VLA1553
Chikungunya Vaccine Candidate

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Overview of Today‘s Presentation

- Introduction to VLA1553
- Evidence Supporting the Serological Endpoint
- Clinical Study Overview
  - Key Immunogenicity Data
  - Key Safety Data

Introduction to VLA1553

Live-attenuated CHIKV vaccine candidate targeting long-lasting immunity with a single dose

Vaccine Candidate VLA1553

- **Live-attenuated CHIKV vaccine candidate, single dose, IM, lyophilized**
- **Based on La Reunion strain of East Central South African genotype**
- **Attenuation by reverse genetics resulting in 60aa deletion within the nsP3 protein**

Target Populations & Geographic Reach

- **Non-endemic countries: Travelers / military / outbreak preparedness in US, EU, CAN**
- **Endemic use: Partnered with CEPI and Instituto Butantan, technology transfer**

VLA1553 is an investigational chikungunya vaccine candidate and is not approved for use in the United States or any other jurisdiction.

Evidence Supporting the Serological Endpoint

After transfer of human post-vaccination sera, neutralizing antibodies conferred sterilizing immunity in non-human primates

Experimental Set-Up[1]:

- Sera from human vaccinees at varying titer levels were transferred to NHPs
- Animals challenged with wild-type chikungunya virus, monitored for fever and viremia
- Protocol agreed with FDA

Results[1]:

- **No fever** in any of the NHPs who received human post-vaccination serum
- **No live, replicating virus** detected
- All animals had **strongly reduced, some undetectable viral RNA** load, depending on titer
  - Determined **pre-challenge titer** resulting in **sterilizing immunity** in NHPs - very conservative approach: **seroresponse defined as a titer of ≥150 in a micro-Plaque Reduction Neutralization Test (μPRNT$_{50}$)**

Further evidence[1]:

Protective titer determined in a **prospective seroepidemiological study** in the Philippines translated into a **μPRNT$_{50}$ of ~49**

1 Roques P, et al. *JCI Insight.* 2022;7(14):e160173. doi: 10.1172/jci.insight.160173.

Clinical Study Overview: Key Immunogenicity Data

Overview of clinical studies

Three clinical trials provide data for initial licensure

Phase 1:

- **Phase 1 study[1]:**
  - **120 healthy adults** aged 18-45 years
  - **Three dose levels** of vaccine studied
  - Included a **re-vaccination** as homologous viral challenge
  - Study generated **safety, immunogenicity, and viremia[2]** data

Phase 3:

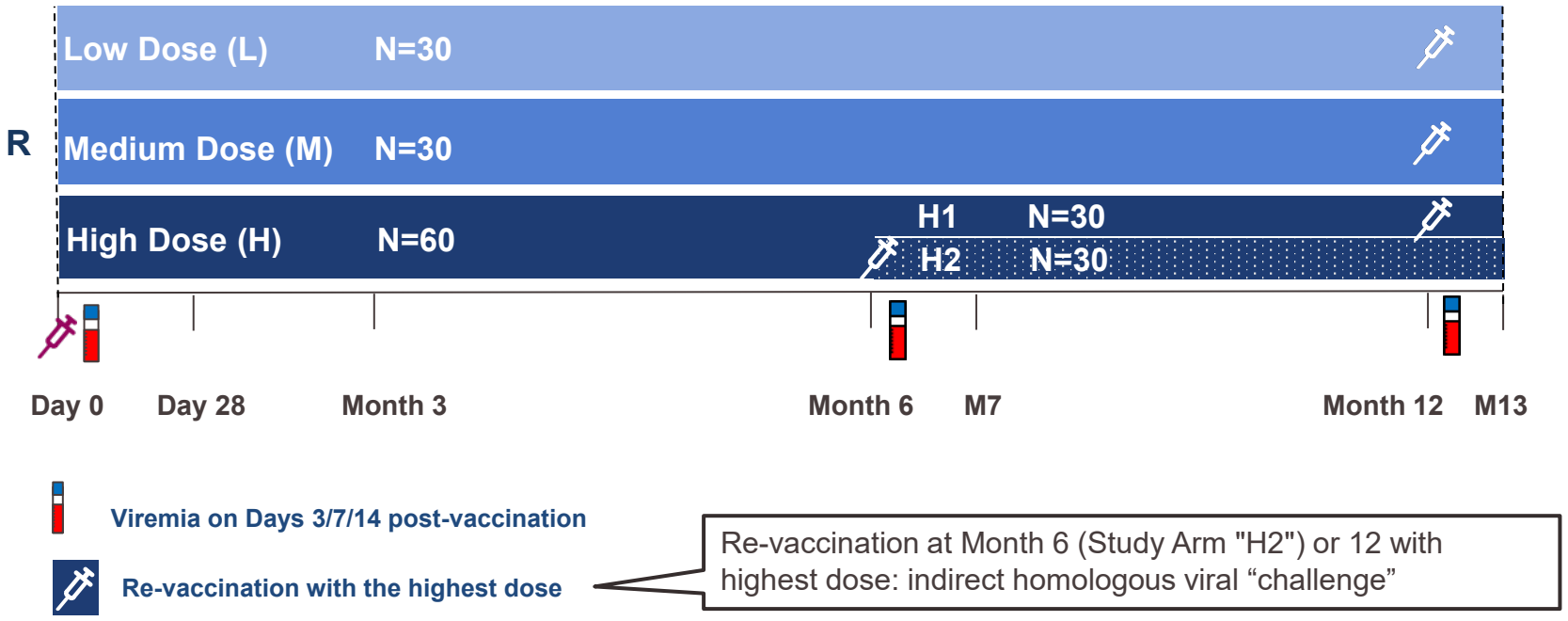
- **Pivotal Phase 3 study:**
  - **4,115 participants** aged ≥18 years
  - RCT comparing **VLA1553 to placebo**
  - Study generated **safety and immunogenicity** data
- **Lot-to-Lot consistency study:**
  - **408 participants** aged **18-45 years**
  - RCT comparing **3 lots of VLA1553**

1 Wressnigg et al. 2020; Lancet Infect Dis 20:1193-1203.
2 Viremia tested by RT-qPCR, readout: CHIKV genome copy equivalents (GCE) detected per 1mL of initial specimen.

Phase 1 Study VLA1553-101 – Study Design

Observer-blinded, randomized, multicenter, dose-escalation study

- **120 healthy volunteers** aged 18 to 45 years (conducted in the US)
- **3 Dose Levels :** approx. $3x10^3$ $TCID_{50}$ (Low), $3x10^4$ (Medium), $3x10^5$ (High) $TCID_{50}$
- **Intramuscular injection**, liquid formulation
- **Serological assay:** μNT_{50} – target strain VLA1553



1 Wressnigg et al. 2020; Lancet Infect Dis 20:1193-1203.

Summary of VLA1553-101 Phase 1 data[1]

Results supported direct progression into Phase 3

- **Excellent immunogenicity** profile in all dose groups after a single dose – **medium dose** selected for further development
- **100% seroconversion*** and **seroresponse** rates** at day 14 in all dose groups
- Neutralizing antibodies **retained in 100%** of participants at **month 12**
- **Absence of anamnestic neutralizing antibody response following re-vaccination** - single dose sufficient to induce sustaining high titer neutralizing antibodies
- After **re-vaccination,** vaccinees were **protected from vaccine induced viremia** and associated clinical symptoms as early indication of VLA1553's efficacy

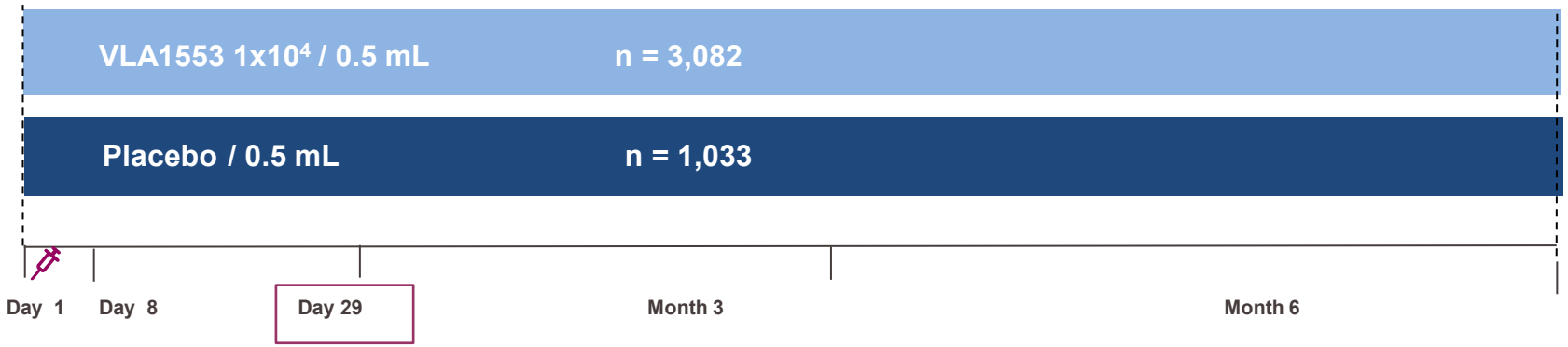
As antibody levels reached plateau in all dose groups after one dose, no further dose and schedule data needed to be generated in a Phase 2 study

*Seroconversion defined as the proportion of subjects achieving a CHIKV-specific neutralizing antibody titer of μNT_{50} ≥20.
** Seroresponse defined as the proportion of subjects achieving a CHIKV-specific neutralizing antibody titer of $\mu PRNT_{50}$ ≥150.
1 Wressnigg et al. 2020; Lancet Infect Dis 20:1193-1203.

Pivotal Study Design (VLA1553-301)

Multicenter, randomized, placebo-controlled double-blind Phase 3 study in 4,115 adults aged 18 years and above, conducted in US

- **Primary Endpoint:** Proportion of participants with seroresponse (CHIKV neutralizing antibody titer ≥150 by μPRNT$_{50}$) for baseline negative participants 28 days post-vaccination
  - FDA non-acceptance threshold: Lower bound of the 95%CI for the seroresponse rate at Day 29 needed to exceed 70%
- **Solicited adverse events** captured for **10 days** following vaccination
- Recruitment stratified by age, younger (18-64 years, N=3,652) and older adults (≥65 years, N=463)
- 3:1 Randomization to VLA1553 and Placebo
- Immunogenicity subset: first 462 participants enrolled at selected sites



n = number of participants in the safety population

Demographic Data (VLA1553-301)

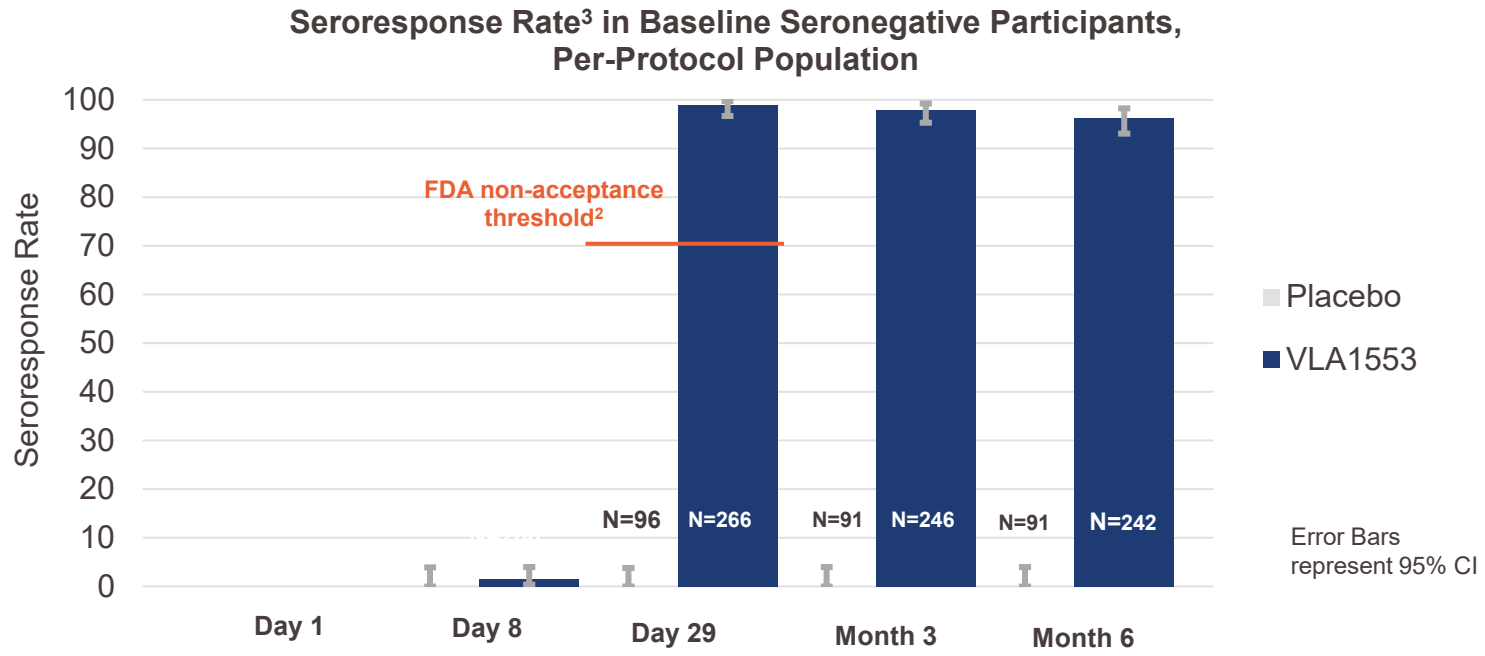
Similar baseline characteristics between VLA1553 group and Placebo

	VLA1553 N=3,082	**Placebo** N=1,033
Gender n (%)		
Female	1682 (54.6)	569 (55.1)
Male	1400 (45.4)	464 (44.9)
Race n (%)		
American Indian or Alaskan Native	27 (0.9)	5 (0.5)
Asian	51 (1.7)	17 (1.6)
Black or African American	451 (14.6)	122 (11.8)
Native Hawaiian or Other Pacific Islander	13 (0.4)	5 (0.5)
White	2456 (79.7)	853 (82.6)
Other	84 (2.7)	31 (3.0)
Age at screening (years)		
Mean	45.1	45.0
(Min/Max)	18, 88	18, 94
Age Group n (%)		
18 years - 64 years	2736 (88.8)	916 (88.7)
≥ 65 years	346 (11.2)	117 (11.3)

Safety Population

Pivotal Study Met Primary Endpoint (VLA1553-301)

Induced seroresponse[1] in 98.9% of participants; exceeding threshold agreed with FDA[2]

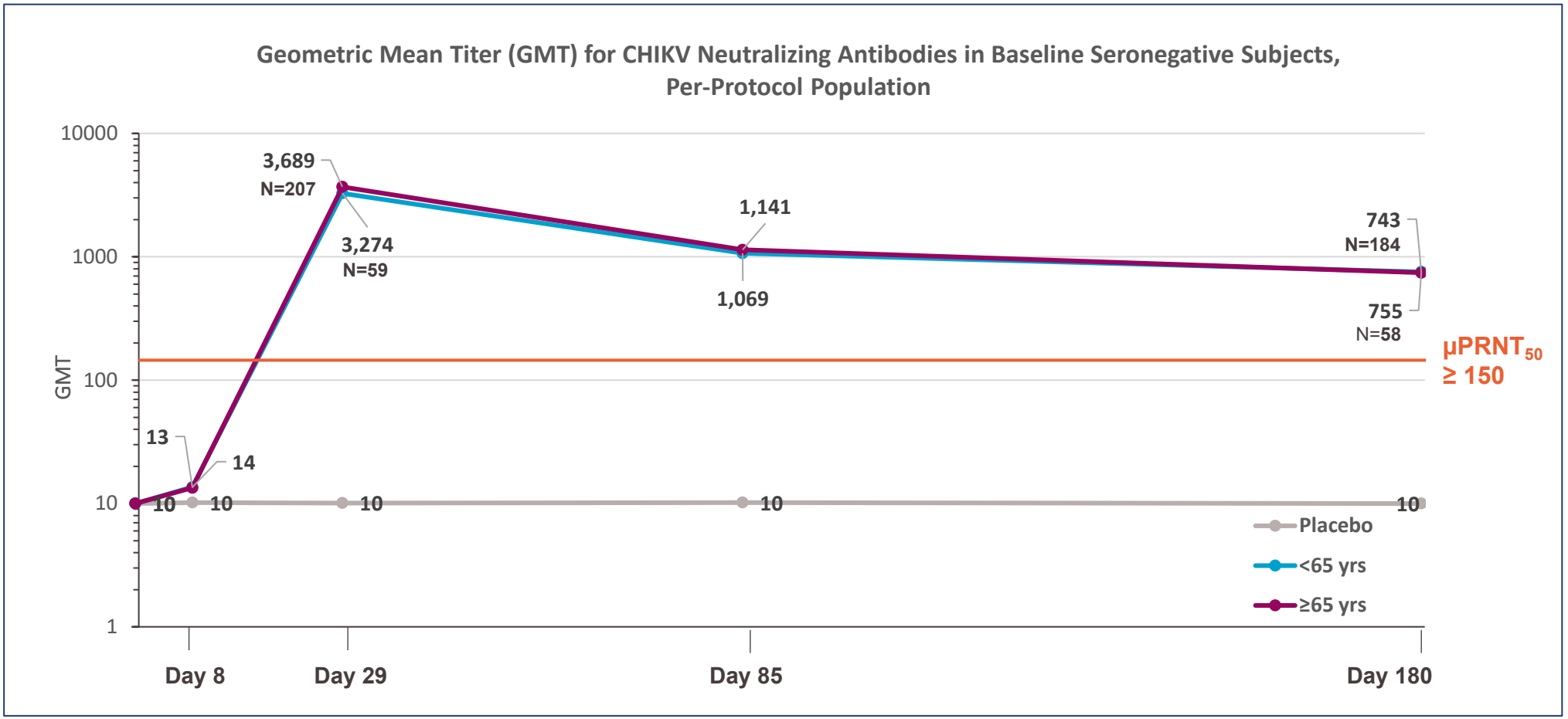


- **Per-Protocol population: 362 / 462 participants from immunogenicity set**
- **Day 29 Seroresponse rate (SRR):**
  - **98.9% (263/266, 95% CI: 96.7- 99.8) vs placebo 0% (0/96, 95%CI 0.0 - 3.8)**
- **High SRR was maintained after six months at 96.3% (233/242, 95% CI: 93.1 - 98.3)**

1 CHIKV neutralizing antibody titer ≥150 by μPRNT$_{50}$; 2 The lower bound of the 95% Confidence Interval for the SRR at Day 29 in the VLA1553 group needed to exceed 70%; 3 The proportion of participants with seroresponse, determined by μPRNT$_{50}$ for baseline negative participants 28 days post-vaccination

Neutralizing Antibodies By Age Group (VLA1553-301)

Equally immunogenic in participants 18-64 or ≥65 years



Chikungunya virus neutralizing antibody titers were determined using a $\mu PRNT_{50}$ assay. Values below the quantification limit are set to 10 (Half Lower Limit of Quantification).

Lot-to-Lot Consistency Study (VLA1553-302)

Immunogenicity profile consistent with pivotal study

Study Design:

- Multicenter, randomized, double-blind Phase 3 trial in 408 adults, aged 18 to 45 years, conducted in US
- Primary Endpoint: GMT for CHIKV neutralizing antibodies on Day 29 post-vaccination

Results:

- **Lot-to-Lot consistency demonstrated**. GMT Ratio CI's within the defined acceptance margins of 0.67 and 1.5
- **Seroresponse[1] in 97.8% of participants** 28 days after a single vaccination and 96.0% at Day 180

	Lot 1 N=122	Lot 2 N=118	Lot 3 N=122
Day 29 Geometric Mean Titer	**2556.7**	**2767.7**	**2613.7**
95% CI for GM	[2056, 3180]	[2310, 3316]	[2128, 3210]

1 CHIKV neutralizing antibody titer ≥150 determined by $\mu PRNT_{50}$ for baseline negative participants

Clinical Study Overview: Key Safety Data

Summary of Adverse Event (AE) Rates (VLA1553-301)

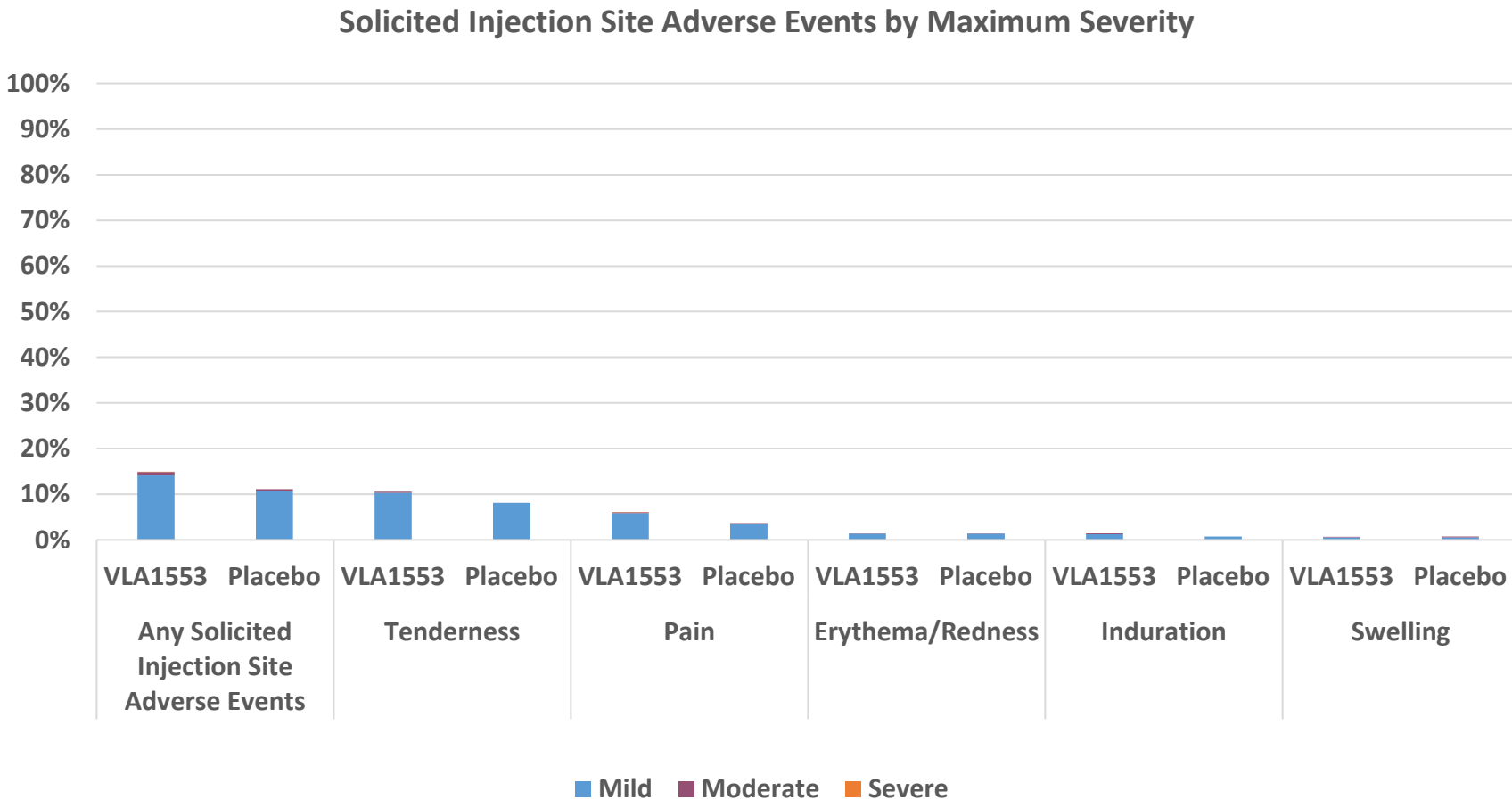
VLA1553 vaccine candidate generally well tolerated

AE Category	VLA1553 N=3,082 n (%)	Placebo N=1,033 n (%)
Any AE [95% CI] p-value[a]	**1926 (62.5)** [60.8, 64.2]	**463 (44.8)** [41.8, 47.9] *<0.0001*
Any Related AE [95% CI] p-value[a]	**1575 (51.1)** [49.3, 52.9]	**322 (31.2)** [28.4, 34.1] *<0.0001*
Any Severe[b] AE [95% CI] p-value[a]	**104 (3.4)** [2.8, 4.1]	**14 (1.4)** [0.7, 2.3] *<0.0001*
Any Related Severe AE [95% CI] p-value[a]	**62 (2.0)** [1.5, 2.6]	**1 (0.1)** [0.0, 0.5] *<0.0001*

a P-value from Fisher's Exact test for difference between the study arms.
b Severe (grade 3): incapable of work or usual activity and requiring medical intervention. Injection site AEs and systemic AEs were rated based on the FDA Guidance on Toxicity Grading Scales

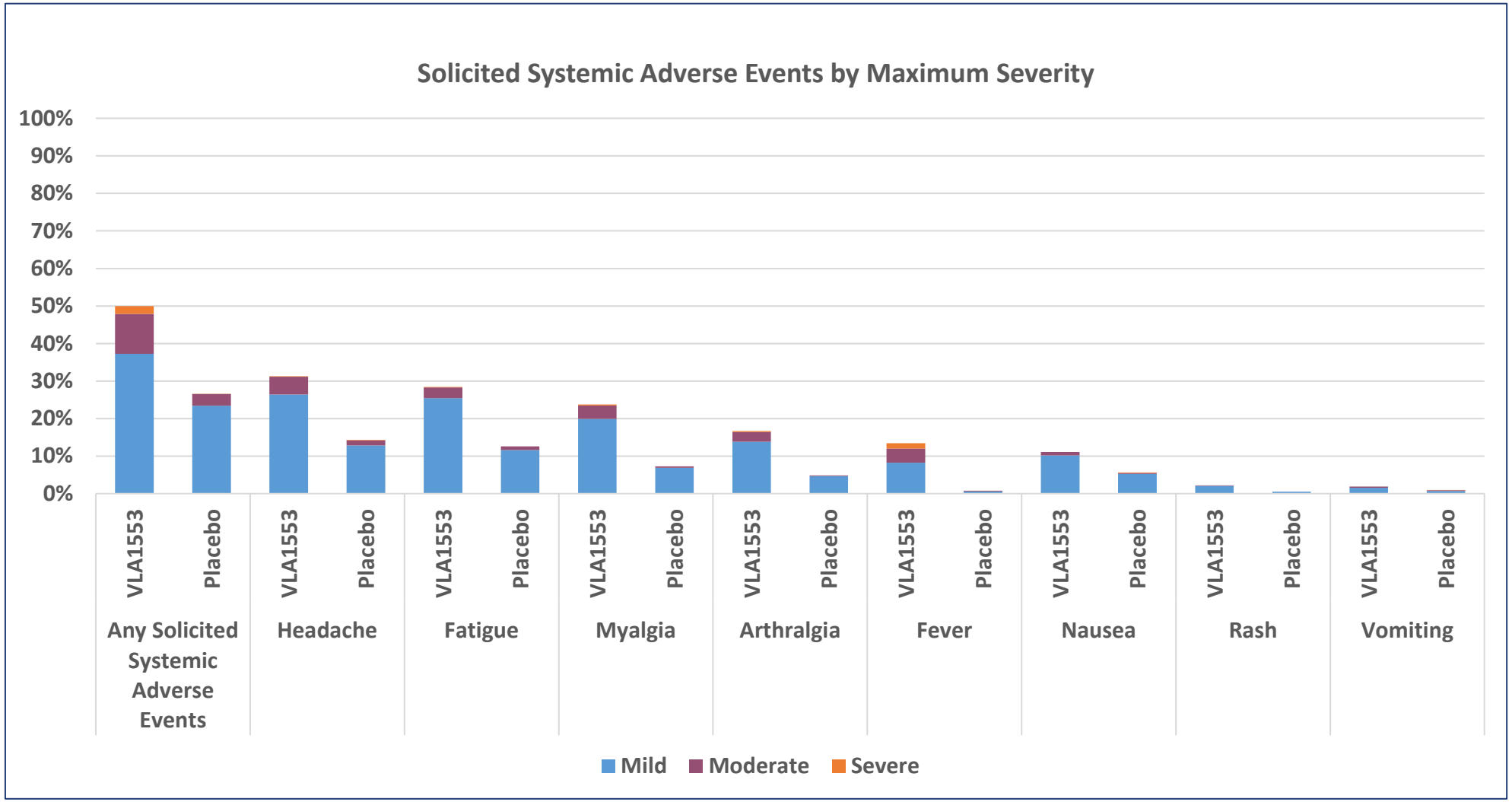
Pivotal Phase 3 Solicited Local AE Within 10 Days After Vaccination (VLA1553-301)

Local AEs in 15% of participants, majority of AEs mild-moderate



Pivotal Phase 3 Solicited Systemic AE Within 10 Days After Vaccination (VLA1553-301)

Generally well tolerated, majority of AEs mild-moderate



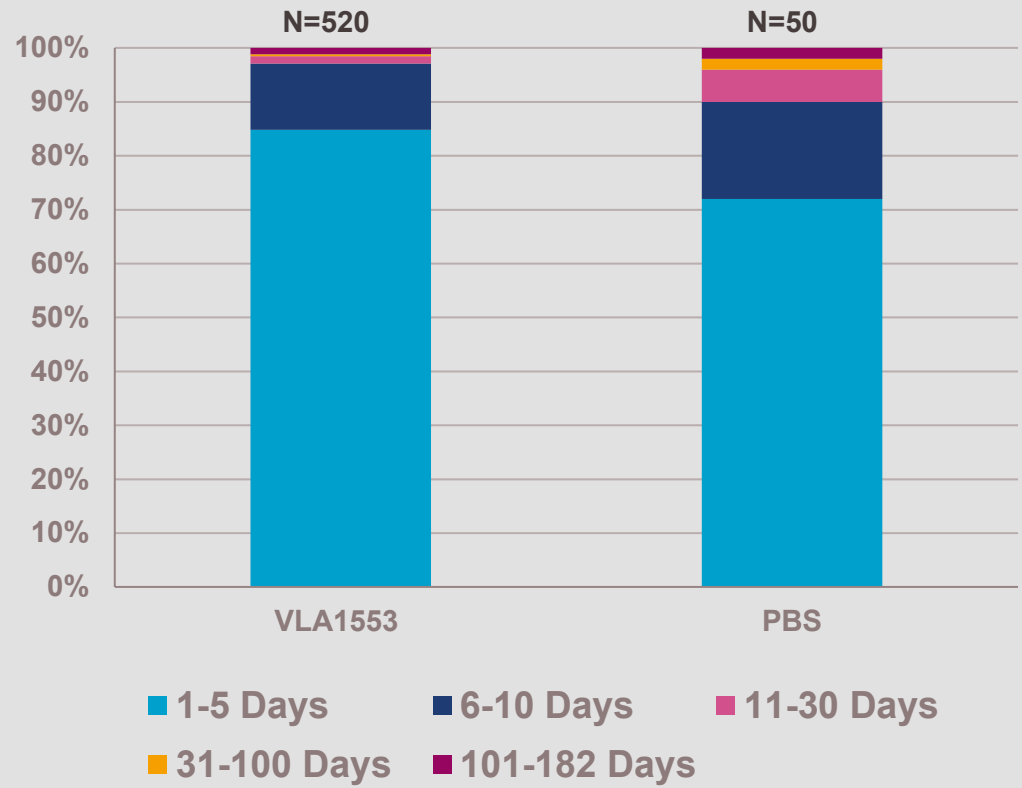
Details on Post-Vaccination Arthralgia (VLA1553-301)

Similar duration of arthralgia with VLA1553 and placebo

Arthralgia Rates

- **VLA1553:**
  - **17% (n=520) any arthralgia**
  - **0.5% (n=15) duration >11 days**
  - **Longest duration: 182 days**
- **Placebo:**
  - **5% (n=50) any arthralgia**
  - **0.5% (n=5) duration >11 days**
  - **Longest duration: 180 days**

Relative Frequency of Arthralgia Duration



Solicited Arthralgia ie onset within 10 days post-vaccination

Pivotal Phase 3: Serious Adverse Events (VLA1553-301)

Two related serious adverse events, fully recovered

	VLA1553 N=3,082 n (%)	**Placebo** N=1,033 n (%)
Any SAE [95% CI] p-value	**46 (1.5)** [1.1, 2.0]	**8 (0.8)** [0.3, 1.5] 0.0835
Any related SAE [95% CI] p-value	**2 (0.1)** [0.0, 0.2]	**0** [0.0, 0.4] >0.9999

Case #1, 58-year-old female

- **Event:** Myalgia
- **Vaccination:** VLA1553 03 NOV 2020
- **Onset:** 04 NOV
- **Hospitalization:** 06 NOV – 11 NOV
- **Outcome:** recovered 03 DEC
  - Participant has a history of fibromyalgia
  - No other trigger for myalgia could be identified

Case #2, 66-year-old male

- **Event:** Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- **Vaccination:** VLA1553 17 NOV 2020
- **Onset:** 27 NOV
- **Hospitalization:** 27 NOV – 30 NOV
- **Outcome:** recovered 10 DEC
  - Appeared to be related to prolonged fever/symptoms post-vaccination

Pivotal Phase 3: Adverse Events Rates by Age (VLA1553-301)

Similar AE profile in participants 18-64 or ≥65 years

	18-64 years		≥ 65 years	
AE Category	**VLA1553** (N=2,736) n (%)	**Placebo** (N=916) n (%)	**VLA1553** (N=346) n (%)	**Placebo** (N=117) n (%)
Any AE	**1708 (62.4)**	**407 (44.4)**	**218 (63.0)**	**56 (47.9)**
Any Related AE	**1415 (51.7)**	**292 (31.9)**	**160 (46.2)**	**30 (25.6)**
Any Severe[a] AE	**94 (3.4)**	**10 (1.1)**	**10 (2.9)**	**4 (3.4)**
Any Related Severe[a] AE	**58 (2.1)**	**1 (0.1)**	**4 (1.2)**	**0**

a Severe (grade 3): incapable of work or usual activity and requiring medical intervention. Injection site AEs and systemic AEs were rated based on the FDA Guidance on Toxicity Grading Scales

AE Summary Lot to Lot Consistency Study (VLA1553-302)

Safety profile consistent with pivotal phase 3 study

- 408 subjects aged 18-45 years
- 73% of participants (296/408) experienced any AEs
    - No significant differences between lots
- 61% reported solicited AEs
    - 19% local AEs, 57% systemic AEs
    - AEs were mostly mild or moderate
- No related SAEs

VLA1553 Chikungunya Vaccine Candidate
Summary

- **VLA1553 met primary endpoint in a pivotal immunogenicity phase 3 study**
  - Serological endpoint, μPRNT$_{50}$ titer ≥150, agreed by FDA to support accelerated approval
  - **Single dose induced seroresponse in 98.9%** of participants at Day 29
  - Seroresponse was **sustained in 96.3%** of participants at **Day 180**
  - Similar GMT and SRR induced in participants aged 18-64 or ≥65 years of age
- **VLA1553 was generally well tolerated across age groups**
  - Independent DSMB did not identify any safety concern
  - **Majority of AEs mild or moderate** and resolved within 3 days, 2.1% severe solicited AEs (most commonly fever)
- **Safety profile comparable with other licensed vaccines**[1]
- **BLA Submission to FDA initiated**

VLA1553 is an investigational chikungunya vaccine candidate and is not approved for use in the United States or any other jurisdiction

1 E.g. compare FDA prescribing information Comirnaty, Bexsero, Shingrix, YF-VAX, all accelable at https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states

Thank you.

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