Long-term Immunogenicity Following Vaccination with a New, Live-attenuated Vaccine Against Japanese Encephalitis (JE-CV)

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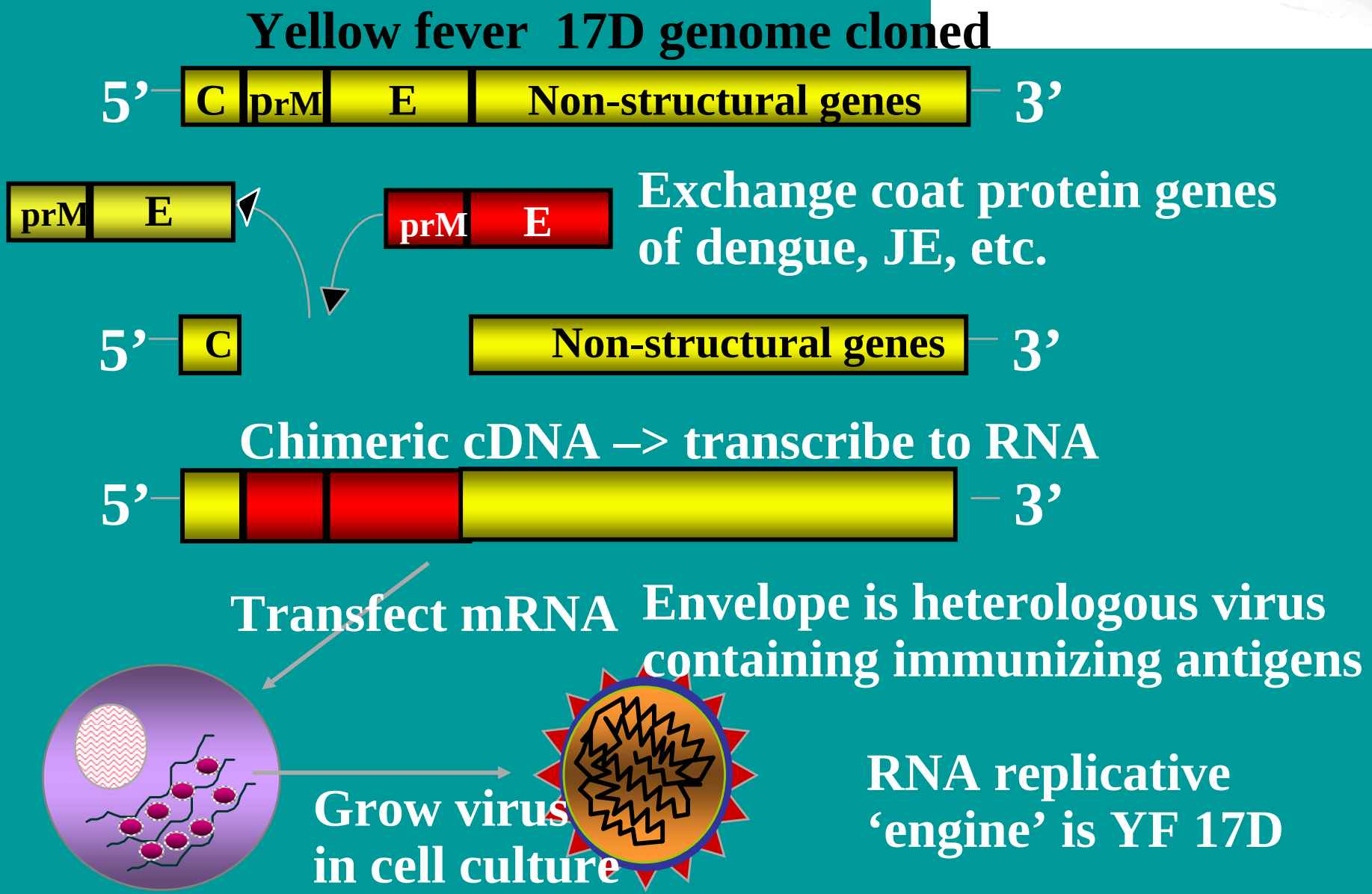
JE-CV - A New JE Vaccine

ChimeriVax™



JE-CV - A New JE Vaccine

- **JE-CV is a live-attenuated vaccine based on :**
  - Envelope proteins (prM and E) of JE live-attenuated SA14-14-2 vaccine

    +

  - Replication engine from Yellow Fever (YF) 17D vaccine

- **Genetic modification of different flaviviruses has been shown to further increase the attenuation of the donor sequences***

* Pugachev et al. (2007) Vaccine 25:6661-6671; McGee et al. (2008) JID 197:693-7

JE-CV - A New JE Vaccine

- sanofi pasteur is continuing the development jointly initiated with Acambis of an innovative JE vaccine previously known as ChimeriVax™-JE
- Virus grown in a well characterized cell line (Vero) using serum-free culture medium
- Freeze-dried formulation
- No preservative or adjuvant
- Single dose for primary immunization

Study One

Durability of immune response up to 12 months following one dose of JE-CV in comparison with the recommended 3 dose-schedule of JE-VAX®

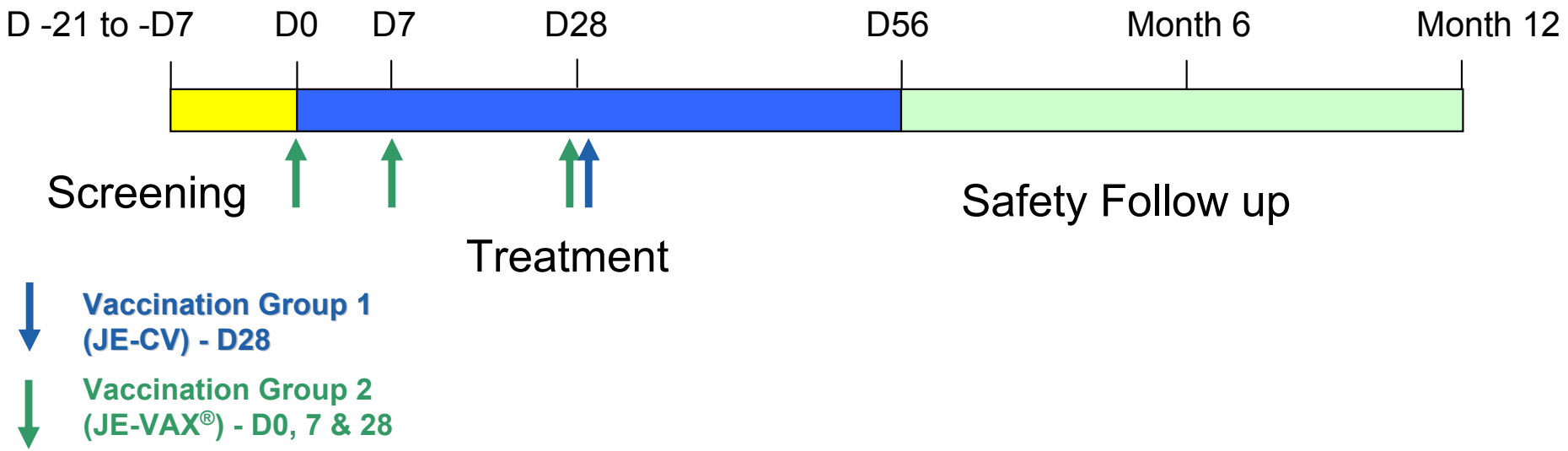
Study 1 - Overview

Study H-040-008: Single centre, randomised, double-blind, active controlled out-patient study in adults – USA

Pilot study to compare immunogenicity of JE-CV against the marketed comparator JE-VAX®

- **Blinded treatment phase up to Day 56 (7 visits), safety follow up phase up to month 6 and 12 (2 visits)**
- **Population: 60 healthy adults (≥18 to ≤49 years old)**

Dose administered (JE-CV): 4.0 $\log_{10}$ PFU



Study 1 - Study Groups

Group	N	D0	D7	D28
1	30	Placebo	Placebo	JE-CV
2	30	JE-VAX®	JE-VAX®	JE-VAX®

Study One – Methods

Ab titers measured by $PRNT_{50}$ against homologous JE virus strain

- JE-CV ⇨ JE-CV virus strain
- JE-VAX® ⇨ Nakayama virus strain

Reasonable threshold Ab level for protection: $PRNT_{50} \geq 1:10$*

Serostatus definitions:

- Seropositive if $PRNT_{50}$ titer ≥1:10, seronegative if <1:10

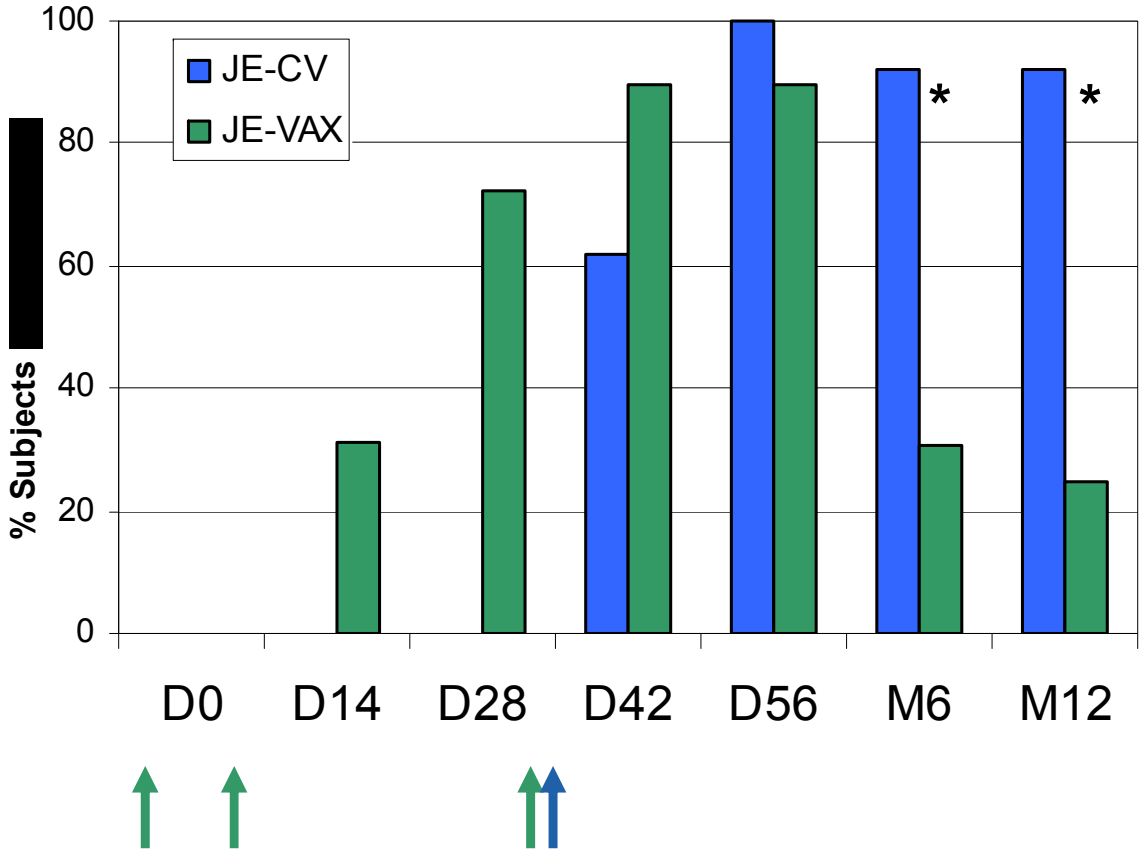
Seroconversion Definitions:

- Subjects seronegative at baseline ⇨ serum dilution $PRNT_{50}$ titer ≥1:10
- Subjects with pre-existing JE neutralizing Abs ⇨ ≥4-fold increase in $PRNT_{50}$ titer between pre- and post-immunization samples

* WHO recommendations Vaccine 23 (2005) 5205–5211. Short communication. Report on a WHO consultation on immunological endpoints for evaluation of new Japanese encephalitis vaccines, WHO, Geneva, 2–3 September, 2004. Joachim Hombach, Tom Solomon, Ichiro Kurane, Julie Jacobson, David Wood

Study One – Seroconversion Rate to Homologous JE Strain over Time

Intent-to-treat population



Vaccination Group 1 (JE-CV) - D28

Vaccination Group 2 (JE-VAX®) - D0, 7 & 28

*: p>0.001

Study One : Immunogenicity conclusions

- **Trend towards higher neutralizing response to the respective homologous virus in JE-CV group compared to JE-VAX® group**
  - **100% of Group 1 (JE-CV) and 89.7% of Group 2 (JE-VAX®) seroconverted to respective homologous virus on Day 56 (*i.e.*, 28 days after a single dose of JE-CV and the third dose of JE-VAX®)**
- **Maximum seroconversion rates, GMTs and mean fold increases were generally observed 42 days after first injection (*i.e.* 14 days after final vaccination of three dose series) in Group 2 (JE-VAX®) and 28 days after a single vaccination in Group 1 (JE-CV).**
- **Significantly higher Ab persistence and seroconversion rate at Month 12 were observed in JE-CV group than in JE-VAX ® group**
  - **92.3% Group 1 (JE-CV) still seroconverted at Month 12 *vs.* 25% in Group 2 (JE-VAX®) (p <0.001)**

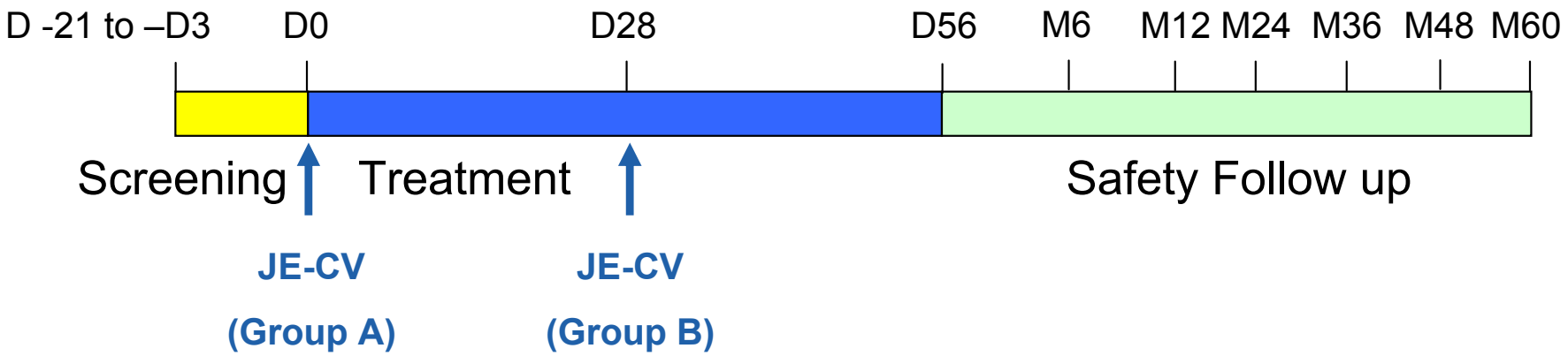
Study Two

Durability of immune response up to 4 years following a single dose of JE-CV

Study Two - Overview

Study H-040-005: Part of a single centre, randomised, double-blind, placebo controlled out-patient cross-over study in adults – Australia

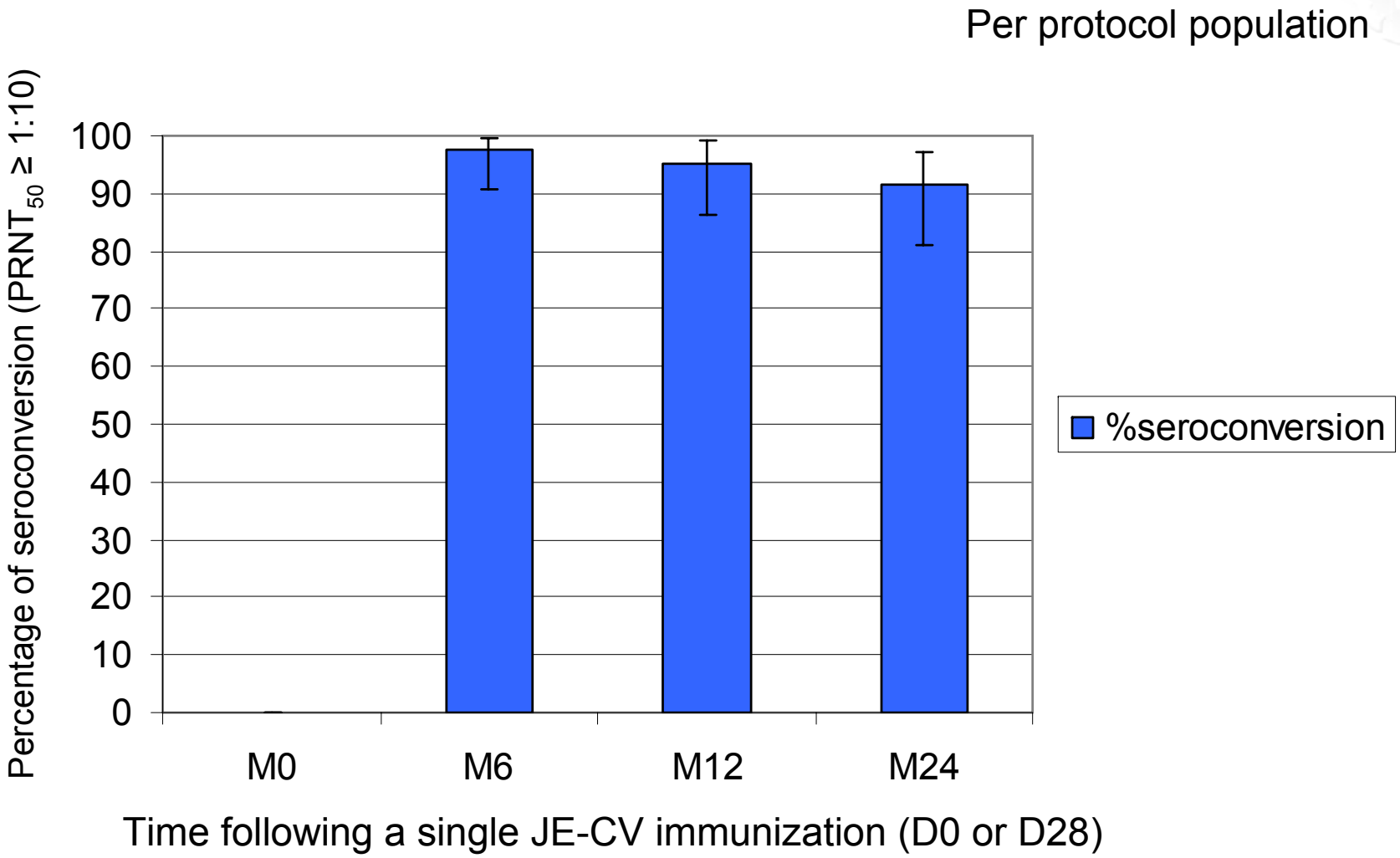
- **Subset of 100 healthy adults (aged ≥18 - ≤55 years)**
- **Dose administered: 3.8 $\log_{10}$ PFU**
- **Immunogenicity assessment 28 days after JE-CV administration, then at M6, M12, M24, M36, and M48 (M60 to be done)**



Study Two – PRNT50 using homologous ChimeriVax JE as challenging virus

- One hundred percent of vaccinees seroconverted by day 56 (N=194)
- GMT 239

Study Two - Long-Term Immunogenicity of JE-CV – Seroconversion rate from M6 to M24



Study Two - Long-Term Immunogenicity of JE-CV - Kaplan-Meier Analysis

Visit	N at risk*	N negative**	N censored**	Kaplan Meier estimate	95% confidence interval
M6	90	0	0	100.0%	[100.0 – 100.0]
M12	79	2	11	97.5%	[94.0 – 100.0]
M24	69	3	8	93.2%	[87,5 – 100.0]
M36	55	1	11	91.5%	[85.0 – 100.0]
M48	37	0	17	91.5%	[85.0 – 100.0]

Intent to treat population

*: At the beginning of the period

**: At the end of the period

Lost to follow-up subjects were censored

Study Two - Immunogenicity Conclusions

- 98.8% seroconversion rate to the homologous virus reached 28 days after a single immunization with JE-CV
- Persistence of high seroconversion rate following a single immunization with JE-CV
  - 97.4% at M6
  - 95% at M12
  - 91.4% at M24
- Probability* greater than 0.9 of remaining seropositive ($PRNT_{50}$ ≥10) from 6 to 48 months after a single dose of JE-CV

* Estimated with Kaplan-Meier survival function

Study Two – GMT of PRNT titers and seroconversion to wild strain JEV genotypes 1-4 at Year 4 post vaccination with JE-CV

	JE g1 (TVP8236)	JE g2 (B1034)	JE g3 (Beij)	JE g4 (JKT9092)
Seroconversion	95/106	81/106	85/106	67/106
	(89.62%)	(76.42%)	(80.19%)	(63.21%)
GMT	92	54	53	49

Overall Conclusions

- High seroconversion rate 28 days following a single dose of JE-CV
- Trend towards higher neutralizing response to the respective homologous virus 28 days after a single JE-CV immunization than 28 days after the third injection of JE-VAX®
- Higher seroconversion rate in favor of JE-CV over JE-VAX® at one year
  - 92.3 % *vs.* 25 % (p <0.001)
- Seroconversion rate remains high during the first two years following a single dose of JE-CV (91.4%)
- Probability greater than 0.9* of remaining seropositive (PRNT50 ≥10) from 6 to 48 months after a single dose of JE-CV
- Long-term protection against JE afforded by a single dose of JE-CV

*** Estimated with Kaplan-Meier survival function**

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Thank you for your attention