

ChimeriVax™-JE Vaccine

Development of a new live, attenuated vaccine
against Japanese encephalitis

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Topics to be covered

- > Introduce ChimeriVax™-JE
 - New JE Vaccine Goals
 - Recombinant (chimeric) vaccine candidate
 - Preclinical safety and efficacy
- > Outline clinical development to date
- > Provide summary of safety, immunogenicity and target product profile

New JE Vaccine Goals

Current JE vaccines	New JE Vaccines
Mouse brain-derived	✓ Manufactured in a more acceptable cell substrate
Multiple dose regimen	✓ Immunize rapidly with single dose (14-21 days) ✓ Durable protection with single booster dose
Reactogenic	✓ Favourable reactogenicity profile, no treatment-related SAEs
Expensive manufacturing process	✓ Efficient manufacturing process less expensive, allows accelerated manufacture

ChimeriVax™-JE

- > Sterile lyophilized live, attenuated vaccine candidate to prevent Japanese Encephalitis (JE)
- > Utilizes ChimeriVax™ technology platform
 - Genes encoding two structural proteins (prM and E) of yellow fever 17D vaccine virus replaced by corresponding genes from attenuated JE strain (SA14-14-2)
 - Vaccine virus propagated in Vero cell cultures without bovine serum
- > Investigational product in the US, Australia and India
 - FDA IND (BB-IND #9167) in 2000
 - CTX (No: 99/2/4014) in Australia in 2002

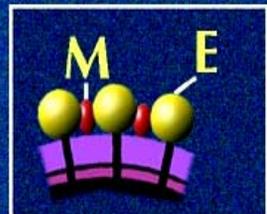
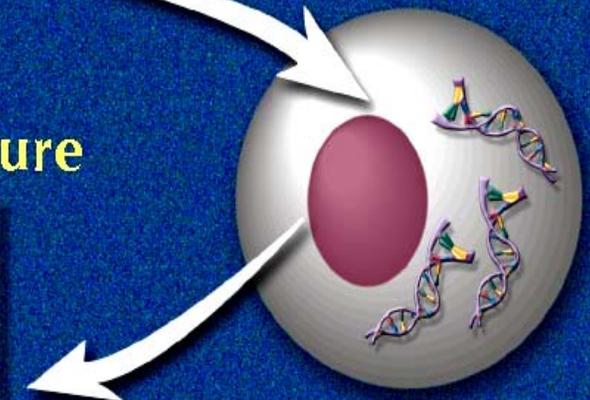
Construction of Chimeric Virus

Full length cDNA → SP6 transcribe to RNA

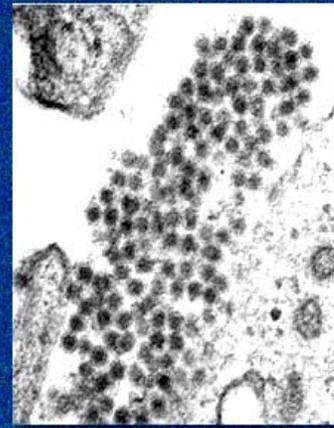


Transfect RNA
(Electroporation)

Grow virus
in Vero cell culture

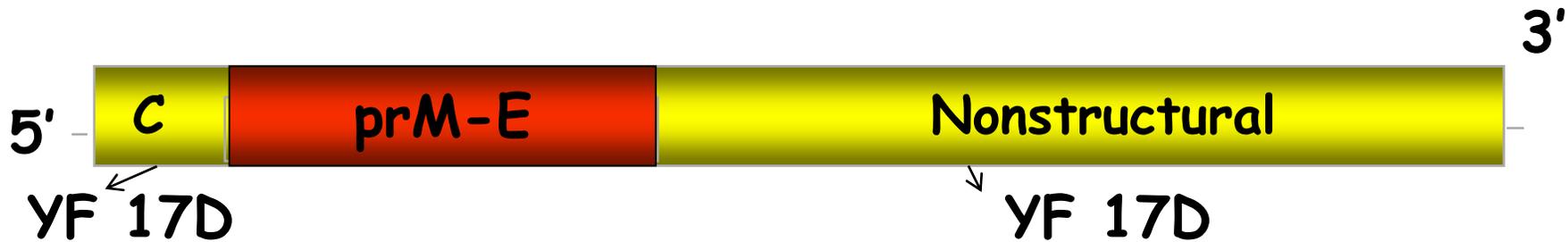


Envelope
proteins
are **JE**



Replicative 'engine' is YF 17D

ChimeriVax™ Platform Technology



prM-E Insert	Status	Comment
Dengue-1	Tetravalent Phase II	Licensed to sanofi pasteur
Dengue-2		
Dengue-3		
Dengue-4		
JE (SA14-14-2)	Phase III	
WN (NY99 wild-type)	In registration (USDA)	Veterinary, Licensed to Intervet
WN (NY99 Δ 107/316/440)	Phase II	

ChimeriVax™-JE Pre-clinical Safety

- > **Neurovirulence**
 - Less neurovirulent than YF 17D vaccine virus (mice, monkeys)
- > **Neuroinvasiveness**
 - Not neuroinvasive (mice, hamsters, monkeys)
- > **Viremia**
 - Low, transient viremia (monkeys)
- > **Extraneural pathology**
 - No organ dysfunction (monkeys)
 - No histopathological lesions (monkeys)
- > **Genetic stability**
 - No genetic changes on repeated passage in vitro or in vivo
- > **Infectiousness for mosquitoes**
 - No oral infection or transmission

ChimeriVax™-JE Preclinical Efficacy

> Mice

- Active immunization protects against wt JE challenge (IP)
- Passive immunization with ChimeriVax™-JE antibody protects against wt JE challenge (IC)

> Monkeys

- Active immunization protects against wt JE challenge (IC)

Manufacturing status

- > Large scale cGMP manufacture in Vero cell culture at Acambis
- > Liquid frozen and lyophilized formulations completed
- > Bulk manufacturing complete to commercial scale
- > Manufacturing and marketing agreement with Bharat Biotech (Hyderabad, India) signed in Nov 2005

Phase 1 and 2 Studies

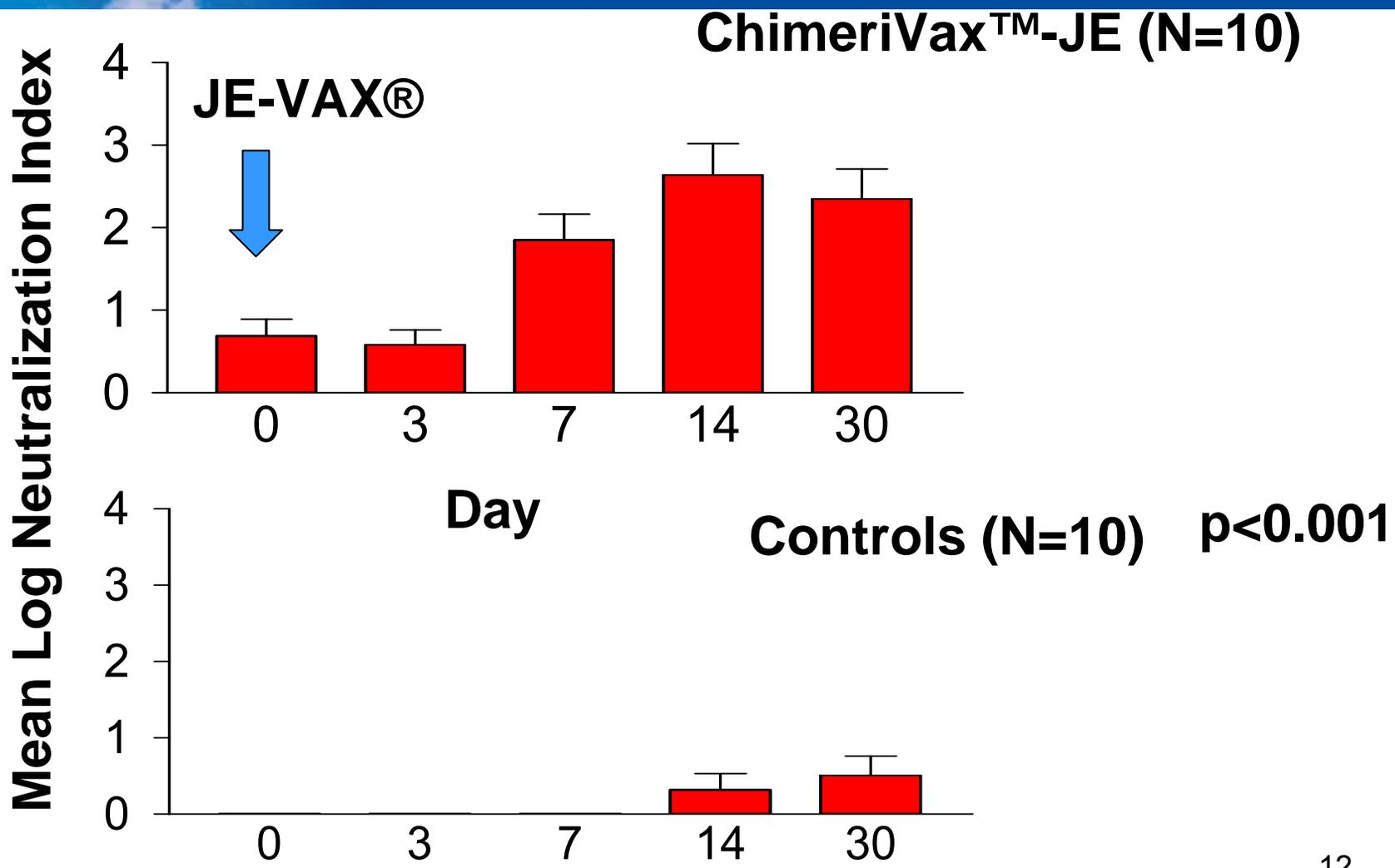
Phase	Study	Site(s)	(n)
1	Proof of principle	USA	36
2	Challenge with JE-VAX [®]	USA	20
2	Dose ranging study	USA	99
2	Duration of immunity / booster at 6 mths	AUS	201
2	YF vaccine interference	AUS	107
2	Bridging study lyophilized vaccine	AUS	128
2	Comparative immunogenicity study	US	60

More than 500 subjects vaccinated
with ChimeriVax™-JE

Lack of interference by prior YF immunity

	YF-naive	YF-immune
Dose (log ₁₀ PFU)	D30 PRNT ₅₀ (GMT)	D30 PRNT ₅₀ (GMT)
ChV-JE 5.8	6/6 (254)	6/6 (327)
4.8	6/6 (128)	6/6 (270)
YF-VAX	3/6 (13)	2/6 (13)

Anamnestic Response to JE Antigen



Absence of Dose Effect with Single Dose

Dose (log₁₀ PFU)	Seroconversion D30 PRNT₅₀	GMT D30 PRNT₅₀
ChV-JE 5.8	10/10	262
4.8	44/44	299
3.8	11/11	210
2.8	10/11	103
1.8	11/11	285
YF-VAX®	1/11	7
Placebo	0/11	5

Adverse Events Following Single Dose

Adverse Event	ChV™-JE (n=201)	Placebo (n=199)
# Subjects with ≥ 1 AE	102 (51%)	110 (55%)
Injection site erythema	4 (2%)	5 (3%)
Injection site pain	7 (4%)	5 (3%)
URI	24 (12%)	35 (18%)
Headache	27 (13%)	20 (10%)
Myalgia	2 (1%)	3 (2%)
Lethargy	11 (6%)	5 (3%)
Fatigue	3 (2%)	2 (1%)
Rash	3 (2%)	1 (1%)

Seroconversion (GMT) after Single Dose

	Day 14	Day 28	Month 6
# subjects evaluable	194	197	191
# (%) seroconversion	145 (74%)	191 (97%)	185 (97%)
Geometric Mean Titer	59	317	152

NT antibodies to homologous (Chimerivax-JE) virus; ITT pop.

Antibody responses to wild-type JE viruses

	ChV™ _{JE}	Genotype I	Genotype II	Genotype III	Genotype IV
Sero-conversion	99%	99%	92%	99%	89%
GMT	314	219	68	209	59

Genotype	Strain	Country	Origin
I	1991 TVP-8236	Korea	Mosquito
II	B 1034/8	Thailand	Pig
III	Beijing	P.R. China	Human
IV	IVJKT 9092 TVP-6265	Indonesia	Mosquito

Test laboratory: Mahidol University; ITT pop (n = 196).

Durable Immunity to 1 year after 1 Dose

	Single inoculation @ Day 0		Booster @ 6 Mo.
Interval	Month 6	Month 12	Month 12
% seroconversion	97% (185/191)	95% (72/76)	99% (79/80)
95% CI	93, 99	87, 99	93, 100
GMT	152	97*	181*

* Significant difference in titers between treatment groups (p = .002, ANOVA). ITT pop. Test laboratory Mahidol University

No major interactions with YF vaccine

Treatment	Seroconversion (GMT) to	
	JE	YF
ChimeriVax™-JE → Stamaril® (n = 36)	100% (646)	94% (2412)
Stamaril® → ChimeriVax™-JE (n = 35)	91% (487)	100% (2516)
ChimeriVax™-JE + Stamaril® (n = 35)	94% (337)	100% (2301)

Seroconversion and GMT (PRNT₅₀), 30 days after sequential or combined administration of JE and YF vaccines; ITT population.

Phase 2 Lyophilized Vaccine Study

- > Multi-center, randomized, double-blind, placebo controlled out-patient study in adults – Australia
- > Objective: to evaluate safety, tolerability and immunogenicity of a single subcutaneous vaccination of a newly derived, lyophilised formulation of ChimeriVax™-JE in healthy adult volunteers, at three dose levels
- > Immunogenicity assessment by seroconversion rates and geometric mean neutralizing antibody titres at each dose level
- > Durability of immune response up to 12 months following ChimeriVax™-JE vaccination, at one of three dose levels

Viremia after Vaccination (lyophilized)

Viremia	Log ₁₀ PFU ChimeriVax™-JE			
	3.0	4.0	5.0	All
	(n=32)	(n=32)	(n=32)	(n=96)
Mean peak viremia (PFU/mL)	4.4	6.6	3.4	4.8
Range, peak viremia (PFU/mL)	0 – 10	0 - 30	0 - 20	0 - 30
Mean duration (days)	0.7	1.4	0.6	0.9
Range, duration (days)	0 – 3	0 – 7	0 - 11	0-11

Phase 2 Comparative Immunogenicity Study

- > Single center, randomized, double-blind, active controlled out-patient study in adults – US
- > Objective: to evaluate antibody and T-cell responses 30 days after a single dose of ChimeriVax™-JE compared to those after 3-dose immunization schedule for JE-VAX® (licensed JE vaccine) in healthy adult volunteers without prior JE immunity
- > Immunogenicity assessment by seroconversion rates and geometric mean neutralising antibody titres, and IFN- γ responses
- > Assessment of durability of immune (antibody and T cell) response over 12 months following primary immunization with ChimeriVax™-JE or JE-VAX®

Phase 3 Pivotal Safety Study

- > Multi-center, randomized, double-blind, placebo-controlled out-patient study in adults – US/Australia
- > Objective: to evaluate safety and tolerability 30 days after a single dose of ChimeriVax™-JE compared to placebo (diluent)
- > Total of 2000 subjects (1600 ChimeriVax™-JE, 400 placebo)
- > Completed enrollment, treatment period and 6 month follow-up

Phase 3 Pivotal Efficacy Study

- > Multi-center, randomized, double-blind, active controlled out-patient study in adults – US/Australia
- > Objective: to evaluate immunologic efficacy 30 days after a single dose of ChimeriVax™-JE compared to efficacy after 3 doses of JE-VAX®
- > Immunogenicity assessment by seroconversion rates and geometric mean neutralizing antibody titres
- > Total of 816 subjects (408 ChimeriVax-JE, 408 JE-VAX®), statistically powered to show non-inferiority
- > Clinical consistency of 3 lots of ChimeriVax™-JE
- > Completed enrollment and treatment periods

Phase 2 Pediatric Study

- > Multi-center, randomized, double-blind, active controlled out-patient age-ranging study in children and infants (<10 years to ≥ 9 months old) without prior JE exposure – India
- > Objective: to evaluate safety, reactogenicity and immunogenicity of ChimeriVax™-JE compared to 2 doses of mouse brain vaccine (MBV, Kasauli)
- > Immunogenicity assessment by seroconversion rates and geometric mean neutralizing antibody titers
- > Assessment of potential interaction of ChimeriVax™-JE with measles vaccine (Serum Institute)

Safety Profile of ChimeriVax-JE

- > Adverse events (AEs) in ChV™-JE vaccinees mainly mild to moderate. Commonly reported adverse events included constitutional symptoms (headache, malaise, fatigue), myalgia, diarrhea, and injection site reactions
- > AE rates were similar or less than those seen after vaccination with approved yellow fever vaccines (YF-VAX®, STAMARIL®), used as active comparators
- > No large differences in the incidence of AEs compared to placebo (diluent) recipients
- > One treatment-emergent SAE considered possibly related to ChimeriVax™-JE vaccination
 - Acute viral illness with diarrhea and fever 9 days after vaccination

Immunogenicity Profile of ChimeriVax™-JE

- > A single inoculation elicits JE-neutralizing antibodies in 97% of subjects within 28 days of vaccination
 - 74% seroconversion within 14 days of single dose
- > A single vaccination results in neutralizing antibodies against all 4 JE genotypes circulating in Asia
 - Range 89-99% seroconversion
- > After a single inoculation, JE-specific neutralizing antibodies persist for at least 12 mo. in 95% of subjects; duration studies ongoing
- > ChimeriVax™-JE may be given 30 days before, 30 days after, or simultaneously with YF 17D vaccine

ChimeriVax™-JE Target Product profile

- > Live, attenuated vaccine for prophylaxis of Japanese encephalitis
- > Single dose for primary protection
- > Well tolerated for all ages, including children > 9 months
- > Low viremia, not transmitted by mosquito vectors
- > Effective (immunogenicity >90%)
- > Rapid immunity (within 14 days of vaccination)
- > Durable immunity (to 5 years after vaccination)
- > May be co-administered with licensed vaccines (measles)
- > Contraindicated for persons with immune suppression, pregnancy, lactation

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