **Proposed indication:** prevention of disease caused by CHIKV infection in individuals 12 years of age and older
  - **Proposed contraindications:** hypersensitivity, including severe allergic reaction (anaphylaxis), to any component
- It was agreed with regulators to use a defined threshold of serum neutralizing antibodies as a surrogate endpoint of efficacy in phase 3 clinical trials

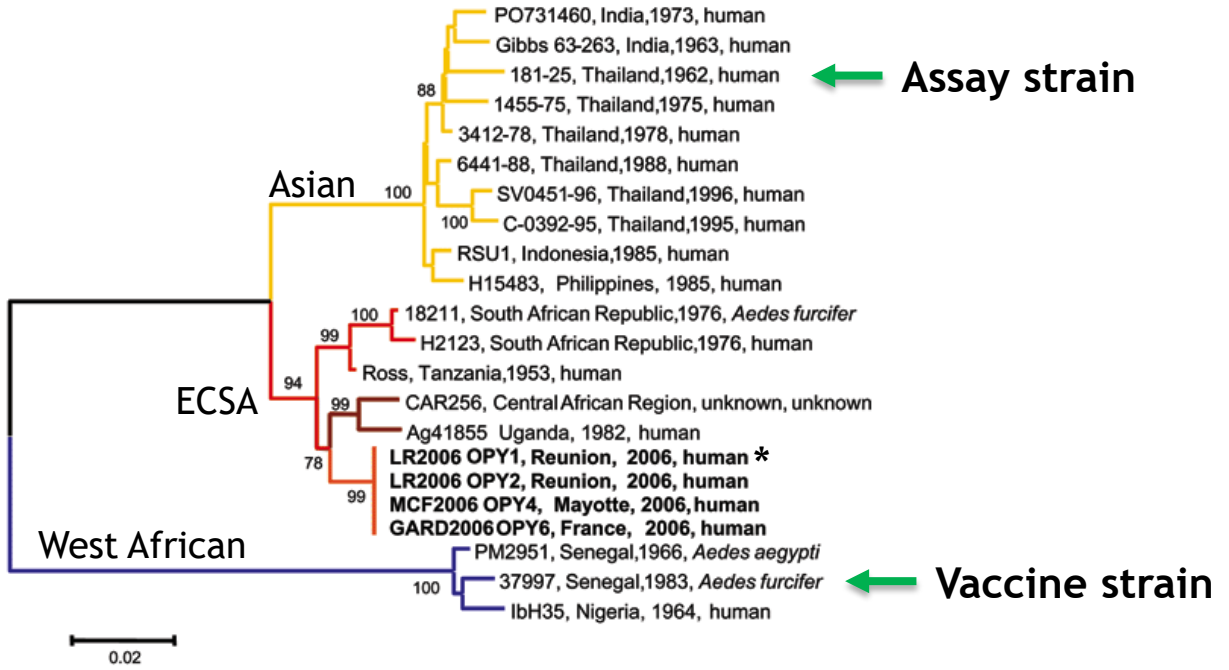
CHIKV, chikungunya virus; VLP, virus-like particle; BLA, Biologics License Application; PDUFA, Prescription Drug User Free Act

1. Bennett SR, *et al*. Lancet Infect Dis. 2022;22(9):1343–1355. 2. Basore K *et al*. Cell. 2019 Jun 13;177(7):1725-1737. 3. Sun S, *et al*. ELife. 2013;2:e00435

CHIKV-luciferase assay developed to evaluate vaccine efficacy measures cross-neutralization

- CHIK181/25 live-attenuated virus (Asian lineage AF15561) engineered to express luciferase transgene (CHIKV-luc assay reporter)
- Neutralization assay based on 80% (NT_{80}) reduction of luciferase activity following Vero cell infection with CHIKV-luc
- CHIKV-luc virus used in the assay is heterologous to the CHIKV VLP (Asian vs West African)

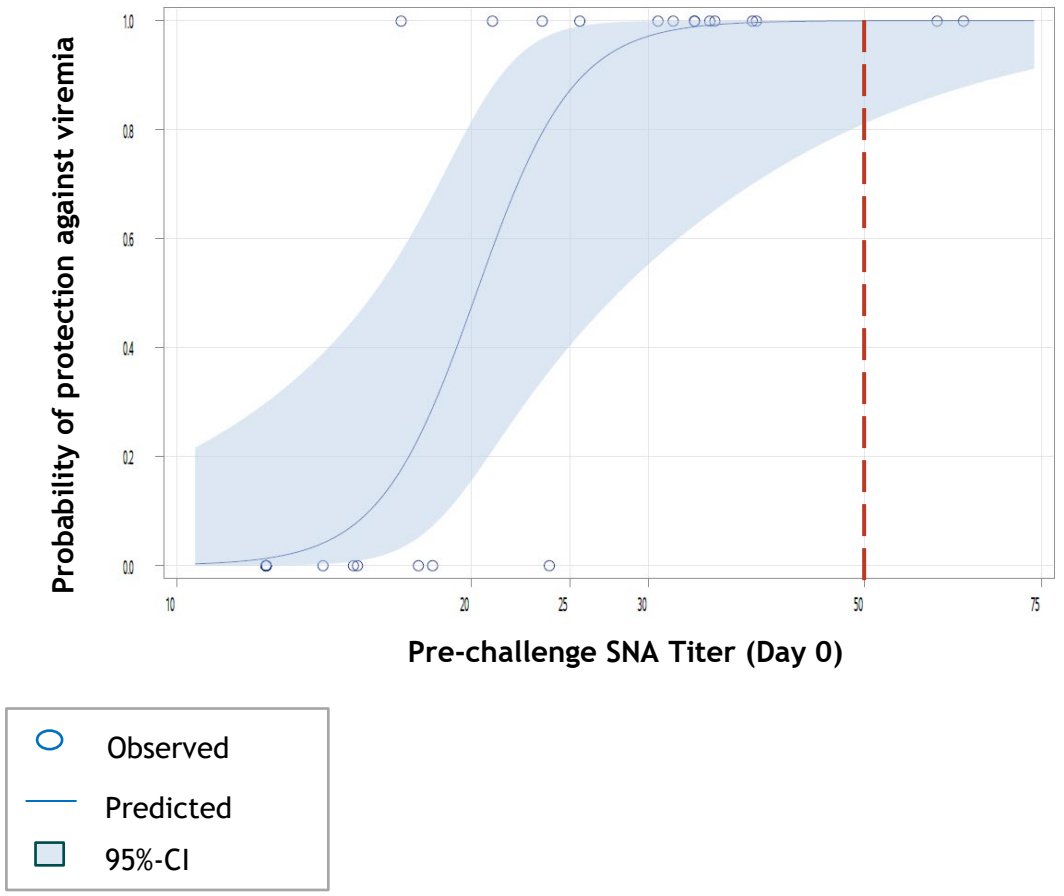
Phylogenetic analysis of CHIKV isolates based on a 1kb fragment in the E1 gene[1]



1. Parola P, de Lamballerie X, Jourdan J, Rovery C, Vaillant V, Minodier P, *et al*. Emerg Infect Dis. 2006;12(10):1493-1499.

ECSA, East-Central-South-African * CHIKV strain that was used as a challenge in nonhuman primate serum transfer study (next slide)

Conservative serum neutralizing antibody (SNA) threshold chosen for phase 3 study immunogenicity endpoints based on NHP data & regulatory agency recommendations



Serum passive transfer and challenge study in NHP

- NHPs received pooled sera from human participants vaccinated with CHIKV VLP at various dilutions intravenously and were challenged with CHIKV 24 hours later
- Logistic regression model:
  - SNA titer of 50 results in 99.97% [81-100] probability of protection against viremia
- Regulatory agencies* proposed and agreed a more conservative SNA titer threshold of 100 to be an acceptable surrogate endpoint

CHIKV, chikungunya virus; NHPs, nonhuman primate; SNA, serum neutralizing antibodies; CI, confidence interval
Data presented at ESCMID Global 2024 (not yet published in a peer-reviewed article)
*FDA and EMA

CHIKV VLP vaccine clinical program

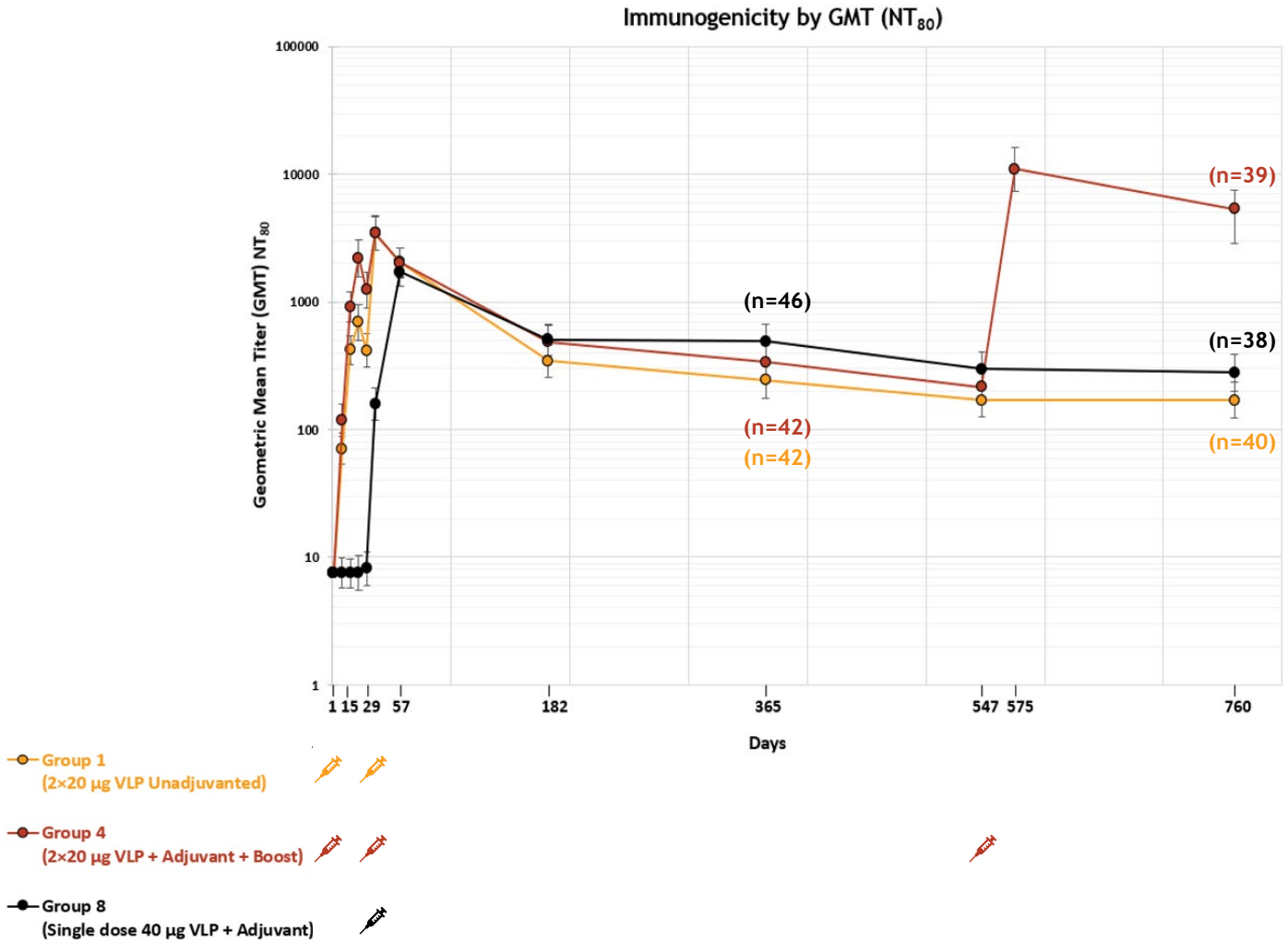
Study description	Study design	Study phase and number	Age range (years)	Number of participants (vaccine recipients)
• Dose- and dose-schedule finding	randomized, double-blind, parallel-group	Phase 2[1] PXVX-CV-317-001	18 - 45	445 (441)
• Immunogenicity & Safety and tolerability of 40ug dose	open label	Phase 2[2] EBSI-CV-317-010	18 - 45	25 (25)
• Immunogenicity and safety in prior alphavirus vaccine recipients	open label, parallel-group	Phase 2[3] EBSI-CV-317-002	18 - 65	60 (60)
• Immunogenicity & Safety and tolerability • Lot-to-lot consistency	randomized, double-blind, placebo-controlled	Phase 3[4] (pivotal) EBSI-CV-317-004	12 - <65	3254 (2790)
• Immunogenicity & Safety and tolerability	randomized, double-blind, placebo-controlled	Phase 3[5] (pivotal) EBSI-CV-317-005	≥65	413 (206)

1. Bennett et al. Safety and immunogenicity of PXVX0317, an aluminium hydroxide-adjuvanted chikungunya virus-like particle vaccine: a randomized, double-blind, parallel-group, phase 2 trial. Lancet Infect Dis. 2022;22(9):1343-55.
2. ClinicalTrials.gov ID: NCT05065983; 3. ClinicalTrials.gov ID: NCT03992872; 4. ClinicalTrials.gov ID: NCT05072080; 5. ClinicalTrials.gov ID: NCT05349617. 6. Chang *et al*. Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: a phase 1 dose-escalation trial. Lancet, vol. 384,9959 (2014):2046-52. 7. Goo *et al*. A virus-like particle vaccine elicits broad neutralizing antibody responses in humans to all chikungunya virus genotypes. J Infect Dis, vol. 214,10 (2016):1487-1491. 8. Chen *et al*. Effect of a chikungunya virus-like particle vaccine on safety and tolerability outcomes: A randomized clinical trial. JAMA, vol. 323,14 (2020):1369-1377. 9. McCarty *et al*. Chikungunya virus virus-like particle vaccine is well tolerated and immunogenic in chikungunya seropositive individuals. Vaccine, vol. 41,42 (2023):6146-6149. 9
BLA, Biologics license application

Immune response according to dose and dosing schedule

PXVX-CV-317-001
Phase 2

Single 40 µg CHIKV VLP adjuvanted dose had superior immunogenicity after first vaccination, showed a rapid and durable response, and was well-tolerated



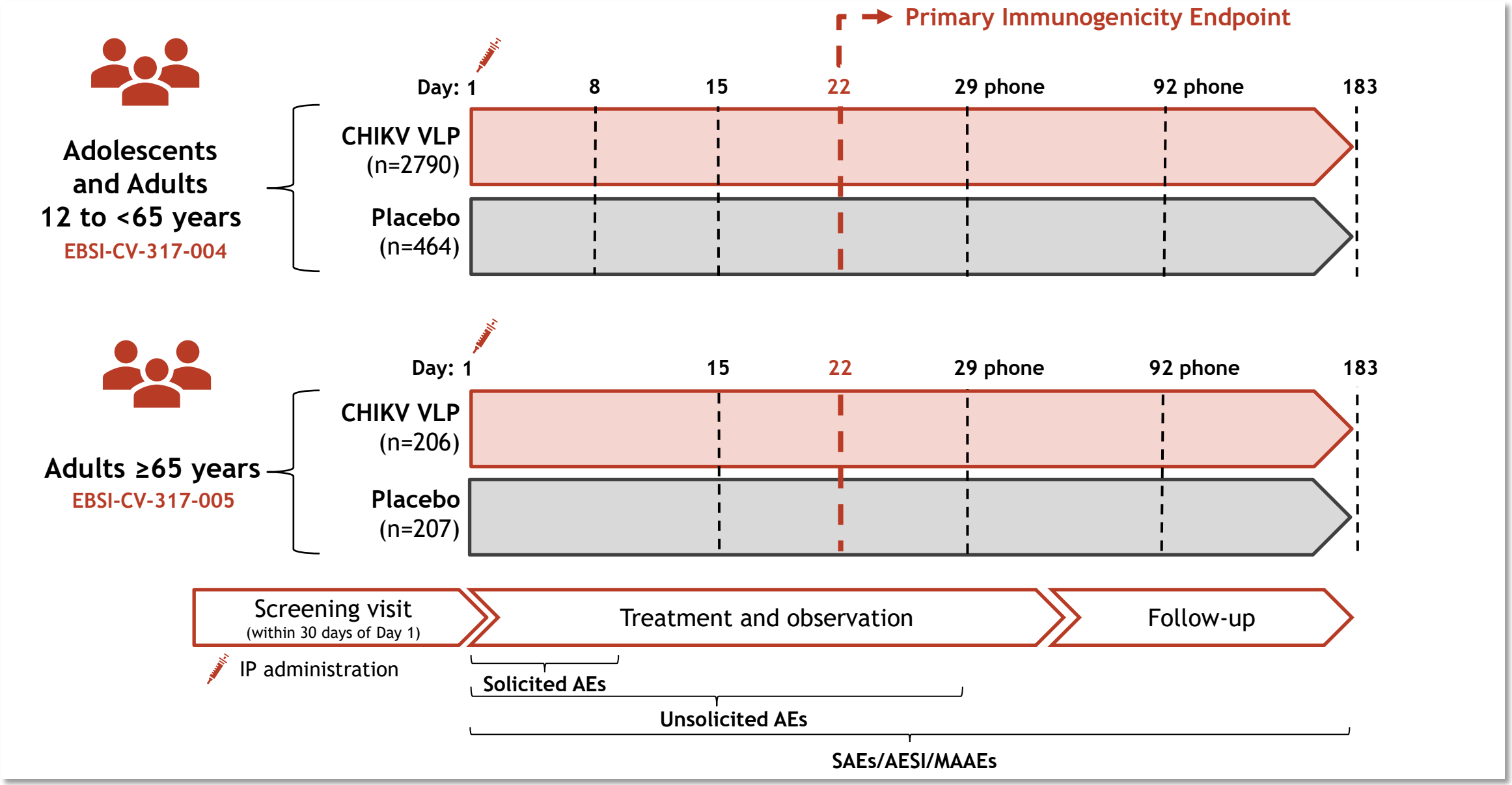
- At year 1, Group 8 had significantly higher GMTs vs Group 1 (491.7 vs 243.4; p-value=0.0019); this was maintained at year 2 (279.7 vs 169.8; p-value=0.0369)
- AEs mostly mild to moderate; no serious treatment-related unsolicited AEs
- Local AEs more frequent in 40 ug adjuvanted CHIKV VLP group (40%) than in unadjuvanted group (23%)

Primary Endpoint: GMT of anti-CHIKV SNA level on Day 57 (28 days after last vaccination); adjuvant = aluminum hydroxide
Vertical bars denote 95% confidence interval. GMT = geometric mean titer; NT_{80} = Neutralization Titer showing 80% neutralization
Bennett *et al*. Lancet Infect Dis. 2022;22(9):1343-55.

Pivotal phase 3 studies

EBSI-CV-317-004 in individuals 12 to <65 years
EBSI-CV-317-005 in individuals ≥65 years

Design of the two pivotal phase 3 studies



Richardson *et al*. Safety and Immunogenicity of an Adjuvanted Chikungunya Virus (CHIKV) Virus-like Particle (VLP) Based Vaccine in Two Pivotal Phase 3 Trials, ≥12 Years of Age. IDWeek oral presentation, 14 October 2023, Boston, MA.
AE = adverse event; AESI = adverse event of special interest; MAAE = medically attended adverse event; SAE = serious adverse event

Primary and key secondary objectives in phase 3 studies

EBSI-CV-317-004
12 to <65 years of age

Coprimary:

- SNA GMT at Day 22 versus placebo
- Difference in seroresponse rate[1] versus placebo at Day 22
- Safety
- Lot consistency of anti-CHIKV SNA GMT at Day 22 (18 to 45 years)

Key Secondary:

- Seroresponse rates at Day 8, Day 15, Day 183 versus placebo

EBSI-CV-317-005
≥65 years of age

Coprimary:

- SNA GMT at Day 22 versus placebo
- Difference in seroresponse rate[1] versus placebo at Day 22
- Safety

Key Secondary:

- Seroresponse rates at Day 15 and Day 183 versus placebo

[1] Seroresponse rate (considered the presumptive seroprotection rate) was defined as the percentage of participants who achieve a CHIKV-luc neutralization titer (NT_{80}) ≥100
GMT = geometric mean titer; SNA = serum neutralizing antibody

Balanced demographic characteristics in study including adolescents and adults 12 to <65 years of age

Characteristic[1]	CHIKV VLP (n=2794)	Placebo (n=464)	Total (N=3258)
Age (years)			
Mean (SD)	39 (14.3)	39 (14.4)	39 (14.3)
Age group, n (%)[2]			
12 to 17 years	217 (7.8)	37 (8.0)	254 (7.8)
18 to 45 years	1636 (58.6)	270 (58.2)	1906 (58.5)
46 to 64 years	941 (33.7)	157 (33.8)	1098 (33.7)
Sex, n (%)[2]			
Male	1358 (48.6)	233 (50.2)	1591 (48.8)
Female	1436 (51.4)	231 (49.8)	1667 (51.2)
Race, n (%)[2]			
White	2043 (73.1)	341 (73.5)	2384 (73.2)
American Indian or Alaska Native	30 (1.1)	2 (0.4)	32 (1.0)
Asian	79 (2.8)	16 (3.4)	95 (2.9)
Black or African American	534 (19.1)	89 (19.2)	623 (19.1)
Native Hawaiian or Other Pacific Islander	6 (0.2)	4 (0.9)	10 (0.3)
Multiracial	78 (2.8)	8 (1.7)	86 (2.6)
Not reported	24 (0.9)	4 (0.9)	28 (0.9)
Ethnicity – n(%)[2]			
Hispanic or Latino	506 (18.1)	71 (15.3)	577 (17.7)
Not Hispanic or Latino	2226 (79.7)	379 (81.7)	2605 (80.0)
Not reported	61 (2.2)	14 (3.0)	75 (2.3)
Unknown	1 (<0.1)	0	1 (<0.1)
BMI (kg/m^2)			
Mean (SD)	26.79 (4.53)	26.46 (4.61)	26.74 (4.54)

[1] Demographic characteristics of the IEP are displayed. [2] Percentages are based on the number of participants in each study arm.
BMI, body mass index; CHIKV, chikungunya virus; IEP, immunogenicity-evaluable population; LLOQ, lower limit of quantitation; SD, standard deviation; VLP, virus-like particle; Bavarian Nordic data on file.

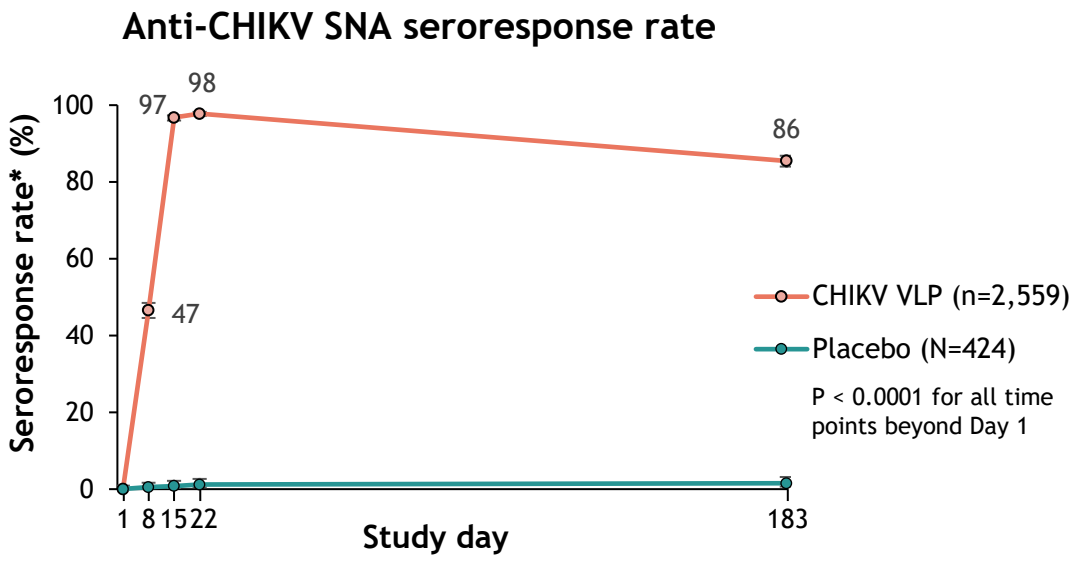
Balanced demographic characteristics in study including adults ≥65 years of age

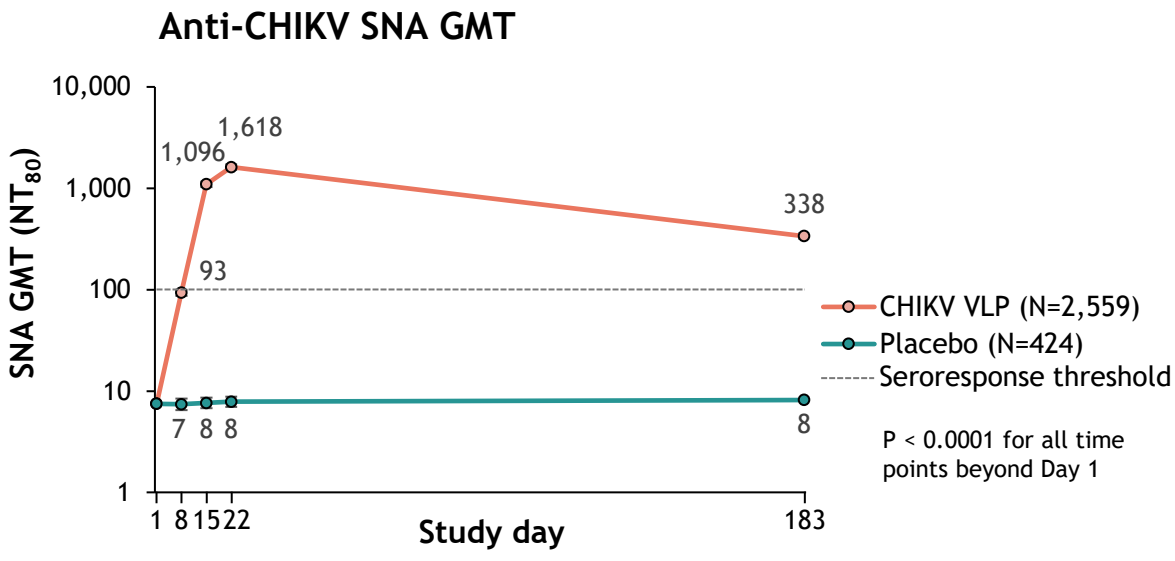
Characteristic[1]	CHIKV VLP (n=206)	Placebo (n=207)	Total (N=413)
Age (years)			
Mean (SD)	71 (5.3)	71 (4.5)	71 (4.9)
Age group, n (%)[2]			
65 to 74 years	159 (77.2%)	159 (76.8%)	318 (77.0%)
≥75 years	47 (22.8%)	48 (23.2%)	95 (23.0%)
Sex, n (%)[2]			
Male	81 (39.3%)	90 (43.5%)	171 (41.4%)
Female	125 (60.7%)	117 (56.5%)	242 (58.6%)
Race, n (%)[2]			
White	176 (85.4%)	168 (81.2%)	344 (83.3%)
American Indian or Alaska Native	1 (0.5%)	1 (0.5%)	2 (0.5%)
Asian	4 (1.9%)	1 (0.5%)	5 (1.2%)
Black or African American	20 (9.7%)	29 (14.0%)	49 (11.9%)
Multiracial	4 (1.9%)	5 (2.4%)	9 (2.2%)
Not reported	1 (0.5%)	3 (1.4%)	4 (1.0%)
Ethnicity – n(%)[2]			
Hispanic or Latino	93 (45.1%)	90 (43.5%)	183 (44.3%)
Not Hispanic or Latino	112 (54.4%)	116 (56.0%)	228 (55.2%)
Not reported	1 (0.5%)	1 (0.5%)	2 (0.5%)
BMI (kg/m^2)			
Mean (SD)	27.3 (3.98)	27.6 (3.90)	27.5 (3.94)

[1] Demographic characteristics of the IEP are displayed. [2] Percentages are based on the number of participants in each study arm.
BMI, body mass index; CHIKV, chikungunya virus; IEP, immunogenicity-evaluable population; LLOQ, lower limit of quantitation; SD, standard deviation; VLP, virus-like particle; Bavarian Nordic data on file.

Rapid induction of robust anti-CHIKV seroresponse rates and GMT in adolescents and adults 12 to <65 years of age

(immunogenicity evaluable population)



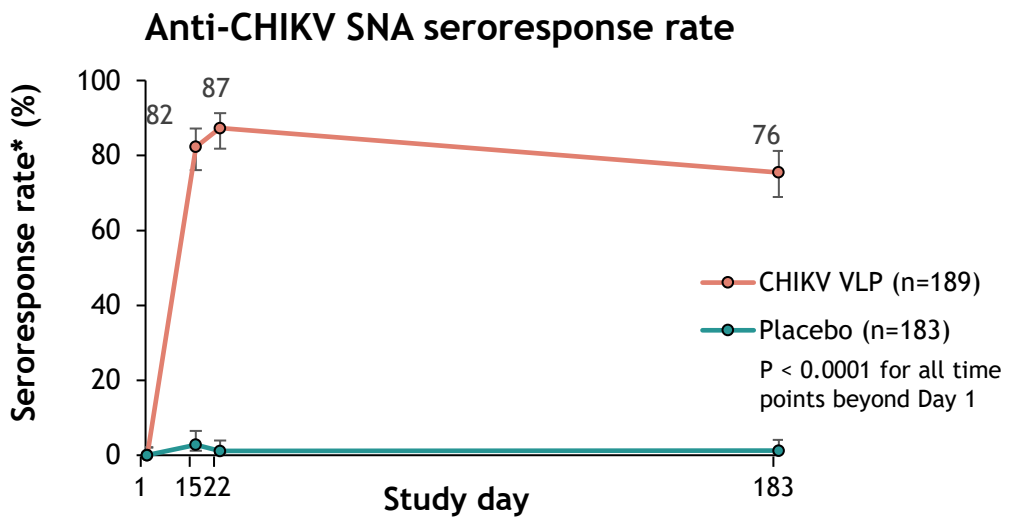


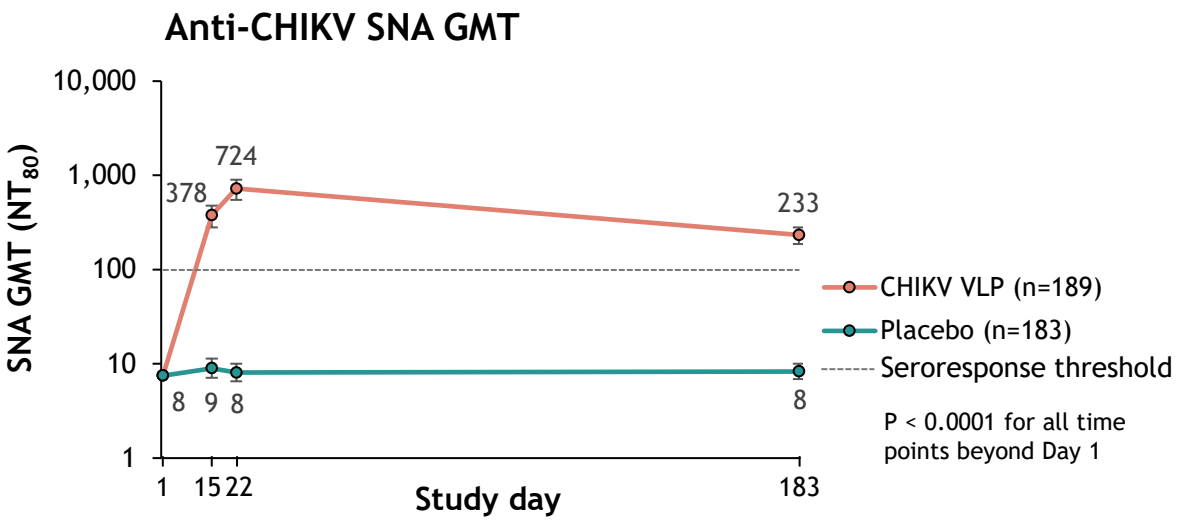
- All co-primary endpoints were met:
  - At Day 22, the seroresponse rate difference between vaccine and placebo group was 96.6% (95% CI: 95.0%, 97.5%)**
  - At Day 22, the vaccine group GMT was significantly higher than that for placebo (1618 vs. 8; P<0.0001, ANOVA)
  - The pairwise lot comparison of SNA response to CHIKV VLP vaccine in adults aged 18 to 45 years demonstrated equivalence
- All key secondary endpoints were met

* Seroresponse rate (considered the presumptive seroprotection rate) was defined as the percentage of participants who achieved an anti-CHIK SNA NT_{80} titer ≥100
** Success criterion met: lower bound of the two-sided 95% CI on the difference in seroresponse rates between CHIKV VLP vaccine and placebo groups ≥70%;
Vertical bars denote 95% confidence interval; CI = confidence interval; GMT = geometric mean titer; IEP = immunogenicity evaluable population; SNA = serum neutralizing antibody; LLOQ =
Note: 15 was the lower limit of quantitation (LLOQ) for the human SNA assay, so results <LLOQ were set to a titer of LLOQ/2 or 7.5 for analysis
Data presented at IDWeek 2023, Data not yet published in a peer-reviewed article.

Rapid induction of robust anti-CHIKV seroresponse rates and GMT in adults ≥65 years of age

(immunogenicity evaluable population)

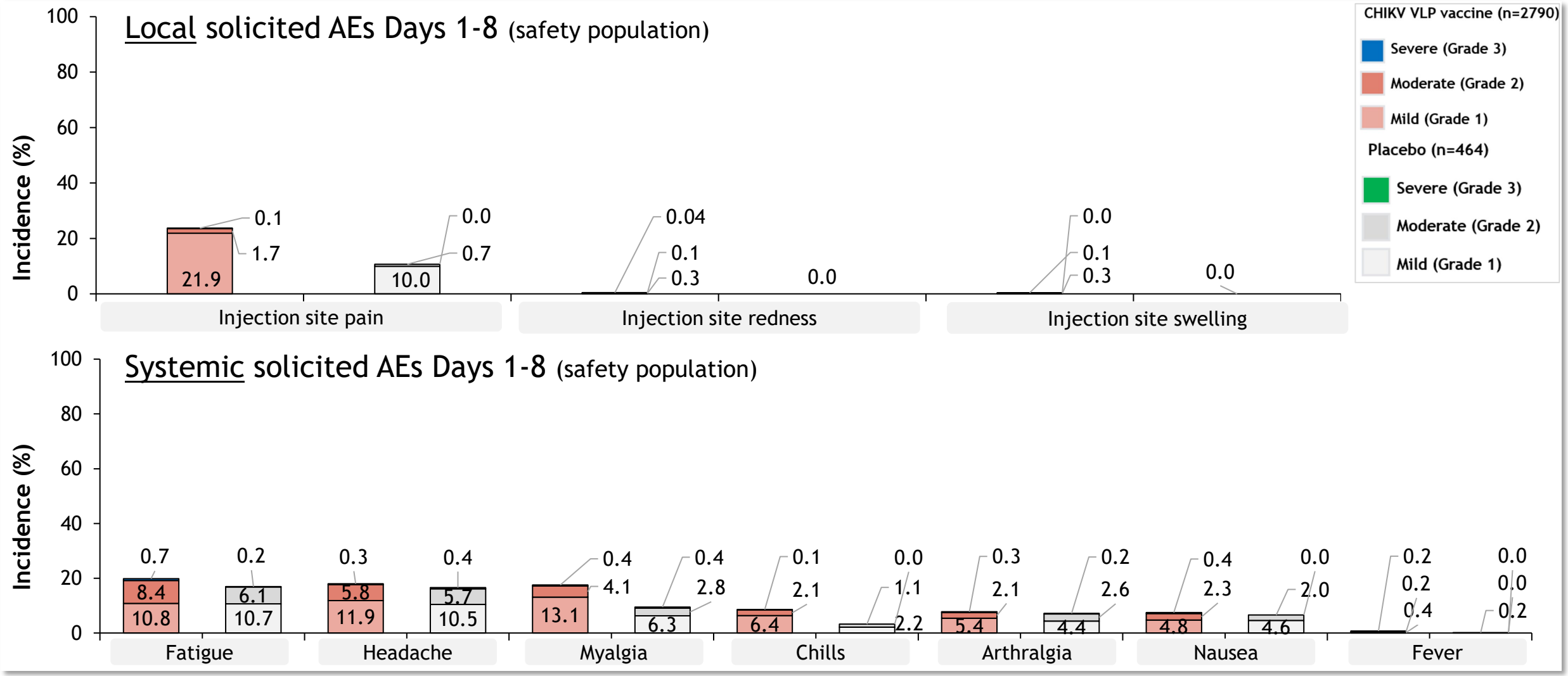




- All co-primary endpoints were met
  - At Day 22, the seroresponse rate difference between vaccine and placebo group was 86.2% (95% CI: 72.3%, 84.6%)**
  - At Day 22, the vaccine group GMT was significantly higher than that for placebo (724 vs. 8; P<0.0001, ANOVA)
- All key secondary endpoints were met

* Seroresponse rate (considered the presumptive seroprotection rate) was defined as the percentage of participants who achieved an anti-CHIK SNA NT_{80} titer ≥100
Vertical bars denote 95% confidence interval; CI = confidence interval; GMT = geometric mean titer; IEP = immunogenicity evaluable population; SNA = serum neutralizing antibody; LLOQ = lower limit of quantitation
Note: 15 was the LLOQ for the human SNA assay, so results <LLOQ were set to a titer of LLOQ/2 or 7.5 for analysis
Data presented at IDWeek 2023, Data not yet published in a peer-reviewed article.

CHIKV VLP vaccine was well-tolerated in individuals 12 to <65 years of age

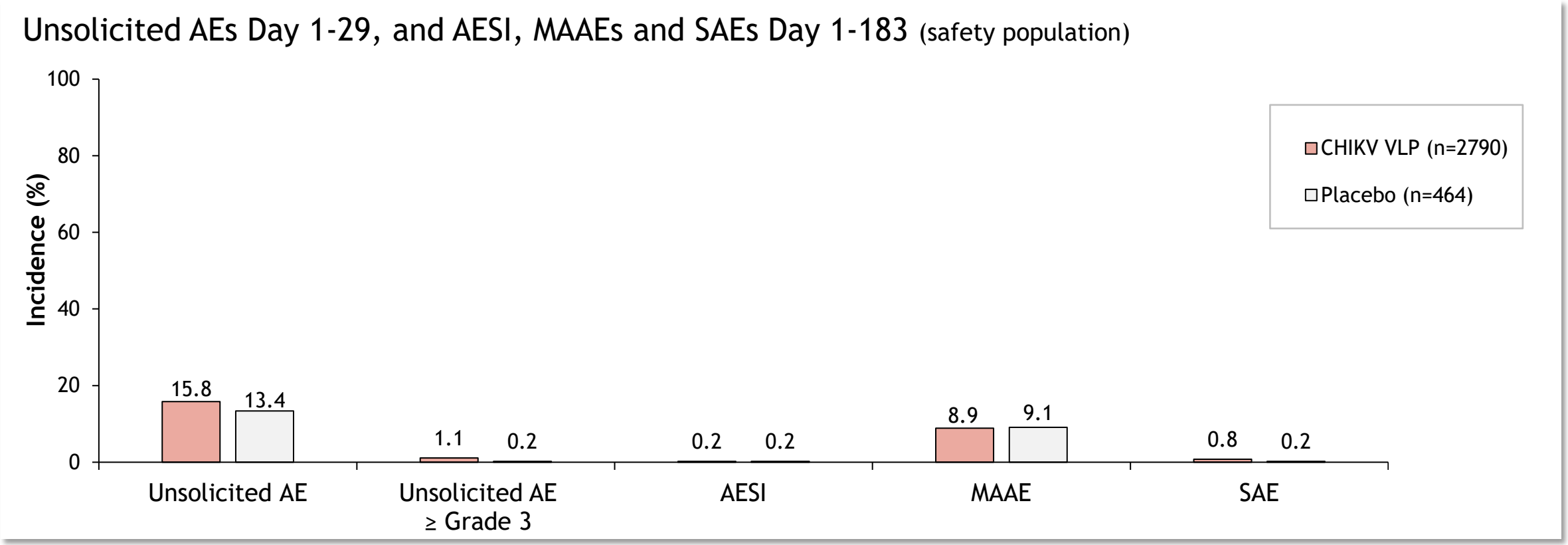


- Grade 3 (severe) local solicited AEs occurred in 5 (0.2%) CHIKV VLP vaccine recipients (4 injection site pain and 1 injection site redness); no placebo recipients reported ≥Grade 3 events.
- Grade 3 (severe) systemic solicited AEs occurred in 41 (1.5%) CHIKV VLP vaccine recipients and in 2 (0.4%) placebo recipients.

AEs = adverse events

Note: One grade 4 (potentially life-threatening) systemic solicited AE of 105°F fever was recorded in the electronic diary by a CHIKV VLP vaccine recipient, but the site deemed this entry an error.

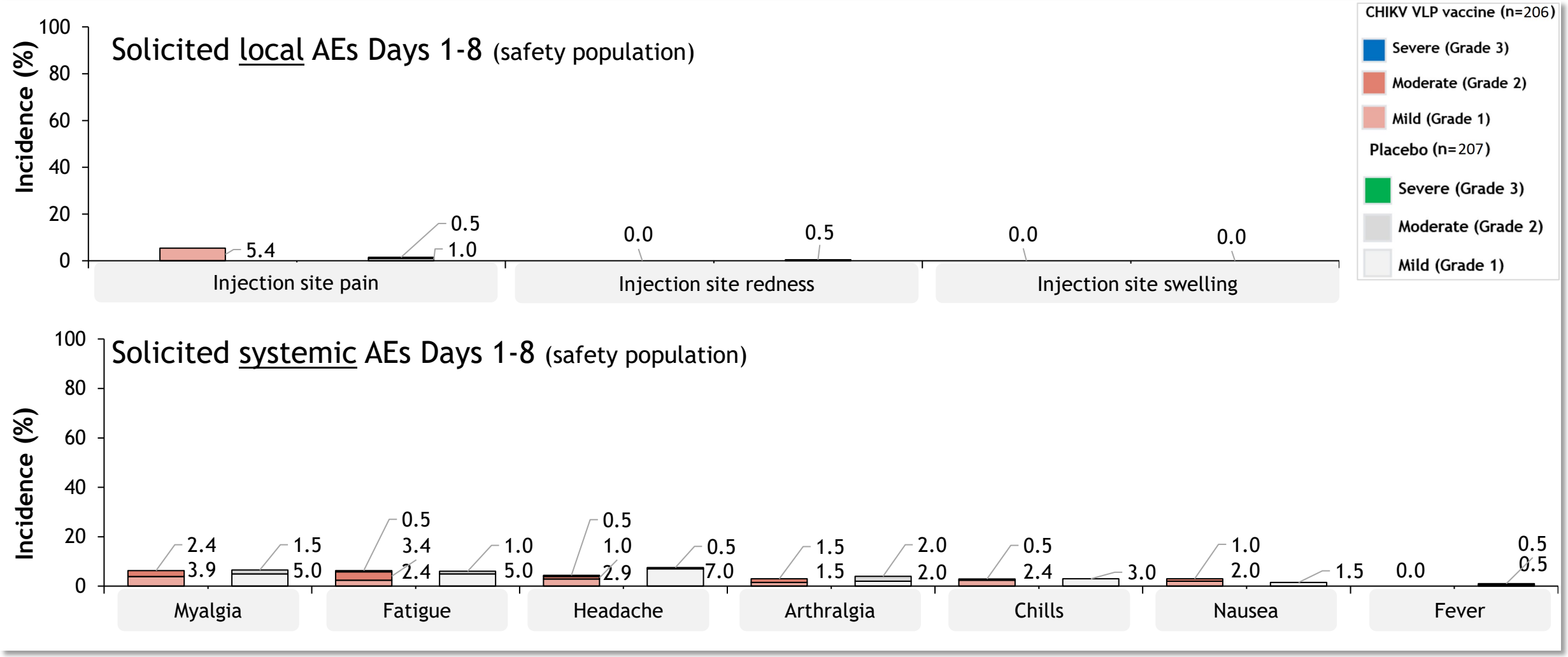
Incidence of AESI and MAAE did not differ between the CHIKV VLP vaccine group and the placebo group in individuals 12 to <65 years of age



- AESI defined as defined as new onset or worsening arthralgia that was medically attended
- One participant in the CHIKV VLP vaccine group had a severe (Grade 3) treatment-related unsolicited AE of dehydration, which resolved without medical intervention
- There was one investigator assessed possibly related SAE (PT: retinal detachment) in the CHIKV VLP vaccine group that was assessed by the sponsor and independent SMC Chair as unrelated due to prior medical history of seeing 'black spots' in the right eye (the same eye with the retinal detachment) 1 month pre-study

AE = adverse event; AESI = adverse event of special interest; MAAE = medically attended adverse event; SAE = serious adverse event; SMC = safety monitoring committee; PT = preferred term
Data presented at IDWeek 2023, Data not yet published in a peer-reviewed article.

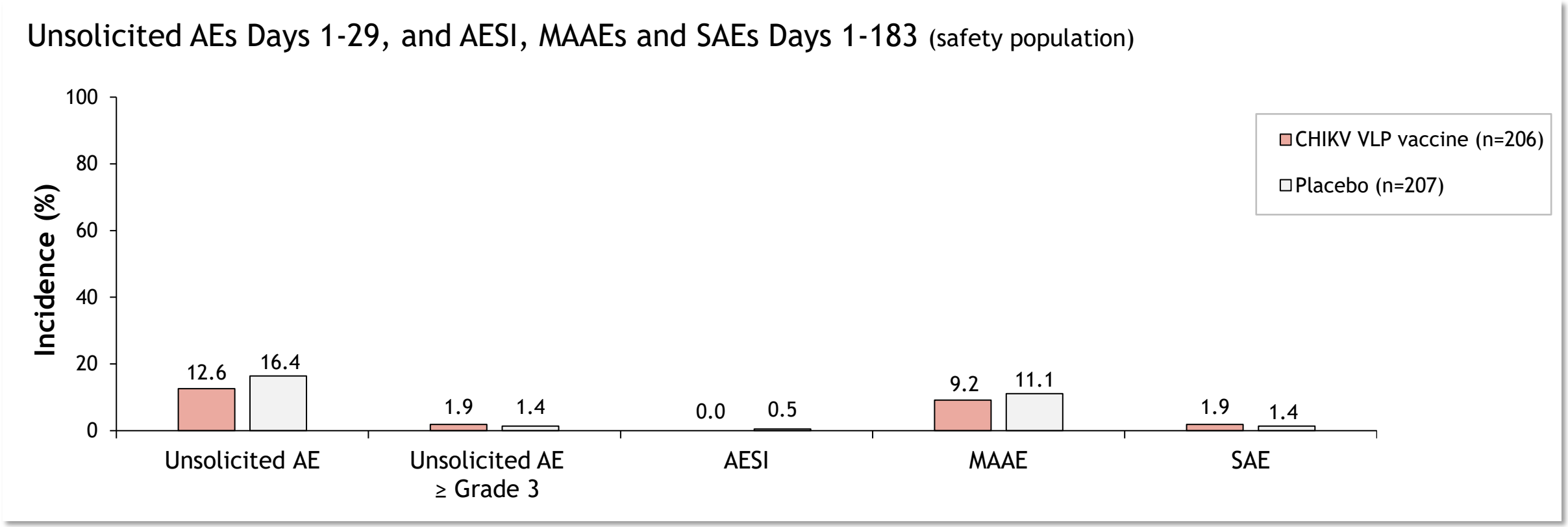
CHIKV VLP vaccine was well-tolerated in individuals ≥65 years of age



- No participants experienced a grade 3 (severe) or higher local solicited AE
- Solicited AEs occurred at similar rates between groups and were of grade 1 (mild) or 2 (moderate) intensity, except for one participant in the vaccine group who experienced two grade 3 (severe) systemic solicited AEs (headache and fatigue)

AEs = adverse events

Incidence of AESI and MAAE did not differ between the CHIKV VLP vaccine group and the placebo group in individuals ≥65 years of age



- AESI defined as defined as new onset or worsening arthralgia that was medically attended
- Fatigue and myalgia were the only treatment-related unsolicited AEs that each occurred in more than one participant
- No SAE was considered treatment-related

AE = adverse event; AESI = adverse event of special interest; MAAE = medically attended adverse event; SAE = serious adverse event; SMC = safety monitoring committee
Data presented at IDWeek 2023, Data not yet published in a peer-reviewed article.

Analysis of serious adverse events, arthralgia, arthritis and osteoarthritis across clinical trials[1] reveals no safety signal

Event	CHIKV VLP vaccine 40/300 µg (N=3141) n (%)	Placebo (N=675) n (%)
Any Serious AEs	31/3141 (0.99)	4/675 (0.59)
Related Serious AEs[2]	0	0
Solicited AE of arthralgia	230/3114 (7.39)	41/661 (6.20)
Arthralgia Grade 3	7/3114 (0.22)	1/661 (0.15)
Arthralgia duration >15 days	0	0
Unsolicited Arthritis	1 (0.03)	0
Related arthritis	0	0
Unsolicited osteoarthritis	1 (0.03)	0
Related osteoarthritis	0	0

[1] Study PXVX-CV-317-001 Groups 8 and 10: 40 µg dose with 300 µg adjuvant single dose; studies EBSI-CV-317-002, EBSI-CV-317-010, EBSI-CV-317-004, and EBSI-CV-317-005. [2] There was 1 SAE (PT: retinal detachment) in the CHIKV VLP vaccine group that was considered possibly treatment-related by the study investigator but was assessed by the sponsor and independent SMC Chair as unrelated due to prior medical history

Summary: CHIKV VLP vaccine

- Single dose vaccine based on VLP technology, suitable for broad populations
- PDUFA target action date: Feb 14th, 2025
- Proposed indication: prevention of disease caused by CHIKV infection in individuals 12 years of age and older

- Phase 3 trials demonstrated rapid and robust immune response in individuals 12 years of age and older
- Durable and boostable immune response in a phase 2 trial

- Well-tolerated
- No treatment related SAEs as determined by sponsor
- Most solicited and unsolicited adverse events mild or moderate in intensity

PDUFA, FDA Prescription Drug User Free Act