IXIARO® Draft Presentation for ACIP

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A New Inactivated, Vero Cell Culture-Derived Japanese Encephalitis Vaccine (IXIARO®, IC51) for Adult Travelers

COMPARISON OF IXIARO® AND JE-VAX®

Component	IXIARO®	JE-VAX®
Virus Strain	SA_{14}-14-2	Nakayama
Virus Seed	Attenuated	Wild-type
Virus Growth	Vero Cells	Mouse Brains
Adjuvant	Aluminum Hydroxide	None
Stabilizers	None	Porcine Gelatin
Preservative	None	Thimerosal
Format	Liquid	Lyophilized
Dose	2 Doses, Days 0,28 6 mcg/0.5mL	3 Doses, Days 0,7,28 1.0 mL

Note: Awaiting final approval on use of IXIARO® tradename

IMMUNOLOGICAL INDICATOR OF EFFICACY

» Efficacy trials of any new JE vaccine not feasible because of ethical issues

» FDA licensure of IXIARO® will be based on immunogenicity criteria (non-inferiority versus licensed vaccine)

» Indicator of Efficacy: $PRNT_{50} \geq 1:10$ (Serum dilution giving a 50% reduction in a **P**laque **R**eduction **N**eutralization **T**est)

» WHO Expert Panel accepts $PRNT_{50} \geq 1:10$ as protective (Hombach et al, 2005)

Hombach et al 2005. Vaccine 23; 2005: 5205-5211

PHASE 3 CLINICAL TRIALS WITH IXIARO®

» 3,558 subjects exposed to IXIARO® in Phase 3 Trials

» 3,504 subjects exposed to 2 doses

» In total, over 7,150 doses of IXIARO® have been administered

Study	Objective	IXIARO® Subjects	Controls
IC51-301	Pivotal Immunogenicity vs JE-VAX®	430	437
IC51-302	Pivotal Safety vs Placebo	2,012	663
IC51-303	Long-term Safety and Immunogenicity Follow-up	2,283 181	975 82
IC51-308	Concomitant Vaccination with HAVRIX®	127	65

STUDY
IC51-301

DESIGN OF PHASE 3 NON-INFERIORITY IMMUNOGENICITY STUDY OF IXIARO® VERSUS JE-VAX®

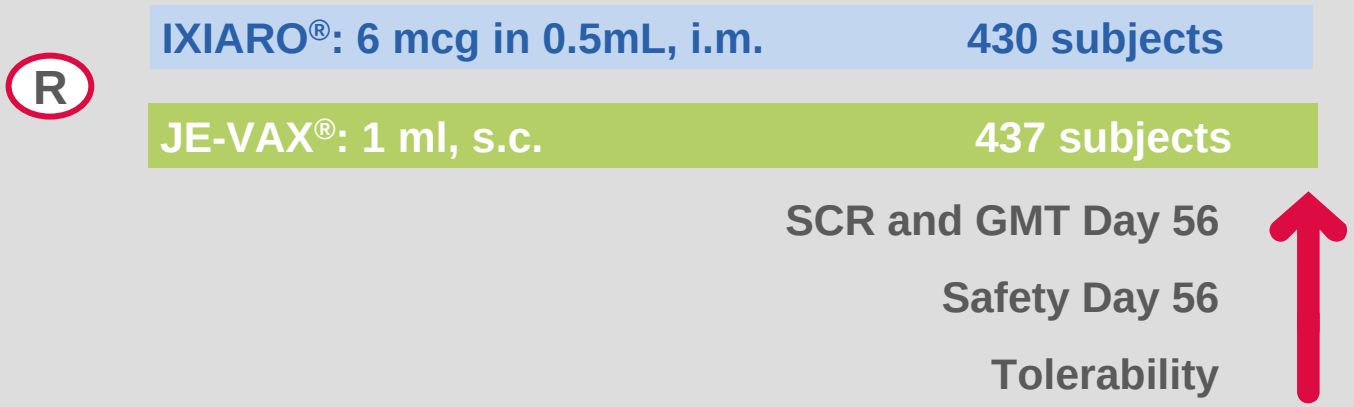
Population

» 867 subjects randomized; healthy adults ≥ 18 years of age; 11 sites in North America and Europe

Treatment Groups

» IXIARO®: 2 Injections Days 0/28, Placebo Day 7

» JE-VAX®: 3 Injections Days 0/7/28



Challenge strain for all $PRNT_{50}$: SA_{14}-14-2

STUDY
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SUMMARY OF SAFETY DATA FOR STUDY IC51-301

Overview of Adverse Events Following Immunization (AEFIs)

	IXIARO® N=428 n (%) [95%CI]	JE-VAX® N=435 n (%) [95%CI]
Subjects having at least one AEFI:		
» One serious	1* (0.2) [0.04, 1.31]	0 (0.0) [0.00, 0.88]
» One possibly or probably related	159 (37.1) [32.71, 41.82]	149 (34.3) [29.95, 38.83]
Subjects who:		
» Terminated due to an AEFI	7 (1.6) [0.79, 3.34]	8 (1.8) [0.93, 3.59]
» Died	0 (0.0) [0.00, 0.89]	0 (0.0) [0.00, 0.88]

* Myocardial Infarction; judged as unlikely related

STUDY
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SUMMARY OF TOLERABILITY DATA FOR STUDY IC51-301

Local Tolerability Symptoms up to 7 Days after Any Vaccination

	IXIARO® N=421 n (%)	JE-VAX® N=427 n (%)	p-Value*
Any Local Tolerability Symptom	**227 (54)**	**295 (69.1)**	**p<0.0001**
Any Severe Local Tolerability Symptom	**9 (2.1)**	**59 (13.8)**	**p<0.0001**
» Pain	0 (0.0)	6 (1.4)	
» Itching	0 (0.0)	4 (0.9)	
» Tenderness	1 (0.2)	6 (1.4)	
» Hardening	4 (1.0)	22 (5.2)	
» Swelling	3 (0.7)	23 (5.4)	
» Redness	4 (1.0)	46 (10.8)	

* Fisher's exact test

N = Number of subjects with at least one record in subject diary

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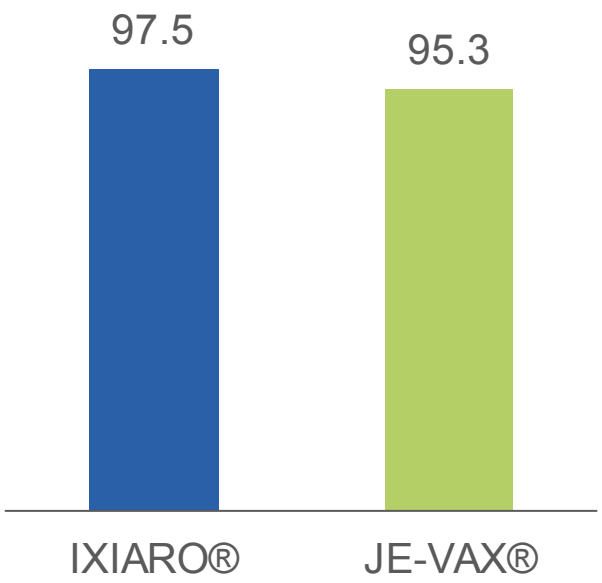
SEROCONVERSION RATE OF IXIARO® COMPARED TO JE-VAX®

Seroconversion Rates (SCR) at Day 56 – PP Population

4 weeks after the last vaccination

% Seroconversion



	IXIARO® N=365 n (%)*	JE-VAX® N=370 n (%)*
Seroconverted ($PRNT_{50} \geq 1:10$)	352 (97.5)	347 (95.3)
» Risk difference estimator (%)**	1.05 [-1.33; 3.43]	

* Based on number of observed values

** Mantel-Haenszel type risk difference estimator for seroconversion with 95% confidence interval, stratified for center and age group; SCR based on observed values only

Non-Inferiority Margin: Difference in SCR < 10%

Demonstrated if 95% CI for SCR difference does not fall below -10%

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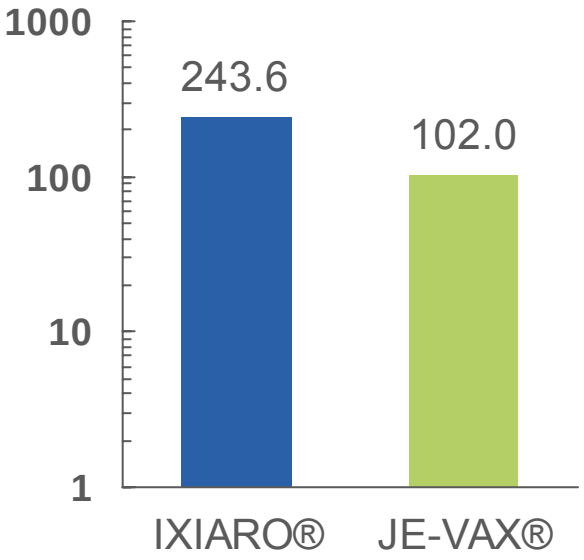
NON-INFERIORITY OF IXIARO® COMPARED TO JE-VAX® PRIMARY EFFICACY COMPARISON

Geometric Mean Titers (GMT) at Day 56 – PP Population

4 weeks after the last vaccination

log GMT



	IXIARO® N=365	JE-VAX® N=370
Geometric Mean Titer*	243.6	102.0
SD	1163.1	221.0
Minimum	5	5
Maximum	19783	1864
GMT ratio estimator**	2.33 [1.97 ; 2.75]	

* Based on observed values

** Estimate for GMT ratio with confidence interval (from ANOVA with factors center, age group and treatment)

Non-Inferiority Margin: GMT Ratio IXIARO®/JE-VAX® > 1/1.5

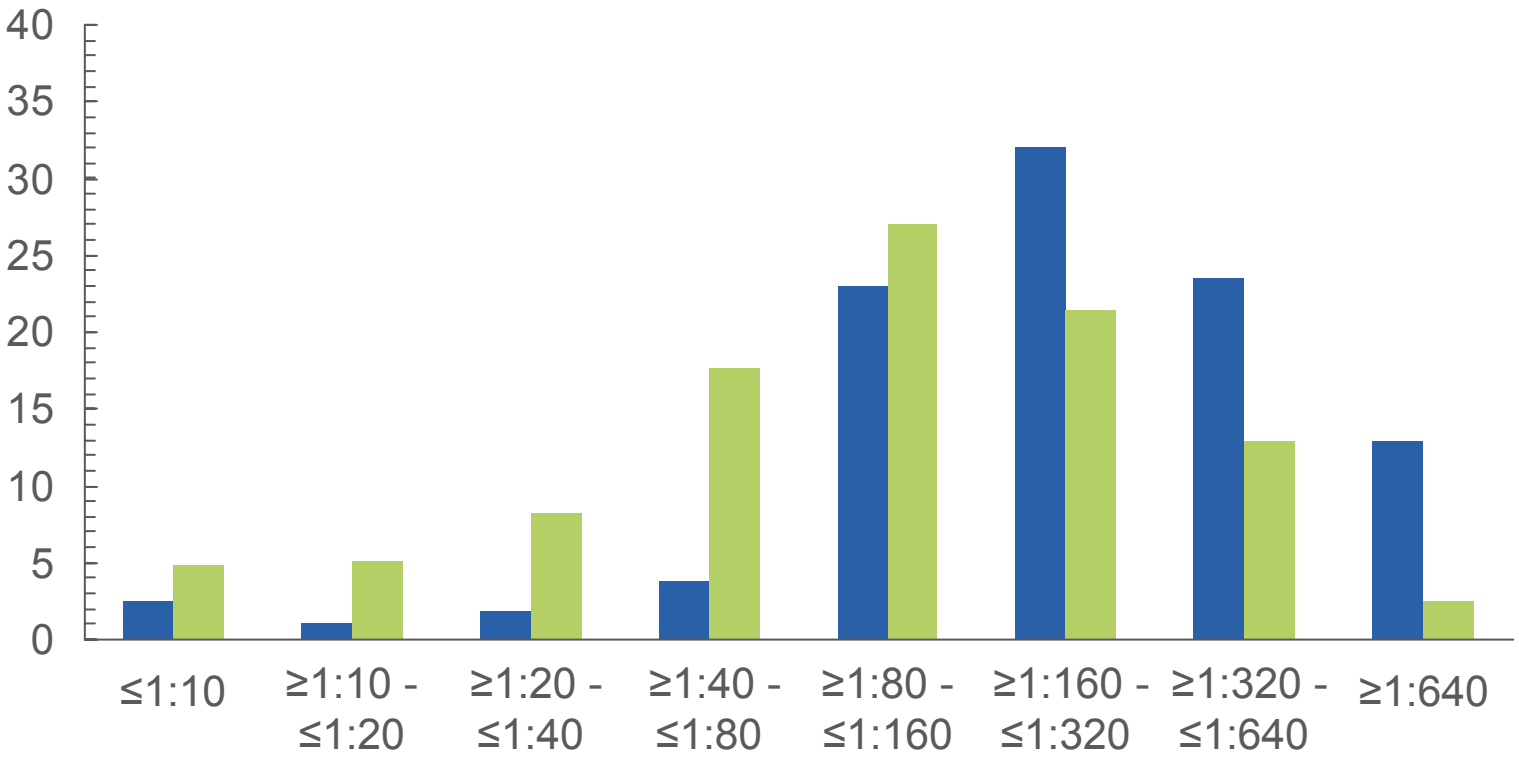
Demonstrated if 95% CI for GMT ratio does not fall below 1/1.5 (0.67)

DISTRIBUTION OF $PRNT_{50}$ OF IXIARO® COMPARED TO JE-VAX®

Distribution of $PRNT_{50}$ at Day 56 – PP Population

4 weeks after the last vaccination

Percent of Subjects Achieving Titer Threshold



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IXIARO®
JE-VAX®

N IXIARO®: 361
N JE-VAX®: 364

LONG TERM IMMUNOGENICITY DATA FOR IXIARO®

» 181 subjects on IXIARO®, 82 subjects on JE-VAX®

» 2 and 6 months post-vaccination data for IXIARO® and JE-VAX®

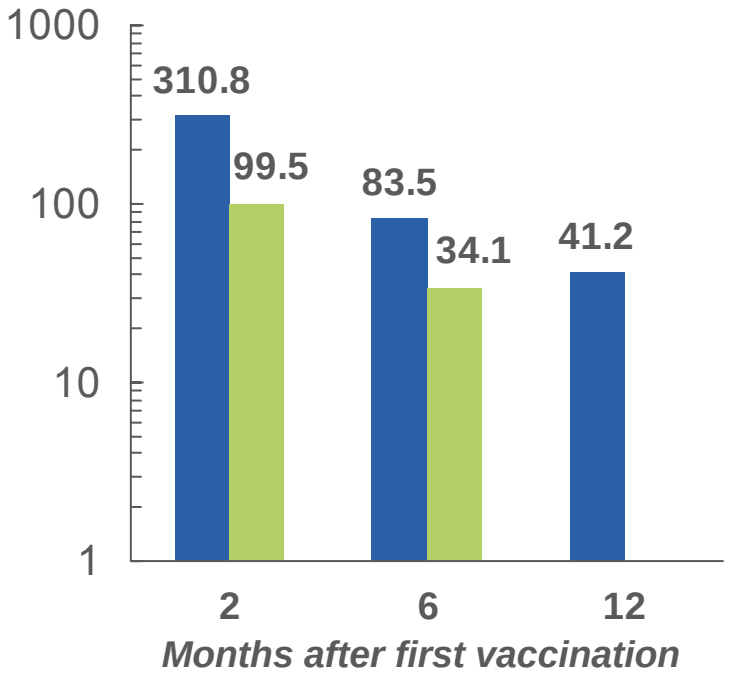
» 12 months data for IXIARO®

STUDY
IC51-303

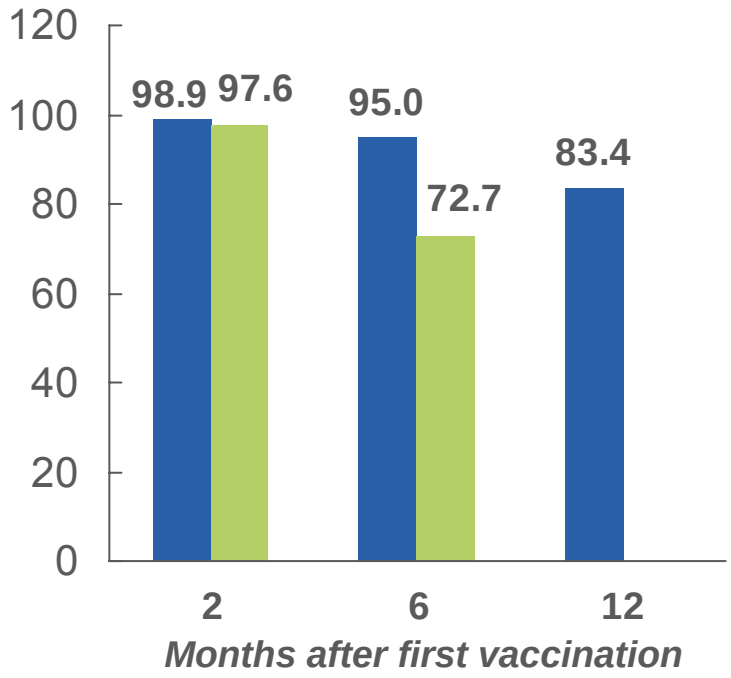
IXIARO®

JE-VAX®

log GMT



Subjects with $PRNT_{50}$ ≥ 1:10 [%]



N IXIARO®: 181

N JE-VAX®: 82

STUDY
IC51-302

DESIGN OF PHASE 3 SAFETY STUDY OF IXIARO® VERSUS PLACEBO*

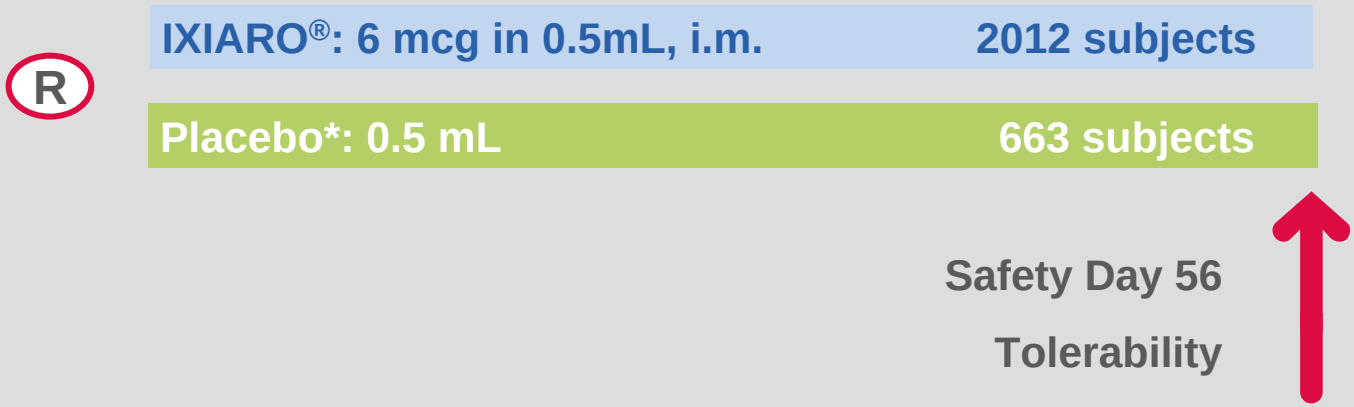
Population

» 2,675 subjects randomized; healthy adults ≥ 18 years of age; 39 sites in 8 countries (US, AT, DE, IR, RO, UK, AU, NZ)

Treatment Groups

» IXIARO®: 2 injections Days 0/28, i.m.

» Placebo*: 2 injections Days 0/28, i.m.



* Placebo: Phosphate-buffered saline solution with 0.1% $Al(OH)_3$

STUDY
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SUMMARY OF SAFETY DATA FOR IXIARO® AND PLACEBO

Overview of Adverse Events Following Immunization (AEFIs)

	IXIARO® N=1,993 n (%)	Placebo N=657 n (%)	p-Value*
Subjects having at least AEFI:			
» one serious	10 (0.5)	6 (0.9)	0.2487
» one possibly or probably related	774 (38.8)	254 (38.7)	0.9632
» one medically attended	254 (12.7)	80 (12.2)	0.7350
Subjects who:			
» terminated due to an AEFI	12 (0.6)	5 (0.8)	0.5857
» died	0 (0.0)	0 (0.0)	
Subjects having:			
» Any local tolerability symptom	1095 (54.9)	365 (55.6)	0.7160
» Any systemic tolerability symptom	768 (38.5)	260 (39.6)	0.7073

* Fisher's exact test

STUDY
IC51-302

SAFETY DATA FOR IXIARO® AND PLACEBO

Adverse Events Following Immunization (AEFIs) of Special Interest

	IXIARO® N=1,993 n (%)	Thereof: Related*, Severe	Placebo N=657 n (%)	p-Value**
» Pyrexia	64 (3.2)	–	20 (3.0)	0.8984
» Rash***	26 (1.3)	1	10 (1.5)	0.6980
» Rash maculo-papular	2 (0.1)	–	–	1.0000
» Rash pruritic	–	–	1 (0.2)	0.2479
» Injection site rash	1 (0.1)	–	–	1.0000
» Paraesthesia	4 (0.2)	–	2 (0.3)	0.6419
» Pruritus***	4 (0.2)	–	2 (0.3)	0.6419
» Pruritus generalized	1 (0.1)	–	–	1.0000
» Hypersensitivity***	1 (0.1)	–	–	1.0000
» Drug hypersensitivity	1 (0.1)	–	–	1.0000
» Urticaria localized	1 (0.1)	–	–	1.0000
» Urticaria	–	–	1 (0.2)	0.2479

No cases of: Encephalitis, Meningitis, Anaphylaxis, Convulsions

* Related = investigator judged event as possibly or probably related

** Fisher's exact test

*** Not further specified

POOLED 6 MONTHS SAFETY ANALYSIS

» 7 Studies included in a pooled 6 months safety analysis

» Subjects in follow-up studies were matched with preceding studies and only counted once

» All subjects that received a dose of IXIARO® were analyzed in the IXIARO® group

» 4,715 subjects in the pooled 6 months safety analysis

» 3,558 subjects exposed to IXIARO®

» 3,310 subjects on IXIARO® completed 6 months safety follow-up

Pooled Safety Analysis

ADVERSE EVENTS FOLLOWING IMMUNIZATION POOLED 6 MONTHS SAFETY ANALYSIS (1/2)

Summary of Adverse Events Following Immunization (AEFIs)

	IXIARO® N=3,558 n (%)	JE-VAX® N=435 n (%)	HAVRIX® N=65 n (%)	Placebo N=657 n (%)
Subjects having at least one AEFI:				
» One serious	38 (1.1)	3 (0.7)	–	13 (2.0)
» One related serious	–	–	–	–
» One leading to withdrawal	27 (0.8)	8 (1.8)	–	5 (0.8)
» A fatal	1* (0.0)	–	–	–
» A related fatal	–	–	–	–

* Metastatic Lung Adenocarinoma, judged as unrelated

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ADVERSE EVENTS FOLLOWING IMMUNIZATION POOLED 6 MONTHS SAFETY ANALYSIS (2/2)

Adverse Events Following Immunization (AEFIs) of Special Interest

	IXIARO® N=3,558 n (%)	Thereof: Related*, Severe	JE-VAX® N=435 n (%)	Placebo N=657 n (%)
» Headache	938 (26.4)	27	125 (28.7)	173 (26.3)
» Myalgia	556 (15.6)	9	69 (15.9)	103 (15.7)
» Flu-like illness	489 (13.7)	10	57 (13.1)	82 (12.5)
» Pyrexia	116 (3.3)	2	21 (4.8)	21 (3.2)
» Rash (Any)	62 (1.7)	1	11 (2.5)	13 (2.0)
» Paraesthesia	5 (0.1)	–	1 (0.2)	3 (0.5)
» Convulsion	2 (0.1)	–	–	–
» Pruritus	14 (0.4)	–	1 (0.2)	2 (0.3)
» Hypersensitivity	4 (0.1)	–	2 (0.5)	–
» Drug Hypersensitivity	2 (0.1)	–	–	–
» Urticaria localized	2 (0.1)	–	–	1 (0.2)
» Urticaria	2 (0.1)	–	–	–

No cases of: Encephalitis, Meningitis, Anaphylaxis

* Related = investigator judged event as possibly or probably related

SUMMARY SAFETY AND IMMUNOGENICITY

» Non-inferiority of IXIARO® against the licensed vaccine, JE-VAX®, was demonstrated for Seroconversion Rates as well as for Geometric Mean Titers

» Seroconversion Rates, defined as proportion of subjects achieving a titer of $PRNT_{50} \geq 1:10$, were over 95% for the first 6 months and over 83% after one year

» Systemic tolerability and adverse events were similar between IXIARO®, placebo and JE-VAX®

» IXIARO® appeared to have a more favorable local tolerability profile than JE-VAX®

UPDATE ON REGULATORY AND SUPPLY OF IXIARO®

» BLA has been submitted in December 2007

» Proposed indications as per draft label from BLA:

- **Indicated for active immunization against JE disease for persons 18 years of age and older who are at risk of exposure to JE virus.**
- **Vaccine should be used in persons who plan to reside in or travel to areas where JE is endemic or epidemic, especially if travel will occur during the transmission season.**

» Intercell will be manufacturer and holder of the BLA

- Intercell will distribute IXIARO® to the US military
- Novartis will distribute the vaccine to the US civilian markets

» Intercell will provide sufficient capacities to supply the US&EU travelers markets and the military

intercell
SMART VACCINES

PEDIATRIC INVESTIGATIONAL PLAN FOR IXIARO®

» Safety and immunogenicity will be established in children and adolescents between 1 and 17 years of age

» Studies are ongoing and planned:

- Phase 2 dose confirmation study ongoing in India
- Phase 3 immunogenicity and safety trials in endemic countries in Southeast Asia, to be initiated after adult licensure
- Supportive immunogenicity study to be conducted in US

» Pediatric label is currently projected for the 2010/2011 timeframe

CONCLUSIONS AND OUTLOOK

» Intercell's IXIARO® development program has successfully reached the point of license application submission

- **Phase 3 studies have demonstrated an appealing safety and immunogenicity profile**
- **Current product development results support the adult target population**

» Intercell and Novartis are committed to make IXIARO® available to the target population and to develop the product further

- **Sufficient supply capacities and commercialization capabilities are intended to be provided**
- **Studies to support pediatric use have been initiated and further studies are planned**
- **Technical product life cycle activities will be commenced post licensure**