



**Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Vaccines Research and Review
Division of Vaccines and and Related Product Applications**

Subject: Clinical Review of New Biologics License Application STN# 125280/0 – IXIARO®

Product: IXIARO® (Japanese Encephalitis Vaccine, Inactivated, Adsorbed)

Date of submitted application: 18 December 2007
Date of completed review: 27 March 2009

From: Jeffrey N. Roberts, M.D.
Medical Officer
Vaccine Clinical Trials Branch
Division of Vaccines and Related Products Applications

To: Lewis Markoff, M.D.
Chairperson, BLA Committee
Division of Viral Products

Through: Rosemary Tiernan, M.D., MPH
Team Leader, Vaccine Clinical Trials Branch
Division of Vaccines and Related Products Applications

R. Douglas Pratt, M.D., MPH
Chief, Vaccine Clinical Trials Branch
Division of Vaccines and Related Products Applications

BLA review committee:

Lewis Markoff	Chairperson
Jeff Roberts	Clinical
Li Yu	CMC
Barry Falgout	CMC
Mridul Chowdhury	Biostatistics
Marion Gruber	Repro-Toxicology review
Jean Makie	Promotional labeling and Proprietary name review
Anthony Hawkins	BioResearch Monitoring
Destry Sullivan	Facilities
Richard Daemer	Regulatory Project Manager/DVRPA
Daryll Miller	Regulatory Project Manager/DVRPA
Deanna Shone	Copy Editor

1 General Information

1.1 Medical Officer Review Identifiers and Dates

1.1.1 BLA#: 125280

1.1.2 Related IND's and BLA's

None

1.1.3 Reviewer Name, Division, and Mail Code

Jeff Roberts, M.D.
Division of Vaccines and Related Products Applications
HFM-475

1.1.4 Submission Received by FDA

12/18/07

1.2 Product

1.2.1 Proper Name

Japanese Encephalitis Vaccine, Inactivated, Adsorbed

1.2.2 Trade Name

IXIARO

Clinical Reviewer's Note: In this review, the vaccine is generally referred to as IC51, the name used during the clinical development program. In some cases, the trade name, IXIARO, is used. In the earliest phase of development conducted by the U.S. Army, the vaccine was referred to as JE-PIV.

1.2.3 Product Formulation

IXIARO is a vaccine prepared by propagating Japanese encephalitis virus (JEV) strain SA14-14-2 in Vero cells. Each dose of vaccine contains approximately 6 mcg of purified, inactivated JEV proteins and 250 mcg of aluminum hydroxide in a volume of 0.5 mL. (See Table 1).

As a result of the manufacturing process, IXIARO may also contain: formaldehyde (not more than 200 ppm), bovine serum albumin (not more than 100 ng/mL), host cell DNA (not more than 200 pg/mL), sodium metabisulphite (not more than 200 ppm), host cell proteins (not more than 300 ng/mL), and protamine sulfate (not more than 1 µg/mL). No preservatives, stabilizers, or antibiotics are added to the formulation.

Table 1. IXIARO Formulation per dose

Ingredient	Quantity (per 0.5 ml dose)
Active Ingredients	
Inactivated Japanese encephalitis virus	6 µg -(b)(4)-
Excipients	
Aluminum hydroxide (adjuvant)	0.25 mg
Phosphate buffered saline (PBS)	to 0.57ml

Source: Original BLA 125280, 3.2.P.1 – Description and Composition of the Drug Product, p.4

1.3 Applicant

Intercell AG

1.4 Pharmacologic Class

Vaccine

1.5 Proposed Indication

IXIARO is indicated for active immunization for the prevention of disease caused by Japanese encephalitis virus (JEV) in persons 17 years of age and older.

1.6 Dosage Forms and Routes of Administration

IXIARO is a liquid suspension for intramuscular injection. The vaccine is supplied in a single dose, pre-filled syringe, in a volume of 0.5 mL per syringe.

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3 Executive Summary

Under Biologics License Application (BLA) 125280, Intercell AG submitted immunogenicity and safety data in support of licensure of their Japanese encephalitis (JE) vaccine, IC51 (trade name, "IXIARO"). The conclusion of this reviewer is that licensure of IC51 for the proposed indication of prevention of disease caused by Japanese encephalitis virus (JEV) in persons 17 years of age and older is warranted based on review of the clinical data and other relevant information.

ACIP recommends vaccination against JEV for certain travelers at risk for infection during visits to endemic regions. The only currently available U.S.-licensed JE vaccine, JE-VAX, has been manufactured by Biken in Japan, but future supplies are uncertain. IC51 is expected to fill an anticipated need for immunization against JEV among U.S. military personnel and civilians traveling to JE-endemic areas.

IC51 is produced in Vero cell culture using the attenuated JE strain, SA14-14-2. It is formalin-inactivated, aluminum-adsorbed, and packaged in a pre-filled syringe containing approximately 6µg of JEV proteins in a volume of 0.5mL. The recommended vaccination regimen is one dose intramuscularly on Day 0 and Day 28.

The material reviewed in-depth herein includes the pivotal Phase III immunogenicity study (IC51-301); the pivotal Phase III safety study (IC51-302); a vaccine co-administration study (IC51-308); and pooled immunogenicity and pooled safety data sets. The clinical development plan also included Phase I and Phase II dose and regimen-finding studies, an antibody kinetics immunogenicity study, long term immunogenicity and safety studies, and two lot consistency studies. Each study submitted to the BLA is briefly summarized in Appendix 1.

Because safe and effective vaccines against JE are available, a placebo-controlled field trial of true efficacy of a JE vaccine in development would be considered unethical. Broad consensus has developed around the use of the Plaque Reduction Neutralization Test (PRNT) as a surrogate measure of JE vaccine efficacy. FDA agrees with defining seroconversion as PRNT50 titer of $\geq 1:10$. In study IC51-301, IC51 demonstrated immunogenicity by meeting a predefined

statistical standard for non-inferiority compared to JE-VAX as measured by seroconversion rates (SCR) and geometric mean titers (GMT).

Safety was examined primarily in the placebo-controlled, Phase III study, IC51-302. In this trial, IC51 was similar to placebo in terms of adverse events and tolerability profile, and no concerning safety signals were apparent in the system organ class analysis. The pooled safety data, which included 3558 subjects treated with at least one dose of IC51, also demonstrated an acceptable safety profile. In these analyses, IC51 compared favorably to JE-VAX, particularly in terms of local tolerability. Among all the subjects who received at least one dose of IC51, there was one death, which occurred in a 70 year old female who was diagnosed with metastatic lung adenocarcinoma one month after completing the vaccination regimen. This outcome was considered unrelated to study drug.

In the pooled data set of 3558 subjects who received at least one dose of IC51, there was one case of dermatomyositis and one case of multiple sclerosis, both temporally related to vaccination. Causality could not be determined based on the available data. Review of the entire safety dataset did not reveal a pattern suggestive of a safety signal with regard to the two named events. The post-marketing pharmacovigilance plan includes a study in military personnel powered to detect a doubling or tripling of rare, serious events.

IC51 is expected to be given to individuals who will be receiving other vaccines concomitantly before traveling. The sponsor conducted a study to investigate co-administration of IC51 with a Hepatitis A vaccine, HAVRIX (Study IC51-308). By predefined statistical standards, co-administration met non-inferiority criteria versus individual administration of each vaccine. In addition, there was no evidence of compromised safety with co-administration.

Anticipating that travelers may not always plan ahead, the sponsor conducted a study to evaluate antibody kinetics of a 2X dose (12 mcg) of IC51. Seroconversion rates were only marginally better in the short term after a 2X dose compared to the single dose (12 mcg versus 6 mcg, respectively). This study showed that travelers cannot expect high rates of protection until at least day 35 of the proposed regimen (6 µg at days 0 and 28).

Under the Pediatric Research Equity Act (PREA), the sponsor is required to conduct post-marketing studies to investigate the safety and efficacy of IC51 in a pediatric population. Intercell was granted a deferral of pediatric studies because studies in adults are sufficient to consider the license application for adults. Therefore, no data in subjects <18 years of age were submitted in support of licensure. (The approved indication is for persons "17 years of age and older" because CBER considers the data from subjects ≥18 years of age submitted in the license application to be applicable to persons 17 years of age).

During the review process, Intercell requested a partial waiver from PREA requirements for infants <12 months old. After considering multiple factors, including ethical issues, potential interference of maternal antibodies, and the sponsor's extensive investigation of feasibility, CBER granted this waiver, concluding that necessary studies are impracticable. CBER has determined that PREA requirements will be adequately addressed in the sponsor's post-marketing pediatric development program, which includes studies in ~2100 subjects from 12 months through 16 years of age. (See Section 11.4).

Based on multidisciplinary review of the data submitted for licensure, CBER did not identify issues that would have required the input or opinion of an independent panel of experts. Therefore, CBER determined that it was not necessary to refer the application to an FDA advisory committee.

4 Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls (CMC)

During CBER's pre-approval inspections of the Livingston, Scotland facility the applicant was cited for nineteen FDA 483 items related to facility, manufacturing, product, and quality issues. The responses to the FDA 483 items were received, reviewed, and found to be acceptable.

There are no ongoing or pending investigations and no compliance actions with respect to the above facilities or their products. Therefore, the Office of Compliance and Biologics Quality, Division of Case Management does not object to the approval of this submission. The facilities reviewer considers this submission approvable on the basis of the facilities information provided.

4.2 Animal Studies of Reproductive and Developmental Toxicology

The sponsor performed a developmental toxicity study in rats to evaluate the potential reproductive risk of this vaccine. There were no observed treatment related effect on the incidence of major and minor abnormalities and skeletal variants in the offspring of dams treated with the test article. However, in the group of dams that received IC-51 1 week prior to mating and then again on GD6, there were delays in in utero ossification in some regions in some of the fetuses. This was not observed in the group treated with 3 injections of vaccine. Control group data for the incidence of incomplete ossification appeared to be in the range of what is observed in the historical control data.

After reviewing the historical control data and multiple other parameters reported in the study, CBER's reviewer concluded that the observed higher incidences of incomplete ossification of fetuses in the group in question did not appear to be a vaccine related event.

4.3 Statistics

A CBER statistician reviewed the data from the pivotal immunogenicity trial, IC51-301, the two lot consistency trials, IC51-309 and -310, and the pivotal safety trial, IC51-302. The reviewer came to the following conclusions:

- 1) In IC-301, the results support the non-inferiority of IC51 to JE-VAX with regard to both co-primary endpoints – seroconversion rate and geometric mean titer at Day 56.
- 2) The two lot consistency studies were reviewed. In IC51-309, statistical criteria for lot consistency were not met for the three study lots. However, statistical criteria for lot consistency were met in IC51-310, the trial of three commercial lots.
- 3) IC51 had a comparable general safety profile with JE-VAX (IC51-301) and with placebo as well (IC51-302).

5 Clinical and Regulatory Background

5.1 Disease to be Studied and Available Interventions

Japanese encephalitis virus is the most common cause of viral encephalitis in Asia, with ~50,000 cases reported annually. Infection is frequently subclinical; only 1 in 250-500 infected individuals manifest clinical disease. However, symptomatic disease results in ~ 25% death rate and 30%-40% of survivors are left with serious neurological sequelae. No effective treatment exists; intervention consists of supportive measures (Diagana et al).

There are no reports of JE occurring in North America, so the risk to residents of the U.S. is based on travel to endemic regions (Erlanger et al). The risk varies depending on several factors, and it is difficult to accurately assess (ACIP MMWR report, 1993).

5.2 Information from Pharmacologically Related Products, Including Marketed Products

JE-VAX is the only US-licensed JE vaccine currently available. The Advisory Committee on Immunization Practices (ACIP) recommendations for JE vaccination for travelers can be summarized as follows:

- 1) Offer JE vaccine to travelers spending >1month in an endemic area during JE transmission season.
- 2) Consider vaccine for shorter stays if travel will include extensive outdoor activities in rural areas.
- 3) Short-term travelers whose visits are restricted to major urban areas generally should not be advised to receive the vaccine.

5.3 Previous Human Experience with the Product Including Foreign Experience

Human experience with IC-51 (referred to as JE-PIV in early development) is limited to the clinical development program documented in the BLA. Every study, including early phase studies, is briefly summarized in Appendix 1.

5.4 Regulatory Background Information

Clinical development of IC-51 proceeded with oversight from the FDA, the European Medicines Agency (EMA), and several individual European national agencies.

6 Clinical Data Sources, Review Strategy and Data Integrity

6.1 Material Reviewed

6.1.1 BLA #125280 - Files Reviewed

The following files formed the basis for the clinical review:

WRAIR-0763 – Clinical Study Report
WRAIR 0815 – Clinical Study Report
IC51-301 – Clinical Study Report
IC51-302 – Clinical Study Report
IC51-303 – Interim Analysis Report
IC51-304 – Clinical Study Report
IC51-308 – Clinical Study Report
IC51-309 – Clinical Study Report
IC51-310 – Clinical Study Report
IC51-311 – Clinical Study Report
Safety Overview Month 6 Analysis Report
Summary of Clinical Safety
Integrated Summary of Safety
Summary of Clinical Efficacy
Integrated Summary of Efficacy
Pediatric Development Plan
Request for Partial Waiver for Pediatric Population <1 year
Quality Overall Summary, Drug Substance

6.1.2 Literature

Advisory Committee on Immunization Practices. Inactivated Japanese Encephalitis Virus Vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 1993 Jan 8;42(RR-1):1-15.

Bryan JP, Henry CH, Hoffman AG, South-Paul JE, Smith JA, Cruess D, Spieker JM, de Medina M. Randomized, Cross-Over, Controlled Comparison of two Inactivated Hepatitis A Vaccines. Vaccine. 2000 Nov 22;19(7-8):743-50.

Diagana M, Preux PM, Dumas M. Japanese Encephalitis Revisited. J Neurol Sci. 2007 Nov 15;262(1-2):165-70.

Erlanger TE, Weiss S, Keiser J, Utzinger J, Wiedenmayer K. [Past, Present, and Future of Japanese Encephalitis](#). Emerg Infect Dis. 2009 Jan;15(1):1-7.

Hombach J, Solomon T, Kurane I, Jacobson J, Wood D. Report on a WHO Consultation on Immunological Endpoints for Evaluation of new Japanese Encephalitis Vaccines, WHO, Geneva, 2-3 September, 2004. Vaccine. 2005 Nov 1;23(45):5205-11.

Plotkin SA, Orenstein WA, Offit, PA., ed. Vaccines. 5th Edition. Philadelphia, PA: Saunders/Elsevier, 2008.

6.2 Table of Clinical Studies

Table 2 below lists the completed studies submitted to the BLA originally or as amendments. See Appendix 1 for brief summaries of the completed and ongoing studies in the BLA.

Table 2. Completed Studies Submitted to the BLA

Study Identifier	Type of Study	Study Design	Number of Subjects	Treatment Groups
WRAIR 763	Phase I dose and regimen finding, safety	Randomized (1:1:1:1), controlled, single-blind,	25	IC51 Grp 1: 0.4 mcg i.m. (Days 0 and 28; placebo on Day 7) IC51 Grp 2: 0.4 mcg i.m. (Days 0, 7 and 28) IC51 Grp 3: 2.0 mcg i.m. (Days 0 and 28; placebo on Day 7) IC51 Grp 4: 2.0 mcg i.m. (Days 0, 7 and 28)
WRAIR 815	Phase II dose and schedule finding, safety	Randomized (1:1:1:1) active controlled, open-label,	24	IC51 Grp 1: 6.0 mcg i.m. (Days 0 and 28) IC51 Grp 2: 6.0 mcg i.m. (Days 0, 14 and 28) IC51 Grp 3: 12.0 mcg i.m. (Days 0 and 28); JE-VAX®: 1.0 ml s.c. (Days 0, 7 and 28).

IC51-301	Phase III pivotal efficacy – non-inferiority vs control	Randomized (1:1), active controlled, multi-center, observer blinded,	867	IC51: 6.0 mcg i.m. (Days 0 and 28) and placebo ¹ i.m. on Day 7 JE-VAX®: 1.0 ml s.c. (Days 0, 7 and 28)
IC51-302	Phase III pivotal safety	Randomized (3:1 IC51: placebo), placebo-controlled, multi-center, double-blind,	2683	IC51: 6.0 mcg i.m. (Days 0 and 28) Placebo ¹ : 0.5 ml i.m. (Days 0 and 28)
IC51-303	Phase III efficacy and safety follow-up	Multicenter, uncontrolled follow-up study	<i>6-month</i> IC51: 2283 JE-VAX®: 338 Placebo: 637 <i>12-month</i> IC51: 181	No treatment given (follow-up data acquired on subjects originally enrolled in IC51-301 and IC51-302)
IC51-304	Phase III dose and schedule finding, antibody kinetics	Randomized (1:1:1), controlled, multi-centre, observer blinded	374	IC51 Grp A: 6.0 mcg i.m. (Days 0 and 28) and placebo ¹ i.m. (Day 0) IC51 Grp B: 12.0 mcg i.m. (Day 0) and placebo ¹ i.m. (Day 28) IC51 Grp C: 6.0 mcg i.m. (Day 0) and placebo ¹ i.m. (Days 0 and 28)
IC51-308	Phase III safety and efficacy – co-administration with hepatitis A vaccine, HAVRIX	Randomized (1:1:1), controlled, multi-centre, single-blind	192	IC51 6.0 mcg i.m. (Days 0 and 28) and placebo ¹ i.m. on Day 0 HAVRIX® 1.0 ml i.m. (Day 0) and placebo ¹ i.m. on Days 0 and 28 IC51 6.0 mcg i.m. (Days 0 and 28) and HAVRIX® 1.0 ml i.m. (Day 0)
IC51-309	Phase III safety and efficacy – equivalence of study batches	Randomized (1:1:1), controlled, multi-center, double-blind	639	IC51 Batch A 6.0 mcg i.m. (Days 0 and 28) IC51 Batch B 6.0 mcg i.m. (Days 0 and 28) IC51 Batch D 6.0 mcg i.m. (Days 0 and 28)
IC51-310	Phase III safety and efficacy – equivalence of commercial	Randomized (1:1:1), controlled, multi-center, double-blind	389	IC51 Batch A 6.0 mcg i.m. (Days 0 and 28) IC51 Batch B 6.0 mcg

	batches			i.m. (Days 0 and 28) IC51 Batch C 6.0 mcg i.m. (Days 0 and 28)
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¹Placebo was a PBS solution containing 0.1% aluminum hydroxide as an adjuvant.

6.3 Review Strategy

All the clinical data were examined. Each clinical study was briefly summarized. (See Appendix 1).

The following studies were reviewed in detail:

IC51-301 pivotal phase III efficacy
IC51-302 pivotal phase III safety
IC51-308 phase III non-inferiority of co-administration with HAVRIX

Study reports analyzing safety and immunogenicity in populations pooled from the appropriate studies in the BLA were reviewed. In some cases, post-hoc statistical analyses were performed by CBER reviewers.

6.4 Good Clinical Practices (GCP) and Data Integrity

The Division of Inspections and Surveillance performed bioresearch monitoring inspections of eight clinical sites in support of the BLA. The inspections did not reveal any problems that impact the data submitted in the application.

6.5 Financial Disclosures

On Form 3454, the sponsor certified that the following statement is correct:

“As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).”

7 Human Pharmacology

See Section 8.

8 Clinical Studies

8.1 Study IC51-301 (NCT00604708)

Title: OBSERVER BLINDED, RANDOMIZED PHASE 3 STUDY TO INVESTIGATE THE NON-INFERIORITY OF IC51 (JE-PIV) VS. JE-VAX® AS VACCINES FOR JAPANESE ENCEPHALITIS IN HEALTHY SUBJECTS

8.1.1 Objectives/Rationale

Primary objective: To demonstrate the non-inferiority of IC51 (2 x 6 mcg) compared to JE-VAX (3 x 1.0 mL) Japanese encephalitis (JE) vaccine in terms of the seroconversion rate (SCR) and geometric mean titer (GMT) at day 56; four weeks after the last vaccination.

Secondary objectives:

To compare:

- The superiority of IC51 versus JE-VAX SCR and GMT at day 56, provided that non-inferiority has been demonstrated
- The immunogenicity of both vaccines in regards to SCR and GMTs of the North American with the European study population
- The immunogenicity of both vaccines in regards to SCR and GMTs in subjects older versus younger than 50 years of age
- The safety of both vaccines regarding changes in laboratory parameters and adverse events (AEs) including local reactogenicity

8.1.2 Design Overview

This was a multicenter, observer blinded, controlled, randomized phase 3 study.

8.1.3 Protocol

After a two-week screening period, during which inclusion and exclusion criteria were checked, subjects were randomized in equal proportions stratified by age (< 50 versus ≥50 years) to receive either: two injections of IC51 (6 mcg in 0.5 mL) intramuscularly (i.m.) on days 0 and 28 and one 0.5 mL injection with placebo (phosphate-buffered saline [PBS] solution containing 0.1% aluminum hydroxide as an adjuvant) on day 7 (Group A) or three injections of JE-VAX (1.0 mL dose) subcutaneously (s.c.) on days 0, 7 and 28 (Group B); see Table 3. A final evaluation took place four weeks after last vaccination on day 56 or in the event of early termination.

Table 3. Study IC51-301 Treatment Arms

Study Day	Group A: IC51 (IM)	Group B: JE-VAX (SC)
Day 0	Dose #1 (6 mcg)	Dose #1 (1 mL)
Day 7	Placebo (PBS with 0.1% aluminum hydroxide)	Dose #2 (1 mL)
Day 28	Dose #2 (6 mcg)	Dose #3 (1 mL)

8.1.3.1 Population

Healthy adult male or female subjects were recruited at 12 sites in North America and Europe.

8.1.3.1.1 Inclusion/Exclusion Criteria

Inclusion Criteria

- 1) At least 18 years of age.
- 2) In female subjects either childbearing potential terminated by surgery, or one year post-menopausal, or a negative serum pregnancy test during screening, and the willingness not to become pregnant during the study period and 30 days after the last vaccination by practicing reliable methods of contraception.
- 3) Written informed consent obtained prior to study entry (subjects should have given their consent themselves; consent by legal representatives was allowed).

Exclusion Criteria

Subjects who met any of the following exclusion criteria were not included in the study:

- 1) History of clinical manifestation of any flavivirus infection.

- 2) History of vaccination against JE, Yellow fever and Dengue fever (an anti-JEV neutralizing antibody titer $\geq 1:10$ at baseline was acceptable for inclusion; these subjects were part of the safety population and ITT population, but were not analyzed for immunogenicity in the Per Protocol [PP] analysis).
- 3) Use of any other investigational or non-registered drug or vaccine in addition to the study vaccine during the study period or within 30 days preceding the first dose of study vaccine.
- 4) Planned administration of another vaccine during the study period.
- 5) Immunodeficiency including post-organ-transplantation or immunosuppressive therapy.
- 6) A family history of congenital or hereditary immunodeficiency.
- 7) History of autoimmune disease.
- 8) Administration of chronic (defined as more than 14 days) immunosuppressants or other immune-modifying drugs within six months of vaccination. (For corticosteroids, this included prednisone, or equivalent, ≥ 0.05 mg/kg/day. Topical and inhaled steroids were allowed).
- 9) Any acute infections within four weeks prior to enrollment.
- 10) History of severe hypersensitivity reactions (in particular to a component of the IC51 vaccine, e.g., protamine sulphate), anaphylaxis or severe cases of atopy requiring emergency treatment or hospital admission.
- 11) Infection with human immunodeficiency virus (HIV) (a negative test result within 30 days before enrollment was acceptable), hepatitis B or hepatitis C.
- 12) History of urticaria after hymenoptera envenomation, drugs, physical or other provocations, or of idiopathic cause.
- 13) Drug addiction within six months prior to enrollment (including alcohol dependence, i.e. more than approximately 60 g alcohol per day, or conditions which interfered with the study conduct).
- 14) Inability or unwillingness to avoid more than the usual intake of alcohol during the 48 hours after vaccination.
- 15) Known hypersensitivity to thimerosal.
- 16) Diabetes mellitus in subjects receiving insulin therapy, severe cardiopulmonary disorders, history of malignancy in the past five years.
- 17) Subjects with any condition which, in the opinion of the Investigator, made the subject unsuitable for inclusion.
- 18) Pregnancy (positive pregnancy test during screening or at baseline), lactation or unreliable contraception in female subjects.
- 19) Inability or unwillingness to provide informed consent and to abide by the requirements of the study.

8.1.3.1.2 Analysis Populations

For purposes of analysis, three subsets of the recruited subjects were identified: the Intention to Treat (ITT) Population, the Per Protocol (PP) Population, and the Safety Population. The primary immunogenicity analyses were based on the PP analysis population. The ITT analysis population was used for secondary immunogenicity analyses. The safety population was used for all safety and tolerability analyses including demographic data, vital signs, local and systemic tolerability, laboratory data, and AEs.

The populations were defined as follows:

- 1) ITT Population: Includes all subjects that were randomized. Subjects were analyzed according to the treatment group to which they were randomized, rather than by the actual treatment they received.
- 2) PP Population: All randomized subjects without any protocol deviations (as defined below). Subjects who were randomized incorrectly or took the wrong study medications were also excluded.

- 3) **Safety Population:** All subjects who entered the study and received at least one vaccination. All analyses based on the safety population were carried out using the actual treatment received.

The following subjects were considered to have a protocol deviation:

- Subjects with less than three vaccinations
- Subjects who had an anti-JEV neutralizing antibody titer $\geq 1:10$ at baseline
- Subjects with systemic immunosuppressant or immune-modifying concomitant therapy during the study period
- Subjects with any confirmed immunosuppressive or immunodeficient condition, including HIV, HBV, and HCV or a family history of congenital or hereditary immunodeficiency
- Subjects with an acute infection during the screening period or within four weeks before enrollment
- Subjects with active or passive vaccinations besides the study treatment during the study period or within four weeks before enrollment
- Subjects with a history of vaccination against JE, yellow fever, Dengue fever
- Subjects without any post-baseline seroconversion results
- Subject who violated any of the exclusion criteria

8.1.3.2 Products Mandated by the Protocol

Placebo: 0.5ml PBS solution containing 0.1% aluminum. Batch number ICB05/500

IC51: IC51 was available as a suspension of 6 mcg of purified, inactivated virus per 0.5 mL dose in a pre-filled syringe. Each dose contained 0.1% aluminum hydroxide adjuvant (See Section 1.2.3 for details of formulation). Batch number ICB05/501 (corresponds to Batch A in IC51-309, the lot consistency study).

JE-VAX: JE-VAX® is a sterile, lyophilized vaccine for s.c. use manufactured by BIKEN®. JE-VAX® was prepared by inoculating mice ("Nakayama-NIH" strain) intra-cerebrally with JEV. Infected brains were harvested and homogenized in PBS, pH 8.0. The homogenate was centrifuged, the supernatant inactivated with formaldehyde and processed to yield a partially purified, inactivated virus suspension. This was further purified by ultra-centrifugation through 40% sucrose. The suspension was then lyophilized in final containers and sealed under dry nitrogen atmosphere. Thimerosal was added as a preservative to a final concentration of 0.007%. The diluent (sterile water) contained no preservative. Each 1.0 mL dose contained approximately 500 mcg of gelatin, <100 mcg of formaldehyde, <0.0007% Polysorbate 80, and <50 ng of mouse serum protein. No myelin basic protein were detected at the detection threshold of the assay (<2 ng/mL). Prior to reconstitution, the vaccine was a white caked powder, and after reconstitution the vaccine was a colorless transparent liquid. The potency of test vaccine was determined by immunizing mice with either the test vaccine or the JE reference vaccine. Neutralizing antibodies were measured in a plaque neutralization assay performed on sera from the immunized mice. The potency of the test vaccine was no less than that of the reference vaccine.

JE-VAX® was available as single doses in 1.0 mL vials with a vial of diluent (1.3 mL sterile water). Batch numbers EJN213A (US only) and EJN214A (all sites) were used in the study.

8.1.3.3 Endpoints

8.1.3.3.1 Immunogenicity Endpoints

The co-primary endpoints were SCR (anti-JEV neutralizing antibody titer $\geq 1:10$) and GMT at day 56 for the entire study population. Secondary endpoints included:

- SCR and GMT at day 56 for the North American versus the European study population
- SCR at day 28 (last vaccination)

- GMTs for anti-JEV neutralizing antibody at day 28
- SCR and GMT at day 56 for subjects <50 years versus ≥50 years of age

Clinical Reviewer's Note: The Plaque Reduction Neutralization Test (PRNT) is the standard for measuring neutralizing anti-JEV serum antibody levels. A WHO report on immunological endpoints for evaluating JEV vaccines acknowledged a 50% plaque reduction in the PRNT at a dilution of 1:10 as being a "reasonable threshold" for protection (Hombach et al, 2005). CBER agrees with this assessment and accepts the definition of seroconversion rate (SCR) as the percentage of subjects with a PRNT50 titer of ≥1:10.

8.1.3.3.2 Safety Endpoints

Clinical Reviewer's Note: The following is a comprehensive description of the safety assessment program that was implemented for this study (IC51-301). Since the same approach for assessing and documenting safety was used in each phase III study, this description will not be repeated, and the reviews of subsequent studies will instead refer to this section for information on safety assessment. The only exception is IC51-303, a long term follow-up study on subjects originally enrolled and treated under study protocols IC51-301 and IC51-302. The protocol for long-term safety follow-up is described where the interim analysis from IC51-303 is summarized in Appendix 1.

8.1.3.3.2.1 Adverse Events

Definition:

An adverse event (AE) was defined as any untoward medical occurrence in a subject administered an investigational product, whether or not related to treatment. AEs and concomitant diseases were coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Abnormalities already existing before the first administration of the investigational product were not considered as AE's, but were documented as medical history. All new abnormalities or any exacerbation in intensity or frequency (worsening) of a pre-existing condition during or after the first vaccination were documented as treatment emergent adverse events (TEAE).

Pregnancies were not considered AE's for these analyses. MeDRA preferred terms "Pregnancy", "Ectopic pregnancy", "Abortion spontaneous", "Abortion" or "Abortion induced", were therefore analyzed separately.

Reporting:

Each subject was instructed to record all symptoms into a subject diary for seven consecutive days after each vaccination. In addition, at each visit, the Investigator queried the subject about adverse events, performed a symptom-directed physical exam, and recorded these data into an electronic case report form (eCRF).

Serious adverse events (SAE):

An SAE was defined as any untoward medical occurrence at any dose that:

- resulted in death
- was life-threatening
- required in-subject hospitalization or prolongation of existing hospitalization
- resulted in persistent or significant disability/incapacity
- was a congenital anomaly/birth defect
- was another medically important condition (e.g., seroconversion indicative of hepatitis B)

Adverse Event Evaluation:

The National Cancer Institute's Common Terminology Criteria for adverse events (NCI-CTCAE v3.0, 2003 at

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf were used as a clinical and laboratory AE grading scale for assessments of toxicity.

Severity:

Mild: awareness of signs or symptoms, but easily tolerated.

Moderate: discomfort, enough to interfere with usual activity.

Severe: incapable of work or usual activity.

Causality:

Probable: a reaction that followed a reasonable temporal sequence from administration of the investigational product; or that followed a known or expected response pattern to the suspected treatment; or that was confirmed by stopping or reducing the dosage of the treatment; and that could not reasonably be explained by known characteristics of the subject's clinical state.

Possible: a reaction that followed a reasonable temporal sequence from administration of the investigational product; that followed a known or expected response pattern to the suspected treatment; but that could readily have been produced by a number of other factors.

Unlikely: reports not following a reasonable temporal sequence from administration of the investigational product. Also, an event which may have been produced by the subject's clinical state or by other environmental factors was considered unlikely related.

Not related (unrelated): events for which sufficient information existed to conclude that the etiology was unrelated to the medicinal product.

Clinical Reviewer's Note: The determination of causality was made by the individual investigator. Where data stratified by causality is presented in this review, the assessment is that of the investigator and not this reviewer unless otherwise specified.

Classification:

The sponsor classified the AEs as either expected or unexpected.

Expected: an AE that was listed in the current Investigator's Brochure.

Unexpected: an AE which was not listed in the current Investigator's Brochure or it differed because of greater severity or greater specificity.

Outcome:

Recovered/resolved

Recovered/resolved with sequelae

Not recovered/not resolved

Fatal

Unknown

8.1.3.3.2.2 Deaths

A subject's death per se was not an event, but an outcome. The event which resulted in subject's death was fully documented and reported without respect to whether it was considered treatment-related or not.

8.1.3.3.2.3 Local Tolerability

Local tolerability was assessed by the subject and the investigator according to a criteria set for documenting severity of local reactions devised by the sponsor; see Table 4. The size of the reaction in terms of induration, swelling, and erythema was also assessed by the grading scale that FDA has published as a guidance to industry (see Table 5; for the complete FDA document, see: <http://www.fda.gov/CbER/gdlns/toxvac.htm>).

Clinical Reviewer's Note: It was not clear why both criteria sets were used to assess local tolerability. Because the grading criteria devised by the sponsor are more conservative and

because the resulting dataset was more complete (it included symptoms as well as the size of reactions), the reviewer focused on the data generated using Table 4.

Table 4. Sponsor's Grading Scale for Local Reactions

Reaction	Severity			
Pain:	none	mild	moderate	severe
Itching:	none	mild	moderate	severe
Tenderness	none	mild	moderate	severe
Hardening:	none	mild (≤ 1 cm)	moderate (>1 to <3 cm)	severe (≥ 3 cm)
Swelling:	none	mild (≤ 1 cm)	moderate (>1 to <3 cm)	severe (≥ 3 cm)
Redness	none	mild (≤ 1 cm)	moderate (>1 to <3 cm)	severe (≥ 3 cm)

Source: Original BLA 125280, 5.3.5.1.3 - Clinical Study Report IC51-301, p.40

Table 5. FDA Grading Scale for Local Reactions

Grading 0	Grading 1 (mild)	Grading 2 (moderate)	Grading 3 (severe)
< 2.5 cm	2.5 cm – 5.0 cm	5.1 cm – 10.0 cm	> 10 cm

Source: Original BLA 125280, 5.3.5.1.3 - Clinical Study Report IC51-301, p.41

The local tolerability assessments were recorded once daily into a subject diary. Assessments occurred at the same time each day, starting with the day of vaccination, for a total of seven consecutive days. Local tolerability was also assessed by the Investigator at the time of each subject visit according to the severity criteria devised by the sponsor (Table 4).

Local tolerability assessments were not included in the reporting of AE's. Therefore, AE's and local tolerability were analyzed separately.

8.1.3.3.2.4 Systemic Tolerability

Systemic tolerability was assessed according to a subset of AE's (e.g., headache, muscle pain, fever, flu-like symptoms, nausea, vomiting, rash, and excessive fatigue) that were recorded by the subject in the subjects diary and recorded by the Investigator based on the history and symptom-directed physical exam.

8.1.3.3.2.5 Laboratory Parameters

The following laboratory parameters were assessed at time points specified in Table 6 under Surveillance and Monitoring. The assays were performed by local laboratories.

- Hematology: Hemoglobin, hematocrit, erythrocyte count, white blood count, platelets
- Chemistry: creatinine, potassium, sodium, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin
- Urine: urine test sticks were used for determining pH, glucose, protein, bilirubin, urobilinogen, red blood cells, white blood cells, nitrite, ketone and specific gravity

8.1.3.4 Surveillance and Monitoring

Table 6 summarizes the surveillance and monitoring for IC51-301.

Table 6. Surveillance and Monitoring For Study IC51-301

	Screening	Baseline/ Vaccination	Vaccination	Vaccination	Follow-up	Early Termination
	visit 0	visit 1	visit 2	visit 3	visit 4	-
Timing	day -14	day 0	day 7	day 28	day 56	-
Time windows	-14 to -1 days	-	+ 2 days	+/- 4 days	+/- 4 days	-
Informed consent	X					
HIV(1), HBV, HCV-test	X					
Inclusion/exclusion criteria	X	X				
Serum pregnancy test (2)	X					
History & demographic data	X					
Concomitant diseases	X					
Vaccination history(3)	X					
Physical examination, vital signs	X					
Symptom-directed physical exam		X	X	X	X	X
Evaluation of body temperature	X	X	X	X	X	X
Randomization		X				
Study treatment		X	X	X		
IC51 vaccination		X	X (Placebo)	X		
JE-VAX [®] vaccination		X	X	X		
PRNT blood (4)	X			X	X	X
Hematology (5)	X			X	X	X
Clinical chemistry (6)	X			X	X	X
Urine pregnancy test (2)		X	X	X	X	X
Urine test	X	X		X	X	X
Concomitant medications	X	X	X	X	X	X
Local tolerability		X	X	X	X	X
Dispense subject diary (7)		X	X	X		
Collect subject diary			X	X	X	X
Adverse events		X	X	X	X	X
Blood volume	18 mL	-	-	15 mL	15 mL	15 mL
Payment	X				X	X

1. Negative human immunodeficiency virus (HIV) tests that were performed up to 30 days before study inclusion are acceptable [blood: 3 mL]

2. In women of childbearing potential

3. Plaque reduction neutralization testing (PRNT) [blood: 9 mL]

4. All tick-borne encephalitis (TBE) vaccinations received within the last 10 years and other vaccinations received over the last three years were recorded.

5. Hemoglobin, hematocrit, erythrocyte count, white blood count, platelets ethylenediaminetetraacetic Acid [blood: 3 mL]

6. Creatinine, sodium, potassium, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin [Serum: 3 mL]

7. The subjects assessed local tolerability by themselves after each vaccination according to a given schedule.

Source: Original BLA 125280, 5.3.5.1.3 - Clinical Study Report IC51-301 p. 36-37

8.1.4 Statistical Considerations

The primary objective in this study was to determine if IC51 was non-inferior to JE-VAX in terms of the immunogenicity outcomes SCR and GMT. CBER agreed to the following statistical criteria for demonstrating non-inferiority. Non-inferiority of IC51 in terms of SCR and GMT was demonstrated if, in the Per Protocol (PP) Population, the lower bound of the 95% CI for the SCR difference between IC51 and JE-VAX was $>-10\%$ and if the lower bound of the 95% CI for the GMT ratio between IC51 and JE-VAX was $>1/1.5$.

If the primary analysis demonstrated non-inferiority, the statistical plan called for a secondary analysis in the Intention to Treat (ITT) Population to determine if IC51 was superior to JE-VAX in terms of SCR and GMT. Superiority was demonstrated if the lower bound of the 95% CI for the

SCR-difference between IC51 and JE-VAX was >0 and if the lower bound of the 95% CI for the GMT ratio between IC51 and JE-VAX was >1.

8.1.5 Results

8.1.5.1 Populations Enrolled/Analyzed

Among the 1271 subjects recruited, 867 from 10 study centers met inclusion criteria (664 from North America and 203 from Europe). The median age was 41.0 years (with N=24 aged >65 years, which is 6.6% of the per protocol population), the median weight was 76.6 kg and the median BMI was 26.3 kg/m². There were more females (60.8%) than males (39.2%) and the most common race was Caucasian (80.8%) followed by Black (13.1%), Other (5.3%), and Asian (0.8%). All subjects were negative for HIV, HBV and HCV, and the majority (77.8%) had negative anti-flavivirus serology at the screening visit. Overall 107 (12.4%) subjects had received TBE vaccination within the last 10 years and 297 (34.4%) had received any vaccination within the last three years.

Of the 867 subjects randomized to treatment, 430 were randomized to IC51 and 437 to JE-VAX. The IC51 and JE-VAX groups were well-balanced with regard to demographic data; no significant differences were observed in baseline demographic characteristics. Table 7 summarizes the analysis populations.

Table 7. Analysis Populations for Study IC51-301

	IC51 n (%)	JE-VAX® n (%)	Overall n (%)
Randomized subjects	430 (100)	437 (100)	867 (100)
ITT Population	430 (100)	437 (100)	867 (100)
PP Population	365 (84.9)	370 (84.7)	735 (84.8)
Safety Population	428 (99.5)	435 (99.5)	863 (99.5)

Source: Original BLA 125280, 5.3.5.1.3 - Clinical Study Report IC51-301 p. 58

8.1.5.2 Immunogenicity Endpoint/Outcomes

8.1.5.2.1 Primary Immunogenicity Analysis

The two components of the primary analysis were SCR and GMT at Visit 4 (28 days after final vaccine dose) in the PP population.

For SCR, the proportion of subjects who had seroconverted was similar for both treatment groups (96.4% vs. 93.8% for IC51 and JE-VAX®, respectively). Since the lower 95% CI limit of the rate difference (-0.5%) was >-10%, non-inferiority was demonstrated. The GMT was nominally higher in the IC51 group (243.6) versus the JE-VAX group (102.0). Since the lower 95% CI limit for the ratio (IC51 to JE-VAX = 1.9666) was >1/1.5, non-inferiority was demonstrated. (See Table 8).

Table 8. Seroconversion Rates and Geometric Mean Titers After IC51 or JE VAX, Per Protocol Population

Seroconversion Rates			
Time Point	IC51 SCR (n/N) [95% CI]	JE-VAX SCR (n/N) [95% CI]	Rate difference [95% CI]
Pre-Vaccination Screen	0	0	
Day 56 (28 days after IC51 dose #2)	96.4% (352/365) [94.0, 97.9]	93.8% (347/370) [90.9, 95.8]	2.6% [-0.5,6.0]†
Geometric Mean Titers			
Time Point	IC51 N=365 n (GMT) [95% CI's]	JE-VAX N=370 n (GMT) [95% CI's]	GMT ratio estimator [95% CI]
Pre-Vaccination Screen	365 (5.0)◇	370 (5.0)◇	
Day 56 (28 days after IC51 dose #2)	361 (243.6) [216.4, 274.1]	364 (102.0) [90.3, 115.2]	2.33 [1.97, 2.75]‡

†Seroconversion Rates (SCRs): Non-inferiority of IC51 compared to JE-VAX for SCR was demonstrated if the lower bound of the 2-sided 95% confidence interval (CI) for the SCR difference (IC51 minus JE-VAX) was > -10% at Day 56.

‡Geometric Mean Titers (GMTs): Non-inferiority of IC51 compared to JE-VAX for GMTs was demonstrated if the lower bound of the 2-sided 95% CI for the GMT ratio (IC51 /JE-VAX) was >1/1.5 (0.67) at Day 56.

◇Pre-Vaccination titers were negative by definition in the PP population and have been imputed to 5.

Clinical Reviewer's Note: After excluding subjects with protocol deviations, the CBER statistician identified a PP population that included more subjects than the PP population from the sponsor (N = 760 versus 735, respectively). Analysis of the primary immunogenicity endpoints, SCR and GMT, showed non-inferiority of IC51 compared to JE-VAX regardless of which PP population was used. A similar result was also obtained by the CBER statistician in the analysis of the ITT population.

8.1.5.2.2 Secondary Immunogenicity Analysis

All the secondary immunogenicity analyses were based on the ITT population.

Seroconversion Rates

At Visit 4, SCR was slightly higher in the IC51 group compared to JE-VAX® (92.3% vs. 89.9%). With a lower 95% CI limit of the risk difference estimator of -1.62%, this met criteria for non-inferiority, but not for superiority, of IC51 versus JE-VAX.

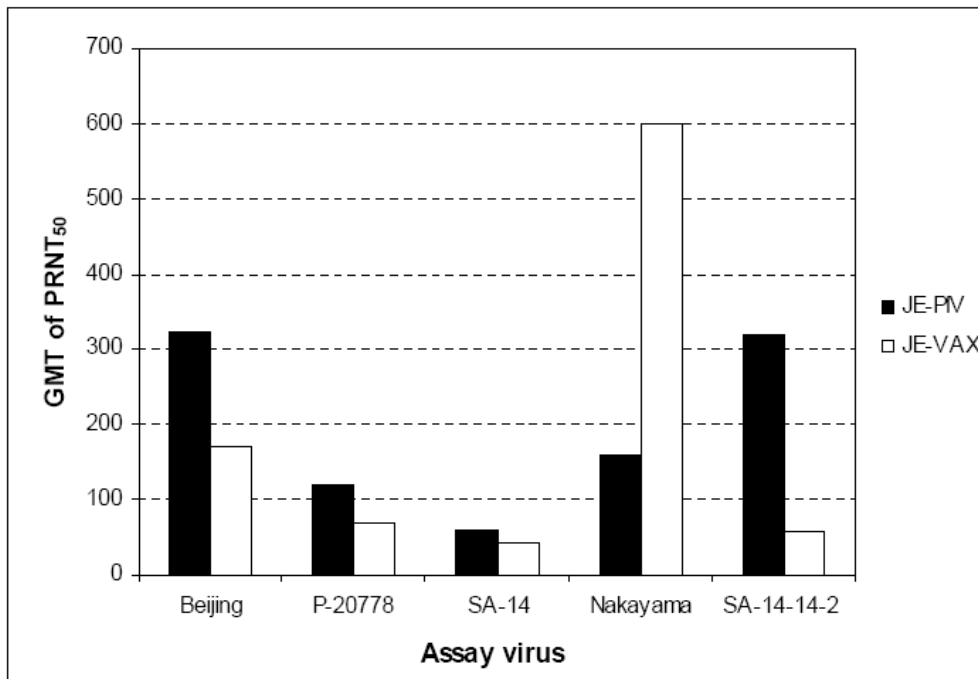
Geometric Mean Titer

At Visit 4, the GMT was higher in the IC51 group compared to JE-VAX® (188.1 vs. 89.0). The lower limit of the 95% CI of the ratio estimator was 1.7495, which met criteria for non-inferiority. Using the sponsor-defined superiority criteria, IC51 was superior to JE-VAX with respect to GMT comparisons in the ITT population.

Clinical Reviewer's Note: The reviewer noted that the input virus used for the PRNT assays was the SA 14-14-2 strain. This strain is homologous to the one used to produce IC51 and heterologous to the one used to produce JE-VAX (Nakayama strain). This likely biases results toward a higher apparent titer for the serum from an IC51 vaccinated subject versus the serum

from a JE-VAX vaccinated subject. The bias would be reversed if the Nakayama strain is used as the input virus. Figure 1 demonstrates the differences in GMT's obtained depending on the input virus (note IC51 was referred to as JE-PIV in early development). Because the SCR's *were not affected* by input virus in similar analyses and because Nakayama input virus introduced a stronger bias toward JE-VAX than SA 14-14-2 toward IC51, CBER accepted the PRNT assay as validated in the development program. However, claims of superiority, particularly with regard to duration of protection, should be viewed with utmost caution. Most subjects who seroconvert initially (at Day 56), have relatively high PRNT titers. Therefore, apparent differences between titers would not be expected to affect SCR, which uses a relatively low titer threshold ($\geq 1:10$). However, titers fall substantially with time. As the mean titer of a group approaches 1:10, more subjects would be expected to fall above or below the 1:10 threshold, *depending on whether homologous or heterologous input virus is used in the assay*. Similarly, the finding stated above – that IC51 met criteria for superiority over JE-VAX in terms of GMT at Day 56 in the ITT population – is not considered by this reviewer to be clinically meaningful.

Figure 1. GMT of PRNT⁵⁰ Titers of JE-PIV or JE-VAX Vaccinated Subjects Against a Panel of JE Viruses†



Source: Original BLA 125280, 5.3.1.4 – Neutralization of JE: Interstrain Comparison Report p.14

†The samples used to generate this data are a randomly picked, blinded set of sera (n = 40) obtained from subjects of the non-inferiority trial IC51 - 301 vaccinated with JE-PIV or JE - VAX.

Stratification by Continent

Analysis of SCR's and GMT's within the European Population and within the North American population revealed no significant differences from the SCR's and GMT's from the entire ITT Population.

Clinical Reviewer's Note: When stratified by Continent, SCR's were slightly lower in North America compared to Europe (SCR = 90.9 vs 97 in North America and Europe, respectively). This difference is possibly due to the higher rates of previous Tick Borne Encephalitis TBE vaccination in Europeans, which may have lead to some degree of anamnestic response to the similar antigens in the JE vaccines. Non-inferiority analyses were not performed separately by Continent, but IC51 achieved numerically higher SCR's than JE-VAX in both populations.

Stratification by Age

The effect of age on the immune response to IC51 and JE VAX® was assessed as a secondary endpoint, comparing subjects over >65 years of age (N = 24 for IC51; N = 19 for JE-VAX) with those ≤65 years of age (N = 341 for IC51; N = 351 for JE-VAX)). In subjects >65 years of age, IC51 was similar to JE-VAX at Day 56 in terms of SCR's (95.8% versus 89.5%, respectively) and GMT's (255.2 versus 96.8, respectively). In addition, within the IC51 group, there were no meaningful differences observed between subjects ≤65 years of age versus those >65 years of age in terms of Day 56 SCR's (96.5% versus 95.8%, respectively) or GMT's (242.8 versus 255.2, respectively).

Clinical Reviewer's Note: Several of the secondary analyses in the ITT Population demonstrated numerically higher SCR's and/or GMT's in the JE-VAX group vs the IC51 group at Visit 3, at which time subjects had received two injections (two injections of vaccine in the JE-VAX group vs one injection of vaccine and one injection of placebo in the IC51 group). For example at Visit 3, SCR was 53.7% and 82.6% for IC51 and JE-VAX®, respectively. The lower 95% CI limit of the risk difference estimator was -35.58%. Therefore, non-inferiority was not demonstrated at Visit 3.) The reviewer considered the Visit 3 data to be of marginal significance compared to the Visit 4 data for comparing overall immunogenicity. However, for people who intend to travel to endemic areas before completing the entire IC51 vaccination regimen, this data could be very important. In the period of approximately 2-5 weeks after beginning the vaccination regimen (for IC51 – intramuscular injection on Days 0 and 28; for JE-VAX, subcutaneous injection on Days 0, 7, 28), a patient vaccinated with IC51 can expect to have a significantly lower chance of achieving seroconversion than a patient vaccinated with the currently licensed vaccine, JE-VAX.

8.1.5.3 Safety Outcomes

All subjects who entered the study and received at least one vaccination (including placebo) were included in the Safety Population analysis. Of the 867 patients randomized, two in the IC51 group and two in the JE-VAX group became ineligible before the first vaccination (three failed exclusion criteria at screening or visit 1 and one withdrew consent), leaving 863 patients in the Safety Population (428 in the IC51 group and 435 in the JE-VAX group). Comparable numbers of subjects in each group received the first, second, and third injections, respectively. Overall, 93.2% received all three injections per protocol. Table 9 documents the percentages in each group.

Table 9. Safety Population: Percentage of subjects that received 1st, 2nd, and 3rd injections

	IC51 n=428 n (%)	JE-VAX n=435 n (%)	Overall n=863 n (%)
Visit 1, injection received	428 (100)	435 (100)	863 (100)
Visit 2, injection received	409 (95.6)	414 (95.2)	823 (95.4)
Visit 3, injection received	401 (93.7)	403 (92.6)	804 (93.2)

IC51: Visit 1 and Visit 3 one injection of 6 mcg in 0.5 mL, Visit 2 one injection of placebo

JE-VAX®: Visit 1, Visit 2 and Visit 3, one injection 1.0 mL

Adapted from original BLA 125280, 5.3.5.1.3 - Clinical Study Report IC51-301 p. 67

8.1.5.3.1 Adverse Events

Table 10 summarizes the data related to treatment-emergent adverse events (TEAE).

Table 10. Overview of Treatment-Emergent Adverse Events: Safety Population

Category	IC51 N=428		JE-VAX [®] N=435		Overall N=863	
	n	(%)	n	(%)	n	(%)
With at least one TEAE	261	(61.0)	264	(60.7)	525	(60.8)
With at least one severe TEAE	14	(3.3)	15	(3.4)	29	(3.4)
With at least one serious TEAE	1	(0.2)	0	(0.0)	1	(0.1)
With at least one possibly/probably related TEAE	159	(37.1)	149	(34.3)	308	(35.7)
With at least one TEAE leading to withdrawal	7	(1.6)	8	(1.8)	15	(1.7)
Who died	0	(0.0)	0	(0.0)	0	(0.0)

Source: Original BLA 125280, 5.3.5.1.3 - Clinical Study Report IC51-301 p.68

In the Safety Population overall, 35.7% of TEAE's were assessed by the investigator as possibly or probably related to vaccination, and there were similar numbers in each group – 159 (37.1%) in the IC51 group versus 149 (34.3%) in the JE-VAX group. When these vaccine-related TEAE's were assessed by system organ class, the most commonly affected was the nervous system – 76 (17.8%) in IC51 versus 80 (18.4%) in JE-VAX, with headache accounting for the vast majority of the adverse events in this category. The numbers of subjects experiencing vaccine-related TEAE's were similar for each group across all system organ classes.

Fifteen subjects overall experienced TEAEs which led to the withdrawal from the study; seven (1.6%) in the IC51 group and eight (1.8%) in the JE-VAX[®] group. In the IC51 group, all events leading to treatment withdrawal were either mild or moderate in intensity. Four events leading to treatment withdrawal was assessed by the investigator to have a possible relationship to study treatment; influenza-like illness (two events), hypersensitivity reaction, and asthma. The remaining events in this treatment group were considered by the investigator as unlikely related or unrelated. In the JE-VAX[®] group, one TEAE leading to withdrawal (toothache) was considered severe in intensity. All other events were mild or moderate. Four events leading to treatment withdrawal had a possible relationship to study treatment; headache, influenza-like illness, injection site swelling, and sunburn. The remaining events in this treatment group were unlikely related or unrelated.

Clinical Reviewer's Note: As noted, one of the secondary analyses stratified AE's by investigator blinded assessment of causality. While these analyses were considered, the reviewer did not seek to make an independent determination of causality.

The severity of TEAE's was similar in each group. The majority were mild or moderate; severe TEAE's occurred in 14(3.3%) versus 15(3.4%) in the IC51 and JE-VAX groups, respectively. The severe TEAE's did not cluster in a particular system organ class.

Serious Adverse Events

One serious adverse event occurred in the study. This was a myocardial infarction (MI), which occurred about 3 weeks after the second vaccination with IC51 in a subject with a history of MI two years prior to entering the study. This event was judged by the investigator as unlikely related to treatment.

Deaths

There were no deaths in either group.

8.1.5.3.2 Evaluation of Laboratory Parameters

For the majority of subjects in either treatment group, hematology, clinical chemistry, and urinalysis values collected at 7 and 28 days after dose #1 and 28 days after dose #2 of IC51 were in the normal range. An assessment of the abnormal values revealed that they did not comprise a pattern of clinical significance and that they were distributed evenly across the two groups. An analysis of hematology and clinical chemistry revealed no significant changes from screening to Visit 3 or Visit 4.

8.1.5.3.3 Local Tolerability

The majority of adverse injection site reactions were reported as mild in both the IC51 and the JE-VAX group. Table 11 displays the percentage of subjects who experienced a moderate or severe injection site reaction (either reported by the subject or noted by the investigator). In general, the local tolerability profile of IC51 appeared to be more favorable compared to JE-VAX®, especially for redness, hardening, itching, and swelling.

Table 11. Moderate or Severe Injection Site Reactions During Vaccination Period*

	IC51 N=428	JE-VAX® N=435
Adverse Reaction	N, %	N, %
Any Symptom	14.3%	39.5%
Pain	6.3%	10.8%
Tenderness	7.0%	10.3%
Redness	3.0%	27.6%
Hardening	3.0%	16.1%
Swelling	2.1%	17.0%
Itching	0.2%	6.4%

*Vaccination period was the 56 days after the first vaccination.

8.1.5.3.4 Systemic Tolerability

Systemic symptoms were most commonly reported one day after vaccination, decreasing over time for both treatment groups. Headache and muscle pain were the most commonly reported symptoms. Headache was reported by 6.9% versus 5.4% of subjects and muscle pain by 8.8% versus 2.9% of subjects in the IC51 and JE-VAX groups, respectively, one day after the first vaccination. The profile was similar between the two groups with the exception of muscle pain, which was higher in the IC51 treatment group at vaccination 1 on Days 0 and 1 (7.9% and 8.4% for IC51 compared to 3.7% and 2.8% in JE-VAX®) and vaccination 2 (4.2% and 4.4% compared to 1.6% and 2.1%, on Days 0 and 1).

Clinical Reviewer's Note: In the subject diary covering systemic tolerability, muscle pain was meant to capture generalized myalgia. However, it was probably confused with injection site pain. Thus, the more frequent reporting of muscle pain in the IC51 group is not unexpected given that IC51 is administered intramuscularly, while JE-VAX is administered subcutaneously.

8.1.6 Reviewer's Comments & Conclusions

CBER accepts a PRNT50 of >1:10 as being a reasonable surrogate of protection against JE virus infection. The design and execution of the trial, as well as the statistical assessment of the results, were sufficient to address the question of non-inferiority of IC51 versus the comparator, JE-VAX, in terms of the acceptable surrogate of protection. In the Per Protocol population, non-inferiority criteria were met for both SCR (96.4% and 93.8% for IC51 and JE-VAX®, respectively)

and for GMT (243.6 and 102.0 for IC51 and JE-VAX®, respectively). Therefore, non-inferiority was demonstrated for the primary immunogenicity analyses.

There was no evidence in this study that the immunogenicity of IC51 is compromised significantly in a geriatric population. However, these data should be interpreted with caution given the low number of subjects evaluated.

The data from this trial did not raise concerns about the safety profile of IC51. The rates of TEAE's were similar comparing the IC51 to the JE-VAX groups. Most TEAE's were mild or moderate in intensity, and they mainly consisted of headache, myalgia and influenza-like symptoms, a constellation of symptoms consistent with previous studies. The one serious adverse event that occurred in the IC51 group was a myocardial infarction (MI) three weeks after the second dose of IC51 in a subject with a history of MI, and this was unlikely related to treatment.

Although the study was not designed to generate definitive data about local tolerability, there was a trend toward a more favorable profile in the IC51 group. Reports from subject diaries documented lower rates of itching, swelling, hardening, and redness in the IC51 group versus the JE-VAX group.

Overall, this trial demonstrated that a two dose regimen (days 0 and 28) of IC51 is non-inferior to the standard three dose regimen (days 0, 7, and 28) of JE-VAX. Compared to JE-VAX, IC51 had an acceptable safety profile and may have a more favorable local tolerability profile.

8.2 Study IC51-302 (NCT00605085)

Title: SAFETY AND TOLERABILITY OF THE JAPANESE ENCEPHALITIS VACCINE IC51. DOUBLE BLIND, RANDOMIZED, PLACEBO CONTROLLED PHASE 3 STUDY

8.2.1 Objective/Rationale

Primary objective:

To investigate the safety and tolerability of IC51 during a vaccination period of 28 days until 4 weeks after the last vaccination compared with an inactive control.

Secondary objectives:

- To analyze the rates of serious adverse events (SAE's) and medically attended adverse events (AEs) in individuals before and after immunization with IC51.
- To assess possible changes in laboratory parameters.

8.2.2 Design Overview

This was a multicenter, double-blind, randomized, placebo-controlled phase 3 study.

8.2.3 Protocol (Objective Information)

After a screening period of up to 4 weeks, during which inclusion and exclusion criteria were checked, subjects were randomized in a 3:1 ratio to receive either: a total of two injections of IC51 (6 mcg, 0.5mL) intramuscularly (i.m.) on Day 0 and Day 28 (Vaccine Group) or a total of two injections of placebo (phosphate-buffered saline [PBS] solution containing 0.1% aluminum hydroxide as an adjuvant, 0.5 mL) intramuscularly on Day 0 and Day 28 (Control Group). A final evaluation took place after four weeks after the last vaccination on day 56 or in the event of early termination.

Clinical Reviewer's Note: The placebo contained the same dose of aluminum hydroxide adjuvant as the study vaccine (IC51). This approach has advantages, primarily that the effect of the inactivated JE virions themselves can be accurately assessed. On the other hand, the overall rates of reactogenicity (both local and systemic) in the study vaccine group would be expected to be obscured to some degree when compared to a group receiving placebo containing adjuvant. The reviewer was cognizant of these effects in the review of the safety data.

8.2.3.1 Population

Healthy adult male or female subjects were recruited at 39 sites in North America, Europe, Israel, Australia, and New Zealand.

8.2.3.1.1 Inclusion/Exclusion Criteria

Inclusion Criteria

- 1) At least 18 years of age.
- 2) In female subjects either childbearing potential terminated by surgery, or were one year post-menopausal, or had a negative serum pregnancy test during screening and the willingness not to become pregnant during the study period and 30 days after the last vaccination by practicing reliable methods of contraception.
- 3) Written informed consent obtained prior to study entry (subjects should have given their consent themselves). Consent by legal representatives was allowed.

Exclusion Criteria

Subjects who met any of the following exclusion criteria were not included in the study:

- 1) Use of any other investigational or non-registered drug or vaccine in addition to the study vaccine during the study period or within 30 days preceding the first dose of study vaccine.
- 2) History of any previous JE vaccination (e.g. JE-VAX®).
- 3) Administration of yellow fever vaccine 30 days before or up to 30 days after study treatment.
- 4) Immunodeficiency including post-organ-transplantation or immunosuppressive therapy.
- 5) A family history of congenital or hereditary immunodeficiency.
- 6) History of autoimmune disease.
- 7) Administration of chronic (defined as more than 14 days) immunosuppressants or other immune-modifying drugs within 6 months of vaccination. (For corticosteroids, this meant prednisone, or equivalent, ≥ 0.05 mg/kg/day. Topical and inhaled steroids, were allowed).
- 8) Any acute infections within two weeks prior to enrollment.
- 9) History of severe hypersensitivity reactions (in particular to a component of the IC51 vaccine, e.g. protamine sulphate), anaphylaxis or severe cases of atopy requiring emergency treatment or hospital admission.
- 10) Known or suspected human immunodeficiency virus (HIV) Infection.
- 11) Drug addiction within 6 months prior to enrollment (including alcohol dependence, i.e. more than approx. 60 g alcohol per day, or conditions which might interfere with the study conduct).
- 12) Inability or unwillingness to avoid more than the usual alcohol intake during the 48 hours after vaccination.
- 13) Subjects with any condition which, in the opinion of the investigator, made the subject unsuitable for inclusion.
- 14) Pregnancy (positive pregnancy test during screening or at baseline), lactation or unreliable contraception in female subjects.
- 15) Inability or unwillingness to provide informed consent and to abide by the requirements of the study.

8.2.3.1.2 Analysis Populations

Safety Population:

All subjects who entered the study and received at least one vaccination were included in the safety population. All analyses based on the safety population were carried out using the actual treatment received.

8.2.3.2 Products mandated by the Protocol

Placebo: PBS solution containing 0.1% aluminum hydroxide as an adjuvant, 0.5 mL administered by i.m. injection. Batch number ICB05/500.

IC51: 6 mcg of inactivated JEV proteins and 0.1% aluminum hydroxide in 0.5 mL of solution injected i.m. Batch numbers ICB05/501 and ICB05/502.

8.2.3.3 Endpoints

8.2.3.3.1 Immunogenicity Endpoints

PRNT titers were performed on a subset of subjects to be followed in the long term follow-up study, IC51-303. No immunogenicity data were reported for this study.

8.2.3.3.2 Safety Endpoints

The methods for assessing, defining, and categorizing safety data, including adverse events, laboratory parameters, physical exams, and local and systemic tolerability, were similar to those used for Study IC51-301. (See Section 8.1.3.3.2).

In addition, the following risk periods were considered for analysis of TEAE's:

- Total study period (first vaccination until last contact); all TEAE's were considered for this period.
- Total vaccination period, (first vaccination until Day 56); all TEAE's with an onset date no later than 56 days after the first vaccination were considered for this period.
- First vaccination period, (i.e. first vaccination until Day 28 or second vaccination); all TEAE's with an onset (date and time) prior to the second vaccination (if the second vaccination is no later than on Day 28) or with an onset date no later than 28 days after the first vaccination (if the second vaccination is later Day 28) were considered for this period.
- Second vaccination period, (i.e. second vaccination until Day 56); all TEAE's with an onset (date and time) equal to or later than the second vaccination but no later than 28 days after the second vaccination were considered for this period.

8.2.3.4 Surveillance and Monitoring

Table 12 summarizes the surveillance and monitoring for IC51-302.

Table 12. Surveillance and Monitoring for Study IC51-302

	Visit 0	Visit 1	Visit 2	Visit 3	Early Termination
Timing	May be done up to 28 days prior to Visit 1	Day 0	Day 28	Day 56	-
Time windows			+/- 4 days	+/- 4 days	-
Informed consent	X				
Inclusion/exclusion criteria	X	X			
Serum pregnancy test (1)	X				
History & demographic data	X				
Concomitant diseases	X				
Physical examination, vital signs	X				
Symptom-directed physical exam		X	X	X	X
Evaluation of body temperature	X	X	X	X	X
Randomization		X			
IC51 vaccination		X	X		
Placebo injection		X	X		
PRNT blood		X (2)	X (2)	X (2)	X (2)
Hematology (3)	X		X	X	X
Clinical chemistry (4)	X		X	X	X
Urine pregnancy test (1)		X	X	X	X
Urine test	X		X	X	X
Concomitant medications	X	X	X	X	X
Local tolerability (5)		X	X	X	X
Dispense subject diary (5)		X	X		
Collect subject diary			X	X	X
Adverse events		X	X	X	X
Blood volume	6 mL	9 mL (6)	6 mL / 15 mL (6)	6 mL / 15 mL (6)	6 mL / 15 mL (6)
Payment	X			X	X

1. In women of childbearing potential

2. Only applicable for subjects with concomitant vaccination [plaque reduction neutralization testing (PRNT) blood: 9 mL]. This analysis was postponed and will be performed, if deemed meaningful, with regard to the results of the concomitant vaccination study IC51-308. Further PRNT samples were drawn and analyzed only for those subjects who participated in the immunogenicity part of the follow-up trial IC51-303, which had a separate protocol with informed consent

3. Hemoglobin, hematocrit, erythrocyte count, white blood count, platelets [Ethylenediaminetetraacetic Acid (EDTA) blood: 3 mL]

4. Creatinine, sodium, potassium, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin [Serum: 3 mL]

5. The subjects assessed local tolerability by themselves after each vaccination according to a given schedule.

6. Only in subjects with concomitant vaccination (please refer to footnote 2) and in subjects who participated in the immunogenicity part of the follow-up study IC51-303

Source: Original BLA 125280, 5.3.5.1.3 - Clinical Study Report IC51-302 p. 37

8.2.4 Statistical Considerations

The study was designed to detect one or more AE's with an anticipated incidence rate of 0.1% and a power of 80%.

8.2.5 Results (Objective Information)

8.2.5.1 Populations Enrolled/Analyzed

A total of 2990 subjects were enrolled into the study and 2683 subjects from 39 study centers met criteria for inclusion and were randomized to treatment: 395 from Australia (including New Zealand), 1665 from Europe (including Israel) and 615 from North America. The median age was

28.0 years, the median weight was 72.0 kg and the median BMI was 23.80 kg/m². There were slightly more females (55.3%) than males (44.7%) and the most common race was Caucasian (91.7%).

Eight subjects from center 2015 were excluded after randomization in accordance with a letter from the Ethics Committee of Berlin which was not made available. The final group of 2675 subjects was randomized in a 3:1 ratio to receive IC51 or placebo, which resulted in 2012 in the IC51 group and 663 in the placebo group. The IC51 and placebo groups were well-balanced with regard to demographic data; no significant differences were observed in baseline demographic characteristics.

The use of concomitant travel vaccinations (approved in each respective country) was permitted 30 days before and during the entire study. However, it was limited to 15% of the total enrolment of subjects assigned to IC51.

8.2.5.2 Effectiveness (Immunogenicity) Outcomes

PRNT titers were performed on a subset of subjects to be followed in the long term follow-up study, IC51-303. No immunogenicity data were reported for this study.

8.2.5.3 Safety Outcomes

Of the 2675 patients randomized, eighteen in the IC51 group and seven in the JE-VAX group became ineligible before the first vaccination, leaving 2650 patients in the Safety Population (1993 in the IC51 group and 657 in the JE-VAX group). Comparable percentages of subjects in each group received the first and second injections. Overall, 98.6% received both injections per protocol. Table 13 displays the percentages in each group.

Table 13. Safety Population: Percentage of subjects that received 1st and 2nd injections

	IC51 n=1993 n (%)	placebo n=657 n (%)	Overall n=2650 n (%)
Visit 1, injection received	1993 (100)	657 (100)	2650 (100)
Visit 2, injection received	1968 (98.7)	645 (98.2)	2613 (98.6)

IC51: Visit 1 and Visit 2 one injection with 6 mcg in 0.5 mL

Adapted from original BLA 125280, 5.3.5.1.3 - Clinical Study Report IC51-302 p. 61

8.2.5.3.1 Adverse Events

In the Safety population overall, 58.9% of subjects in the IC51 group and 56.6% of subjects in the placebo group experienced at least one TEAE during the total study period. Table 14 displays an overview of the analysis of TEAE's.

Table 14. Treatment Emergent Adverse Events (Total Study Period): Safety Population

Category	IC51 N=1993		Placebo N=657		p-value	Overall N=2650	
	n	(%)	n	(%)		n	(%)
Subjects:							
With at least one TEAE	1173	(58.9)	372	(56.6)	0.3159	1545	(58.3)
With at least one severe TEAE	102	(5.1)	34	(5.2)	0.9192	136	(5.1)
With at least one serious TEAE	10	(0.5)	6	(0.9)	0.2487	16	(0.6)
With at least one possibly/probably related TEAE	774	(38.8)	254	(38.7)	0.9632	1028	(38.8)
With at least one medically attended TEAE	254	(12.7)	80	(12.2)	0.7350	334	(12.6)
With at least one TEAE leading to withdrawal	12	(0.6)	5	(0.8)	0.5857	17	(0.6)
Who died	0	(0.0)	0	(0.0)	-	0	(0.0)

N=number of subjects in group; n=number of subject with data; %=percentage of subjects based on number of patients in the group; TEAE=treatment emergent adverse event p-value of Fisher's exact test for comparing treatment groups

Source: Original BLA 125280, 5.3.5.1.3 - Clinical Study Report IC51-302 p.62

In the Safety Population over the total study period, the proportion of subjects that experienced each category of TEAE, including severe, serious, and those leading to withdrawal, were similar in the IC51 group compared to the placebo group.

In the total study period, the most common system organ classes (SOC) for TEAE's were nervous system disorders (29.4% and 27.5% for IC51 and placebo, respectively), general disorders and administration site conditions (22.3% for IC51 and 23.0% for placebo), musculoskeletal and connective tissue disorders (18.0% for IC51 and 18.3% for placebo), infections and infestations (13.8% for IC51 and 13.2% for placebo) and gastrointestinal disorders (10.0% for IC51 and 9.4% for placebo). The most common TEAE's reported in the total study period were headache (28.0% and 26.3% for IC51 and placebo, respectively), myalgia (15.6% for IC51 15.5% for placebo), influenza like illness (12.4% for IC51 11.9% for placebo) and fatigue (11.4% for IC51 11.7% for placebo). When TEAE's were analyzed by risk period (first vaccination period versus second), there remained no meaningful differences between the two groups.

To address causality, the TEAE's assessed by the investigator as possibly or probably related to study treatment were analyzed separately. In the Safety population, 38.8% subjects in the IC51 group and 38.7% subjects in the placebo group experienced related TEAE's. The SOC profile was similar to the one for all TEAE's, and there remained no meaningful difference between the two groups.

Clinical Reviewer's Note: As noted, one of the secondary analyses stratified AE's by investigator blinded assessment of causality. While these analyses were considered, the reviewer did not seek make an independent determination of causality.

TEAE's that required medical attention occurred in 12.7% of subjects in the IC51 group and 12.2% of subjects in the placebo group. The most common SOC's for medically attended TEAE's were infections and infestations (4.9% and 4.1% for IC51 and placebo, respectively). The most common infections were nasopharyngitis, urinary tract infection, and sinusitis; these were

generally balanced across the two groups. All other SOC groupings of medically attended TEAE's were experienced in <2% of subjects overall.

A comparison of the temporal relationship between treatment and occurrence of TEAE's revealed virtually no difference between the IC51 and placebo groups. In both groups, the probability of remaining TEAE-free went from about 90% at 1 hour post vaccination to 75% at 1 day to 50% at 1 month.

In the total vaccination period, no serious AE's occurred within 10 days post vaccination. Serious AE's occurred at a similar rate in the IC51 group versus the placebo group (10 subjects (0.5%) versus 6 subjects (0.9%), respectively). The ten subjects in the IC51 group with severe TEAE's experienced a variety of medical problems and injuries, none of which was assessed as possibly or probably related to the study treatment.

The majority of TEAE's reported were mild or moderate in intensity. The proportion of subjects experiencing at least one severe TEAE was similar for the IC51 group versus the placebo group (5.1% versus 5.2%, respectively). TEAE's did not tend to cluster in any particular SOC when stratified by severity.

Serious Adverse Events:

Sixteen serious adverse events were reported during the study period. Ten subjects receiving IC51 (0.5%) and 6 subjects receiving placebo (0.9%) experienced an SAE, none of which were assessed as related to study treatments. The serious adverse reactions occurring in the IC51 group were as follows: dermatomyositis, two events of appendicitis, rectal hemorrhage, limb abscess (contralateral to the injected arm), chest pain, ovarian torsion, ruptured corpus luteal cyst, and three orthopedic injuries.

Clinical Reviewer's Note: Among the SAE's, the event "dermatomyositis" was of interest because the pathogenesis is autoimmune-mediated. The relevant aspects of the case history are as follows:

Subject 2103-009, Suspected Dermatomyositis:

Subject 2103-009, a 34-year-old Caucasian female with a history of tuberculosis in 1993 (resolved) and hypertension since 2000 (ongoing), was randomized to receive IC51 and was vaccinated on 24 November 2005 and on 22 December 2005. Vaccination history included hepatitis B, poliomyelitis, tetanus and diphtheria, all in 2004. On 02 January 06, the subject presented to an outpatient clinic specializing in rheumatic diseases with a chief complaint of shoulder pain and ischiatic pain. She also reported a 9 month history of shoulder pain, with increased intensity and frequency in the past 3 weeks. Approximately 3 months prior, an orthopedist had diagnosed synovitis and treated the subject with injections into the shoulder. The subject was hospitalized on 03 January 2006 for further diagnostic procedures. Neurological exam was normal. CT of the throat, thorax and abdomen and MRI of the shoulders revealed no abnormal findings. Lab results were remarkable only for an elevated creatinine kinase (CK 346 U/L and CK-MB 3.8 ug/L). Pain was treated with narcotics followed by indomethacin. The subject was discharged from hospital on 05 January 2006 with a diagnosis of "suspected dermatomyositis", and the investigator assessed the outcome as "recovered with sequelae". Due to the elevated serum CK, the subject had a planned second hospital admission on 18th-19th of January 2006 to perform a muscle biopsy of the right deltoid muscle. The biopsy showed mild signs of myopathic abnormalities, including inflammation with primary vasculitis, consistent with dermatomyositis. Indirect immunofluorescence test (MHC I, MHC II; CD4, CD8, CD 68, CD 31) confirmed the diagnosis of dermatomyositis. The event was considered unlikely to be related to study medication by the investigator.

Given that the subject's primary symptoms predated vaccination, the reviewer agrees with the investigator that the event was unlikely related to vaccination. However, the event will be considered in the design of post-marketing studies and pharmacovigilance plans.

Adverse Events Leading to Withdrawal:

A similar proportion of subjects experienced TEAE's leading to treatment withdrawal: 0.6% in the IC51 group versus 0.8% in the placebo group. In the IC51 group, eight TEAE's leading to treatment withdrawal had a possible or probable relationship to study treatment; headache (two events), influenza like illness, allergic dermatitis, injection site pain, nausea, fatigue and rash. The remaining events in the group were considered unlikely to be related or unrelated to study medication.

Clinical Reviewer's Note: Of the subjects who experienced TEAE's leading to withdrawal, two in the IC51 group ("allergic dermatitis" and "rash") were of particular interest because of the possibility of hypersensitivity reactions. The relevant aspects of the case histories are as follows:

Subject 2106-104 - Allergic dermatitis

Subject 2106-104, a 27 year-old Caucasian female with no relevant past medical history, received the first vaccination of IC51 on 31 Oct 2005. Concomitant medications included yasmin. She had a history of tetanus vaccination in 2005. On 01 Nov 2005, she experienced allergic dermatitis (verbatim term: allergic exanthema [breast and neck]). The event was non-serious and moderate in severity. She was treated with dermatop and lorano, and the study drug was stopped. The event resolved 06 Nov 2005. On 29 Nov 2005, the subject terminated the study due to the AE of allergic dermatitis.

Subject 2651-007 - Rash

Subject 2651-007, a 24 year-old Caucasian male with medical history significant for eczema and seasonal allergy, received the first vaccination of IC51 on 21 Nov 2005. Concomitant medications included phenergan, flucloxacilline, prednisone and nerisona. On 25 Nov 2005, he experienced rash (verbatim term: rash). The event was non-serious and the severity was classified as severe. He was treated with flucloxacilline, prednisone and nerisona, and the study drug was stopped. On 19 Dec 2005, he terminated the study due to the AE of rash. The event and the concomitant medications were still ongoing at the end of the study.

Both events may have been related to vaccination with IC51 (although the possibility of a causal link is much stronger for the first case). In addition, no subjects in the placebo group who experienced a TEAE leading to withdrawal reported a rash or other hypersensitivity reaction. However, the overall rate of rash in the two groups was similar (1.3% for IC51 versus 1.5% for placebo), and in the subject diaries of systemic tolerability, the rates of reported rash 1 day after vaccination were similar for both groups (1 day post vaccination 1: 0.3% in IC51 versus 0.2% in placebo; 1 day post vaccination 2: 0.2% in IC51 and 0.3% in placebo). (See Table 15 below). Therefore, the significance of these two events cannot be definitively determined. Post-marketing studies are designed to identify a safety signal with regard to hypersensitivity-associated symptoms, particularly rash.

Deaths:

No deaths were reported during this study.

8.2.5.3.2 Evaluation of Laboratory Parameters

For the majority of subjects in both the IC51 group and the placebo group, hematology, clinical chemistry, and urinalysis values were either in the normal range or, if out of the normal range, were not clinically relevant. An assessment of the abnormal values that were considered clinically relevant revealed that they did not comprise a pattern of clinical significance and that they were distributed across the two groups evenly.

8.2.5.3.3 Physical Examination Findings

Most of the subjects had a normal physical exam at all study visits. There were no notable differences between the IC51 group and the placebo group.

8.2.5.3.4 Local Tolerability

The injection site was assessed by the subject on each of the first 7 days after each injection according to the scale in Table 4 (above), and this was recorded in the subject diary. Table 15 summarizes symptoms reported by this scale one day after vaccination.

Table 15. Injection Site Reactions on Day 1 After Vaccination – Safety Population

Symptom reported		IC51 N=1993		Placebo N=657		Overall N=2650	
		n	(%)	n	(%)	n	(%)
Pain	Vaccination 1	369	(18.5)	102	(15.5)	471	(17.8)
	Vaccination 2	210	(10.5)	62	(9.4)	272	(10.3)
Itching	Vaccination 1	15	(0.8)	11	(1.7)	26	(1.0)
	Vaccination 2	15	(0.8)	8	(1.2)	23	(0.9)
Tenderness	Vaccination 1	414	(20.8)	114	(17.4)	528	(19.9)
	Vaccination 2	295	(14.8)	79	(12.0)	374	(14.1)
Hardening	Vaccination 1	55	(2.8)	24	(3.7)	79	(3.0)
	Vaccination 2	49	(2.5)	12	(1.8)	61	(2.3)
Swelling	Vaccination 1	24	(1.2)	14	(2.1)	38	(1.4)
	Vaccination 2	28	(1.4)	3	(0.5)	31	(1.2)
Redness	Vaccination 1	65	(3.3)	23	(3.5)	88	(3.3)
	Vaccination 2	58	(2.9)	10	(1.5)	68	(2.6)

N=number of subjects in group; n=number of subject with data; %=percentage of subjects based on number of patients in the group

Source: Original BLA 125280, 5.3.5.1.3 - Clinical Study Report IC51-302 p. 96

An analysis of the subset of reactions reported as “severe” revealed no difference between the IC51 group and the placebo group (post vaccination 1: 0.4% in IC51 versus 0.4% in placebo; post vaccination 2: 0.6% in IC51 versus 0.8% in placebo).

In addition to the assessment using Table 4 (above), local tolerability was also assessed by the investigator using a toxicity grading scale similar to the one published by FDA/CBER as a guidance for industry (<http://www.fda.gov/cber/gdlns/toxvac.htm#iii>). This assessment was also made by the subject and recorded in the diary. The vast majority were Grade 0 or Grade 1. Two subjects in the IC51 group had Grade 3 reactions, one with induration and swelling and the other with induration and erythema. The symptoms resolved without sequelae, and both subjects completed the study according to protocol.

Systemic Tolerability

Systemic symptoms were most commonly reported one day after vaccination, decreasing over time for both treatment groups. With some exceptions, the incidence of systemic symptoms was

slightly higher in the IC51 group for both vaccinations. The rates of symptoms reported one day after vaccination are summarized in Table 16.

Table 16: Systemic Reactions on Day 1 After Vaccination – Safety Population

Symptom reported		IC51 N=1993		Placebo N=657		Overall N=2650	
		n	(%)	n	(%)	n	(%)
Headache	Vaccination 1	168	(8.4)	40	(6.1)	208	(7.8)
	Vaccination 2	87	(4.4)	25	(3.8)	112	(4.2)
Muscle pain	Vaccination 1	157	(7.9)	45	(6.8)	202	(7.6)
	Vaccination 2	55	(2.8)	19	(2.9)	74	(2.8)
Fever	Vaccination 1	12	(0.6)	2	(0.3)	14	(0.5)
	Vaccination 2	7	(0.4)	1	(0.2)	8	(0.3)
Flu-like symptoms	Vaccination 1	70	(3.5)	19	(2.9)	89	(3.4)
	Vaccination 2	38	(1.9)	12	(1.8)	50	(1.9)
Nausea	Vaccination 1	36	(1.8)	6	(0.9)	42	(1.6)
	Vaccination 2	20	(1.0)	7	(1.1)	27	(1.0)
Vomiting	Vaccination 1	3	(0.2)	1	(0.2)	4	(0.2)
	Vaccination 2	3	(0.2)	1	(0.2)	4	(0.2)
Rash	Vaccination 1	6	(0.3)	1	(0.2)	7	(0.3)
	Vaccination 2	3	(0.2)	2	(0.3)	5	(0.2)
Excessive fatigue	Vaccination 1	88	(4.4)	26	(4.0)	114	(4.3)
	Vaccination 2	51	(2.6)	18	(2.7)	69	(2.6)

N=number of subjects in group; n=number of subject with data; %=percentage of subjects based on number of patients in the group

Source: Original BLA 125280, 5.3.5.1.3 - Clinical Study Report IC51-302 p. 95

8.2.6 Reviewer's Comments & Conclusions

This trial was adequate in design and execution to address the primary objective of comparing the safety and tolerability of IC51 to placebo control. The reviewer noted that the placebo control contained the same amount of aluminum hydroxide adjuvant as the vaccine. The local toxicity and immune stimulation associated with aluminum hydroxide might be expected to increase the rates of adverse experiences, including injection site reactions, over a true negative background or over a control group injected with PBS alone.

The proportion of subjects experiencing TEAE's in the IC51 group versus the placebo group was similar throughout the study period (58.9% versus 56.6%, respectively). The rates were also similar between groups for several subset analyses, including medically attended TEAE's, possibly or probably related TEAE's, severe or serious TEAE's, and TEAE's leading to withdrawal. Of the serious AE's experienced by ten (0.5%) subjects in the IC51 group, all were assessed by the investigator as unlikely related to treatment. No subjects died during the study.

The temporal relationship between vaccination and reports of TEAE's was similar between the IC51 group and the placebo group. Laboratory data, vital signs, and physical examination results

did not indicate any safety issues with similar results between the two groups. From the subject diary assessments, the systemic and local tolerability profile of IC51 was similar to placebo.

Overall, this trial demonstrated that the safety and tolerability profile of IC51 was similar to aluminum hydroxide-containing placebo.

8.3 Trial IC51-308: (NCT00596271)

Title: SAFETY AND IMMUNOGENICITY OF CONCOMITANT VACCINATION WITH IC51 AND HAVRIX® 1440 IN HEALTHY SUBJECTS. A SINGLE-BLIND RANDOMIZED, CONTROLLED PHASE 3 STUDY

8.3.1 Objective/Rationale

Primary objective: To demonstrate the non-inferiority of IC51 (2 x 6 mcg) + HAVRIX (Hepatitis A Vaccine, Inactivated) as compared to IC51 (2 x 6 mcg) + placebo in terms of the geometric mean titer (GMT) at Day 56, and IC51 (2 x 6 mcg) + HAVRIX as compared to HAVRIX + placebo in terms of the GMT at Day 28; 4 weeks after the last vaccination.

Secondary objectives:

To compare:

- The seroconversion rate (SCR) of the combined vaccination vs. IC51 + placebo at Day 56 and the combined vaccination versus (vs.) HAVRIX + placebo at Day 28.
- The immunogenicity of the combined vaccination vs. IC51 + placebo at Day 28, and the combined vaccination vs. HAVRIX + placebo at Day 56 in terms of the GMT and SCR for anti-JEV antibody titer (plaque reduction neutralization testing, PRNT)/HAV antibodies.
- The safety and tolerability of the combined vaccination vs. IC51 + placebo and HAVRIX + placebo up to 6 months after the first vaccination.

8.3.2 Design Overview

This was a randomized, controlled, multi-center, single-blind Phase 3 study.

8.3.3 Protocol (Objective Information)

After an optional screening period of up to 2 weeks, during which inclusion and exclusion criteria were checked, subjects were randomized in the ratio of 1:1:1, to one of the following three groups:

Group A: two injections of IC51 (6µg intramuscularly [i.m.] on Day 0 and Day 28), and one injection of placebo (0.5mL i.m. on Day 0).

Group B: two injections of placebo (0.5mL i.m. on Day 0 and Day 28), and one injection of HAVRIX (1.0 mL i.m. on Day 0).

Group C: two injections of IC51 (6 mcg i.m. on Day 0 and Day 28), and one injection of HAVRIX 1.0 mL i.m. on Day 0.

A final clinical evaluation took place after 4 weeks of follow-up (Day 56), and a scripted phone call was scheduled 6 months after the first vaccination to assess for adverse events.

8.3.3.1 Population

Healthy adult male or female subjects were recruited. All subjects were advised not to put themselves at risk for Japanese Encephalitis (i.e. traveling into rural regions in endemic countries) or Hepatitis A infection, before the blind was broken.

Inclusion Criteria

- 1) At least 18 years of age.
- 2) In female subjects either childbearing potential terminated by surgery, or were 1 year post-menopausal, or had a negative serum pregnancy test during screening and the willingness not to become pregnant during the entire study period and 30 days after the last vaccination by practicing reliable methods of contraception as specified in the protocol.
- 3) Written informed consent obtained prior to study entry (subjects should have given their consent themselves).

Exclusion Criteria

- 1) History of clinical manifestation of any flavivirus infection.
- 2) History of vaccination against JE, Yellow fever and Dengue fever (an anti-JEV neutralizing antibody titer $\geq 1:10$ at baseline was acceptable for inclusion; these subjects would be part of the safety population, but would not be analyzed for immunogenicity in the per-protocol [PP] analysis).
- 3) History of any previous Hepatitis A vaccination and infection.
- 4) Use of any other investigational or non-registered drug or vaccine in addition to the study vaccine during the study period or within 30 days preceding the first dose of study vaccine.
- 5) Planned administration of another vaccine during the study period.
- 6) Immunodeficiency including post-organ-transplantation or immunosuppressive therapy.
- 7) A family history of congenital or hereditary immunodeficiency.
- 8) History of autoimmune disease.
- 9) Administration of chronic (defined as more than 14 days) immunosuppressants or other immune-modifying drugs within six months of vaccination. (For corticosteroids, this meant prednisone, or equivalent, ≥ 0.05 mg/kg/day. Topical and inhaled steroids were allowed).
- 10) Any acute infections within 4 weeks prior to enrollment.
- 11) History of severe hypersensitivity reactions in particular to a component of the IC51 vaccine (e.g. protamine sulphate) or HAVRIX, anaphylaxis or severe cases of atopy requiring emergency treatment or hospital admission.
- 12) Infection with human immunodeficiency virus (HIV) (a negative test result within 30 days before enrollment is acceptable), Hepatitis B (HBsAg) or Hepatitis C.
- 13) History of thrombocytopenia or a bleeding disorder.
- 14) Drug addiction within 6 months prior to enrollment (including alcohol dependence, i.e. more than approximately 60 g alcohol per day, or conditions which might interfere with the study conduct).
- 15) Inability or unwillingness to avoid more than the usual intake of alcohol during the 48 hours after vaccination.
- 16) Known hypersensitivity to neomycin.
- 17) Diabetes mellitus in subjects receiving insulin therapy, severe cardiopulmonary disorders or history of malignancy in the past 5 years.
- 18) Pregnancy (positive pregnancy test during Screening or at Baseline), lactation or unreliable contraception in female subjects.
- 19) Subjects with any condition which in the opinion of the Investigator made the subject unsuitable for inclusion.
- 20) Inability or unwillingness to provide informed consent and to abide by the requirements of the study.

8.3.3.2 Products Mandated by the Protocol

Placebo: The placebo preparation contained phosphate-buffered saline (PBS) in an adjuvanted formulation (0.1% aluminum hydroxide); it was provided as a 0.5 mL dose in a prefilled syringe. Batch number ICB05/500.

IC51: IC51 was provided as a suspension of 6 mcg of purified, inactivated virus per 0.5 mL dose in a pre-filled syringe. Each dose contained 0.1% aluminum hydroxide adjuvant. (See Section 1.2.3 for details of production and formulation). Batch number ICB05/501 (corresponds to Batch A in the lot consistency study).

HAVRIX: HAVRIX® 1440 is a non-infectious hepatitis A vaccine developed and manufactured by GlaxoSmithKline Biologicals.

HAVRIX® 1440 was provided in 1.0 mL single-dose vials and pre-filled TIP-LOK® syringes. Batch number: AHAVB073BBF.

8.3.3.3 Endpoints

Immunogenicity:

The primary endpoints were:

- GMT for anti-JEV neutralizing antibody at Day 56.
- GMT for HAV antibody at Day 28.

Secondary endpoints included:

- SCR as defined by percentage of subjects with $\geq 1:10$ anti-JEV neutralizing antibody titer (PRNT) at Day 56.
- SCR as defined by percentage of subjects with HAV antibodies ≥ 20 mIU/mL at Day 28.

Safety:

Safety was assessed by monitoring AEs, local and systemic tolerability, and safety laboratory parameters (hematology, serum chemistry, urine). Safety surveillance is documented in Table 17. Adverse events were elicited by study personnel through physical examination and subject interviews. A subject diary was also provided to further assess local and systemic tolerability. The methods and criteria for acquiring safety data was similar to the other Phase III studies. (See Section 8.1.3.3.2 for details).

8.3.3.4 Surveillance and Monitoring

Table 17 summarizes the surveillance and monitoring for IC51-308.

Table 17. Safety Surveillance and Monitoring for Study IC51-308

Timing	Screening	Baseline / Vaccination	Vaccination	Follow-up	Follow-up	Early Termination	Early Termination
	Visit 0 Day -14	Visit 1 Day 0	Visit 2 Day 28	Visit 3 Day 56	Visit 4 Month 6	Before Visit 3	After Visit 3
Time windows	-14 to -1 days		+/- 4 days	+/- 6 days	+/- 14 days	-	
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Serum pregnancy test (1)	X						
History & demographic data	X						
Concomitant diseases	X						
Vaccination History	X						
Physical examination, vital signs	X						
Evaluation of body temperature	X	X	X	X		X	
Symptom-directed physical exam		X	X	X		X	
Randomization		X					
Study treatment							
Group A: IC51+ Placebo		IC51 + Placebo	IC51				
Group B: HAVRIX® 1440 + Placebo		HAVRIX® 1440 + Placebo	Placebo				
Group C: IC51+ HAVRIX® 1440		IC51 + HAVRIX® 1440	IC51				
PRNT blood (2)	X		X	X		X	
HAV-test (ELISA blood) (3)	X		X	X		X	
HIV (4), HBV, HCV-test							
Hematology (4) (5)	X		X	X		X	
Clinical chemistry (6)	X		X	X		X	
Urine pregnancy test (1)		X	X	X		X	
Urine test	X	X	X	X		X	
Concomitant medications	X	X	X	X	X	X	X
Local tolerability		X	X	X		X	
Dispense Subject Diary (7)		X	X				
Collect Subject Diary			X	X		X	
Adverse events		X	X	X	X	X	X
Blood volume	19 mL		19 mL	19 mL		19 mL	

(1) In women of childbearing potential

(2) Plaque reduction neutralization testing (PRNT) blood: 10mL

(3) Enzyme-linked immunosorbent assay (ELISA): 3mL

(4) Negative human immunodeficiency virus (HIV) tests that were performed up to 30 days before study inclusion are acceptable

(5) Hemoglobin, hematocrit, erythrocyte count, white blood count, platelets [Ethylenediaminetetraacetic Acid (EDTA) blood: 3mL]

(6) Creatinine, sodium, potassium, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin [Serum: 3mL]

(7) The subjects will assess local tolerability by themselves after each vaccination according to a given schedule

Source: Original BLA 125280, 5.3.5.1.3 - Clinical Study Report IC51-308, p.36.

8.3.4 Statistical Considerations

The primary objective of this study was to evaluate the non-inferiority of the co-administration of IC51 + HAVRIX® in comparison with IC51 + placebo, and HAVRIX® + placebo regarding the GMT. The non-inferiority margin for the GMT ratio "IC51 + HAVRIX® / IC51 + placebo" and the GMT ratio "IC51 + HAVRIX® / HAVRIX® + placebo" was set to 0.5. Two-sided 95% confidence intervals (CIs) were calculated, a one-sided p-value for non-inferiority below 2.5% was considered statistically significant.

8.3.5 Results (Objective Information)

8.3.5.1 Populations Enrolled/Analyzed

A total of 192 subjects were enrolled in 3 study centers in Western Europe and randomized to three treatment groups: The subjects were generally young (mean age, 25 years; maximum age, 61 years) and Caucasian (95%). All subjects had negative HIV, HBV and HCV viral tests at screening. A total of 27 out of 65 subjects (41.54%) in group A, 22 out of 65 subjects (33.87%) in group B, and 30 out of 62 subjects (48.39%) in group C had received a tick-borne encephalitis (TBE) vaccination in the past 10 years.

Of the 192 subjects randomized to treatment, 65 were randomized to treatment group A (IC51 + placebo), 65 to group B (HAVRIX® + placebo) and 62 to group C (IC51 + HAVRIX®). The three

groups were well-balanced with regard to demographic data; no significant differences were observed in baseline demographic characteristics.

8.3.5.2 Immunogenicity Endpoint/Outcomes

For purposes of analysis, three subsets of the recruited subjects were identified: the Intention to Treat (ITT) Population, the Per Protocol (PP) Population, and the Safety Population. All immunogenicity endpoint analyses were based on the PP analysis population. The safety population was used for all safety and tolerability analyses including demographic data, vital signs, local and systemic tolerability, laboratory data, and AEs.

The analysis populations were defined as follows:

- 1) ITT Population: all subjects randomized. Subjects were analyzed according to the treatment group to which they were randomized, rather than by the actual treatment they received.
- 2) PP Population: All randomized subjects without any major protocol deviations (as defined below).
- 3) Safety Population: All subjects who entered the study and received at least one vaccination. All analyses based on the safety population were carried out using the actual treatment received.

The following subjects were considered to have a major protocol deviation:

- Subjects with less than three vaccinations (Day 0 and Day 28).
- Subjects who had an anti-JEV neutralizing antibody titer $\geq 1:10$ or positive anti-HAV level ≥ 20 IU/mL at Baseline.
- Subjects with systemic immunosuppressant or immune-modifying concomitant therapy during the screening period.
- Subjects with any confirmed immunosuppressive or immunodeficient condition, including HIV, Hepatitis A, B or C infection or a family history of congenital or hereditary immunodeficiency.
- Subjects with an acute infection during the screening period or within 4 weeks before randomization.
- Subjects with active or passive vaccinations besides the study treatment during the study period or within 4 weeks before randomization.
- Subjects with a history of vaccination against JE, yellow fever, Dengue fever.
- Subjects without any post-Baseline SCR results.
- Subjects who were misrandomized or received the wrong study medication.

Table 18 summarizes the analysis populations.

Table 18. Analysis Populations for Study IC51-308

	Group C IC51 + HAVRIX® N=62 n (%)	Group A IC51 + Placebo N=65 n (%)	Group B HAVRIX® + Placebo N=65 n (%)	Overall N=192 n (%)
Randomized subjects	62 (32.29)	65 (33.85)	65 (33.85)	192 (100)
ITT population	62 (32.29)	65 (33.85)	65 (33.85)	192 (100)
PP population	58 (34.52)	58 (34.52)	52 (30.95)	168 (100)
Safety population	62 (32.29)	65 (33.85)	65 (33.85)	192 (100)

Source: [Section 14.1, Table 1](#)

N=number of subjects in group; n=number of subjects with data; %=percentage of subjects based on number of subjects in the population.

Source: Original BLA 125280, 5.3.5.1.3 - Clinical Study Report IC51-308, p. 55

8.3.5.2.1 Primary Immunogenicity Analysis

The primary immunogenicity analyses were performed on both the PP population and the ITT population with similar results. The following is the PP population analysis.

GMT for anti-JEV neutralizing antibody at Day 56:

IC51 + HAVRIX (Group C) versus IC51 + Placebo (Group A): The GMT's for anti-JEV neutralizing antibody in Group C and in Group A at Day 56 were 202.7 and 192.2, respectively, giving a ratio of 1.054 (95%CI: 0.754, 1.474). Since the lower bound of the 95% CI for the GMT ratio was >0.5 (0.7541), criteria for non-inferiority of IC51 given concomitantly with HAVRIX versus IC51 given alone was met.

GMT for anti-HAV antibody at Day 28:

IC51 + HAVRIX (Group C) versus HAVRIX + Placebo (Group B): The GMT's for anti-HAV antibody in Group C and in Group B were 24.0 and 21.7, respectively, giving a ratio of 1.105 (95%CI: 0.812, 1.504). Since the lower bound of the 95% CI for the GMT ratio was >0.5 (0.812), criteria for non-inferiority of HAVRIX given concomitantly with IC51 versus HAVRIX given alone was met.

8.3.5.2.2 Secondary Immunogenicity Analysis

The secondary immunogenicity analyses were performed on both the PP population and the ITT population with similar results. The following is the PP population analysis.

Anti-JEV seroconversion rate (SCR) at Day 56:

IC51 + HAVRIX (Group C) versus IC51 + Placebo (Group A): The SCR's for anti-JEV neutralizing antibody (defined as PRNT50 \geq 1:10) in Group C and in Group A at Day 56 were 100% and 98.2%, respectively, giving a difference of 1.8% (95%CI: -1.7, 5.3). Since the lower bound of the 95% CI for the SCR difference was >-10% (-1.7%), criteria for non-inferiority of IC51 given concomitantly with HAVRIX versus IC51 given alone was met.

Anti-HAV seroconversion rate (SCR) at Day 28:

IC51 + HAVRIX (Group C) versus HAVRIX + Placebo (Group B): The SCR's for anti-HAV antibody (defined as \geq 20 mIU/mL) in Group C and in Group B at Day 28 were 74.1% and 65.4%, respectively, giving a difference of 8.7% (95%CI: -8.4, 25.9). Since the lower bound of the 95% CI for the SCR difference was >-10% (-8.4%), criteria for non-inferiority of HAVRIX given concomitantly with IC51 versus HAVRIX given alone was met.

Among the other secondary immunogenicity analyses (anti-JEV GMT and SCR at day 28 and anti-HAV GMT and SCR at day 56), all demonstrated non-inferiority of concomitant vaccination except for anti-JEV SCR at day 28. In that case, the SCR in Group C (IC51 + HAVRIX) was identical to the SCR in Group A (IC51 + Placebo); both were 67.2%. However, the lower bound of the 95%CI for the difference in SCR's was -17.1%. Because this was higher than the predetermined threshold of -10%, non-inferiority in this analysis was not met.

Clinical Reviewer's Comment: The GMT's and SCR's for anti-HAV antibody at day 28 after vaccination in the HAVRIX + Placebo group were somewhat lower than those generally reported in the literature (e.g. Bryan et al, 2001). In addition, there was some variability from center to center in anti-HAV GMT's. However, it was noted that the anti-HAV GMT's were higher at both day 28 and day 56 in the co-vaccinated group (HAVRIX + IC51) than the HAVRIX only group (HAVRIX + Placebo), and non-inferiority criteria were met in both cases.

8.3.5.3 Safety Outcomes

8.3.5.3.1 Adverse Events

Of the 192 subjects randomized, 100% received at least the first vaccination and were therefore included in the safety population. One subject each from groups B (HAVRIX + Placebo) and C (IC51 + HAVRIX) did not receive the second injection at day 28.

Table 19 summarizes the data related to treatment-emergent adverse events (TEAE).

Table 19. Treatment-emergent Adverse Events for Study IC51-308

	<u>Group C</u> IC51 + HAVRIX® N=62			<u>Group A</u> IC51 + Placebo N=65			<u>Group B</u> HAVRIX® + Placebo N=65		
	n	(%)	n*	n	(%)	n*	n	(%)	n*
<u>Subjects:</u>									
With at least one TEAE	24	(38.7)	55	27	(41.5)	59	31	(47.7)	78
With at least one severe TEAE	3	(4.8)	4	4	(6.2)	5	3	(4.6)	5
With at least one treatment-related TEAE	11	(17.7)	20	13	(20.0)	23	12	(18.5)	24
With at least one medically attended TEAE	7	(11.3)	10	4	(6.2)	5	11	(16.9)	14
With at least one SAE	0	(0.0)	0	1	(1.5)	1	0	(0.0)	0
With at least one TEAE leading to withdrawal	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Who died	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0

Source: [Section 14.1, Tables 91, 92, 93, 94, 95 and 97](#)

N=number of subjects in group; n=number of subjects with data; n*=number of events; %=percentage of subjects based on number of subjects in the group; TEAE=treatment-emergent adverse event.

Treatment-related TEAEs include causality 'possible', 'probable' and missing.

Source: Original BLA 125280, 5.3.5.1.3 - Clinical Study Report IC51-308, p.72

Overall, the rates of TEAE's were similar across groups. None of the subjects experienced a TEAE leading to withdrawal from the study, and there were no deaths.

There was one serious AE in the study, which occurred in group A (IC51 + Placebo). The subject was a 51 year old male who was hospitalized for a seizure that occurred ~6 weeks after he received the first vaccination with IC51. His medical history was significant for a 10 year history of alcoholism and a 15 year history of epilepsy, with recurrent seizures about every 3 months, for which he had refused anti-epileptic therapy. The AE was assessed as "unlikely related" to the study drug.

The most common TEAE's reported in any treatment group were headache (ten subjects [15.4%] in group B, four subjects [6.2%] in group A, and four subjects [6.5%] in group C), influenza like illness (six subjects [9.2%] in group A, three subjects [4.6%] in group B, and three subjects [4.8%] in group C), and fatigue (five subjects each in groups B [7.7%] and C [8.1%], and two subjects [3.1%] in group A).

The most common system organ class (SOC) for TEAE's was general disorders and administration site conditions (13 [20.0%], nine [13.8%] and nine [14.5%] subjects for groups A, B and C, respectively) followed by infections and infestations (eight [12.3%], ten [15.4%] and 11 [17.7%] subjects, respectively), and nervous system disorders (seven [10.8%], 11 [16.9%] and five [8.1%] subjects, respectively).

No safety signals were noted in the analysis of TEAE's by SOC. There were no significant differences between the treatment groups, in terms of the proportion of severe or treatment-related TEAE's that were reported.

8.3.5.3.2 Evaluation of Laboratory Parameters

In terms of hematology, clinical chemistry, and urinalysis values, the mean differences across groups and mean changes across visits were insignificant. Individual abnormal values did not cluster by group and did not comprise a clinically significant pattern.

8.3.5.3.3 Local Tolerability

Local tolerability was assessed according to the scale in Table 20, devised for the study.

Table 20. Sponsor's Grading Scale for Local Reactions

Reaction	Severity			
Pain:	none	mild	moderate	severe
Itching:	none	mild	moderate	severe
Tenderness	none	mild	moderate	severe
Hardening:	none	mild (≤ 1 cm)	moderate (>1 to <3 cm)	severe (≥ 3 cm)
Swelling:	none	mild (≤ 1 cm)	moderate (>1 to <3 cm)	severe (≥ 3 cm)
Redness	none	mild (≤ 1 cm)	moderate (>1 to <3 cm)	severe (≥ 3 cm)

Source: Original BLA 125280, 5.3.5.1.3 - Clinical Study Report IC51-301 p. 40

The injection site was assessed by the subject on each of the first 7 days after each injection according to the scale in Table 20, and this was recorded in a diary. In general, subjects in the co-vaccination group, group C (IC51 + HAVRIX), experienced slightly more local symptoms than subjects in the single vaccination groups, groups A (IC51 + Placebo) and B (HAVRIX + Placebo). On Day 1 after Vaccination 1, pain was reported by 26 [40.63%], 27 [42.18%] and 36 [59.01%] subjects in groups A, B and C, respectively. Pain was less frequently after Vaccination 2, but it

was still more common in group C (22.95%, compared with 14.06% and 17.19% in groups A and B, respectively). Redness was also more common after Vaccination 1 in group C than groups A and B (14.75%, compared with 7.81% and 3.13%, respectively), as was swelling (14.75%, compared with 9.38% and 3.13%, respectively).

8.3.5.3.4 Systemic Tolerability

The most commonly reported symptom was “flu-like symptoms” at Visit 3 (Day 56) by 3.1%, 6.3%, and 6.6% of subjects in groups A, B, and C, respectively. The percentage of subjects reporting systemic symptoms was generally low (<10%), and there were no significant differences between groups.

8.3.6 Reviewer’s Comments and Conclusions

This was a randomized, controlled, single-blind trial to compare the safety and immunogenicity of co-administered IC51 and HAVRIX to the safety and immunogenicity of each vaccine administered separately. It addresses the important issue of concomitant administration of IC51 with another vaccine frequently given to travelers and military/diplomatic personnel. The design of the study was appropriate and the quality of the data appeared to be adequate.

In terms of the primary endpoint comparing the immunogenicity of IC51 alone, HAVRIX alone, and both vaccines administered concomitantly, the data supports the conclusion that co-administration does not interfere with immunogenicity. In the IC51 + HAVRIX group, anti-JEV antibody GMT at day 56 was non-inferior to the GMT at day 56 after IC51 + Placebo. Similarly, in the IC51 + HAVRIX group, anti-HAV antibody GMT at day 28 was non-inferior to the GMT at day 28 after HAVRIX + Placebo. Seroconversion rates were examined in secondary analyses and supported the primary conclusion.

Co-administration of IC51 and HAVRIX did not appear to adversely impact safety compared to separate vaccination. Overall, the safety profile across group A (IC51 + Placebo), group B (HAVRIX + Placebo) and group C (IC51 + HAVRIX) was similar. There were no significant differences between the rates of TEAE’s, including the subset of TEAE’s assessed as treatment-related. The one serious TEAE that occurred in the study (in group A) was assessed as unlikely related to study medication.

Although systemic tolerability was similar across the three treatment groups, local tolerability was somewhat unfavorable in group C (IC51 + HAVRIX) compared to the other two groups. There were numerically higher rates of injection site pain, redness, and swelling in group C than in groups A and B, which had similar local tolerability profiles. In all three groups, both injections (vaccine + vaccine or vaccine + placebo) were given in the same arm. Local tolerability may be improved by administering IC51 and HAVRIX in separate arms.

9 Overview of Effectiveness (Immunogenicity) Across Trials

Study IC51-301, which compared the immunogenicity of IC51 to an active control, JE-VAX, in a non-inferiority design, was the only pivotal study providing evidence of effectiveness in support of licensure. It is reviewed in section 8.1. The other studies submitted to the BLA that contain immunogenicity data on the proposed dose and regimen of IC51 did not include an active control. The relevant immunogenicity data are summarized separately for each supportive study. (See section 9.2.2 below).

9.1 General Discussion of Immunogenicity Endpoints

A trial of field efficacy of a JE vaccine in development would measure the capacity of the vaccine to protect against natural disease as compared to a placebo control. Conducting a study with a placebo control arm in a JE-endemic region would be unethical because safe and effective JE

vaccines already exist. Broad consensus and an abundance of data support the use of a Plaque Reduction Neutralization Test (PRNT50) titer of $\geq 1:10$ as a correlate of protection against JE. Therefore, CBER has accepted this standard surrogate for efficacy for the data generated in support of licensure of IC51.

It should be noted that the strain of the reference virus used in the PRNT50 assay was SA14-14-2, which is the same strain used to produce the vaccine. This could result in higher apparent geometric mean titers in IC51 vaccinated subjects versus those vaccinated with JE-VAX, which is produced using the Nakayama strain. However, JE is known to have just one serotype (i.e, each strain induces an antibody response that cross-neutralizes other strains). Therefore, although the magnitude of the mean titer may vary depending on the assay strain used, the seroconversion rate, which is defined as the percentage of subjects reaching a relatively low titer threshold of 1:10, could be expected to be more uniform, regardless of assay strain, in early measures of immunogenicity (Day 56 after initial vaccination). For further discussion, see Clinical Reviewer Comments under Sections 8.1.5.2.2 and 9.2.5.

9.2 Immunogenicity Findings

Sections 9.2.1 and 9.2.2 are brief summaries of the immunogenicity results/conclusions from each trial submitted to the BLA for which there was immunogenicity data after vaccination with the proposed regimen of 0.5ml containing 6 mcg injected i.m. on Days 0 and 28.

9.2.1 Pivotal Immunogenicity Trial

IC51-301 was a randomized, blinded phase III study to investigate the non-inferiority of IC51 compared to JE-VAX. The 867 subjects (437 subjects in the JE-VAX® group and 430 in the IC51 group) were randomized from 10 centers in North America and Europe. In the PP population, SCR's were 96.4% versus 93.8% and GMT's were 243.6 versus 102.0 for IC51 and JE-VAX, respectively. Criteria for non-inferiority were met for both variables. See section 8.1 for the detailed review.

9.2.2 Immunogenicity Data from Supportive Studies

In addition to the pivotal immunogenicity study, IC51-301, there were five additional studies submitted to the BLA that contained data on the primary immunogenicity outcome of interest: day 56 SCR and GMT after vaccination with the proposed dose and regimen of IC51 (6ug i.m. on Days 0 and 28). These were WRAIR 815, IC51-304, IC51-308, IC51-309, and IC51-310. The immunogenicity data from the PP populations in these studies is summarized below.

Reviewer's Note: CBER identified a total of 1467 subjects who received the proposed dose and regimen (6ug i.m. on days 0 and 28) per protocol. In each dataset, SCR was $\geq 95\%$ and GMT ≥ 128 on day 56 (28 days after the final vaccination).

The following is the summary of the immunogenicity data from each of the five supportive immunogenicity studies.

9.2.2.1 Study WRAIR 815

This was a prospective, randomized, open-label, active-controlled, dose- and schedule-finding phase 2 study to evaluate the immunogenicity of different doses and regimens of IC51 and to compare these with JE-VAX. The 94 subjects were enrolled and randomized as follows:

- Group 1: 6 mcg IC51 (0.5 ml) i.m. injection on Days 0 and 28
- Group 2: 6 mcg IC51 (0.5 ml i.m. injection on Days 0, 14 and 28
- Group 3: 12 mcg IC51 (1 ml) i.m. injection on Days 0 and 28
- Group 4: JE-VAX® 1 ml s.c. injection on Days 0, 7 and 28

Table 21 summarizes the results in the PP population of SCR's and GMT's on day 56 (28 days after the final vaccination).

Table 21. Immunogenicity Results for Study WRAIR 815

Parameter	Group (total dose)			
	1	2	3	4
Dose and Regimen	6 mcg IC51 x 2	6 mcg IC51 x 3	12 mcg IC51 x 2	1 ml x 3 JE-VAX®
n/N	21/22	23/23	23/23	14/19
SCR %	95.45	100.0	100.0	73.68
GMT (n) ¹	327.2 (21)	186.1 (23)	516.3 (23)	128.3 (14)

Source: Adapted from original BLA 125280, 2.7.3 – Summary of Clinical Efficacy, p.22

Results/Conclusions:

The immunogenicity of the 6ug, two dose regimen of IC51 was adequate for selection for development in phase III studies.

9.2.2.2 Study IC51-304 (NCT00595790)

This was a multicenter, observer-blinded, controlled, parallel-group, randomized phase III study to investigate rapid immunogenicity of a one-time, 2x dose (12 mcg instead of 6 mcg) of IC51 compared to the established dosing regimen (6 mcg on days 0 and 28). A total of 374 subjects were randomized to one of three groups (ITT population):

Group A: IC51 6 mcg i.m. at Days 0 and 28 (2x6 mcg);
Group B: IC51 12 mcg i.m. at Day 0 (1x12 mcg);
Group C: IC51 6 mcg i.m. at Day 0 (1x6 mcg).

In terms of the primary outcome, SCR at Day 56 in Group A versus Group B, the 2x, one time dose of 12 mcg did not meet non-inferiority criteria compared to the established regimen (6 mcg on Days 0 and 28). (See Table 22).

Table 22. Seroconversion Rates at Day 56

	PP population N=349	ITT population N=374
Group IC51 1x12 mcg		
Seroconversion rate (n/N)	41.2% (47/114)	40.7% (50/123)
95% CI	[32.2%; 50.3%]	[32.0%; 49.3%]
Group IC51 2x6 mcg		
Seroconversion rate (n/N)	97.3% (110/113)	97.6% (120/123)
95% CI	[94.4%; 100.0%]	[94.8%; 100.0%]
Non-adjusted difference (1x12 mcg vs 2x6 mcg)		
in SCR (%)	(-56.1%)	(-56.9%)
95% CI for difference in SCR(%)	[-65.6%; -46.6%]	[-66.0%; -47.8%]
p-value (two-tailed test)	<0.001	<0.001
p-value (non-inferiority one-tailed test)	>0.99	>0.99

n: Number of seroconverted patients

N: Number of patients included in each population/treatment group

Source: Original BLA 125280, 5.3.5.1.3 – IC51-304 Clinical Study Report, p.53

In some of the secondary analyses, comparing SCR's before the completion of the established regimen (at 56 days), the 2x, one time dose of IC51 met criteria for superiority. For example, SCR's at Day 10 were significantly higher after the 12 mcg dose compared to the 6 mcg dose. (See Table 23).

Table 23. Seroconversion Rates at Day 10

	PP population N=349	ITT population N=374
Group IC51 1x12 mcg		
Seroconversion rate (n/N)	53.9% (62/115)	54.8% (68/124)
95% CI	[44.8%; 63.0%]	[46.1%; 63.6%]
Group IC51 2x6 mcg		
Seroconversion rate (n/N)	21.1% (24/114)	25.8% (32/124)
95% CI	[13.6%; 28.5%]	[18.1%; 33.5%]
SCR difference (1x12 mcg vs 2x6 mcg)		
in SCR (%)	(32.9%)	(29.0%)
95% CI for difference in SCR(%)	[21.1%; 44.7%]	[17.4%; 40.7%]
p-value (two-tailed test)	<0.001	<0.001
p-value (non-inferiority one-tailed test)	<0.001	<0.001

n: Number of seroconverted patients

N: Number of patients included in each population/treatment group

Source: Original BLA 125280, 5.3.5.1.3 – IC51-304 Clinical Study Report, p.54

However, the advantage in terms of SCR's gained by administering the 12 mcg dose was reversed by Day 35, which is 7 days after the second dose of the established regimen. At Day 35, the one-time, 12 mcg dose was clearly inferior to the established regimen. (See Table 24).

Table 24. Seroconversion Rates at Day 35

	PP population N=349	ITT population N=374
Group IC51 1x12 mcg		
Seroconversion rate (n/N)	58.8% (67/114)	56.9% (70/123)
95% CI	[49.7%; 67.8%]	[48.2%; 65.7%]
Group IC51 2x6 mcg		
Seroconversion rate (n/N)	97.3% (110/113)	97.6% (120/123)
95% CI	[94.4%; 100.0%]	[94.8%; 100.0%]
SCR difference (1x12 mcg vs 2x6 mcg)		
in SCR (%)	(-38.6%)	(-40.7%)
95% CI for difference in SCR(%)	[-48.1%; -29.1%]	[-49.8%; -31.5%]
p-value (two-tailed test)	<0.001	<0.001
p-value (non-inferiority one-tailed test)	>0.99	>0.99

n: Number of seroconverted patients

N: Number of patients included in each population/treatment group

Results/Conclusions:

- A single dose of IC51, even at 12 mcg, was inferior to the established regimen (6 mcg at Days 0 and 28) in terms of SCR at Day 56.
- The objective of improving rapid immunogenicity was partially successful in that the 1x12 mcg dose was superior the 6 mcg dose in terms of SCR's on days 10 and 28 (day 10: 55% vs. 26% and day 28: 64% vs. 43%, respectively). However, SCR rates in the 1x12 mcg group on day 35 (57%) were low compared to those achieved in the 2x6 mcg group (98%).

9.2.2.3 Study IC51-308 (NCT00596271)

This was a prospective, randomized, multi-center, single-blind, active-controlled, phase 3 study to investigate co-administration of IC51 with the Hepatitis A vaccine, HAVRIX. Co-administration of

IC51 + HAVRIX met non-inferiority criteria compared to IC51 + Placebo and HAVRIX + Placebo. See section 8.3 for detailed review.

9.2.2.4 **Study IC51-309 (NCT00594958)**

This was a prospective, randomized, multi-center, double-blind, reference-controlled, phase 3 study to demonstrate the equivalence of three IC51 batches in terms of immunogenicity. The three batches were Study Lots ICB05-501 (Batch A), ICB05-502 (Batch B), and ICB05-503 (Batch D). The 636 subjects were enrolled and randomized 1:1:1 into the following three treatment arms:

Batch A: 6 mcg IC51 i.m. injection (0.5 ml) on Days 0 and 28

Batch B: 6 mcg IC51 i.m. injection (0.5 ml) on Days 0 and 28

Batch D: 6 mcg IC51 i.m. injection (0.5 ml) on Days 0 and 28

In terms of GMT, by predefined statistical parameters (for equivalence to be demonstrated, the 95%CI for the GMT ratio had to fall between 0.5 and 2 at day 56 in the PP population), Batch B did not meet equivalence specifications with either Batch A or Batch D. (See Table 25).

Table 25. Immunogenicity (GMT) at Day 56, Per Protocol Population

Parameter	Treatment group (ratio)	Estimate	n	SD	Range	95% CI
PRNT50	IC51 Batch A, N=198	160.71 ¹	197	304.2	5-2391	140.54, 183.76
	IC51 Batch B, N=202	272.24 ¹	202	416.9	5-3017	237.22, 312.43
	IC51 Batch D, N=200	127.56 ¹	200	209.7	5-1399	109.51, 148.57
GMT ratio	(IC51 Batch A/Batch B)	0.5857 ²	NA	NA	NA	0.4840, 0.7087
	(IC51 Batch /Batch D)	1.2406 ²	NA	NA	NA	1.0249, 1.5018
	(IC51 Batch B/Batch D)	2.1183 ²	NA	NA	NA	1.7520, 2.5612

Abbreviations: CI=confidence interval; GMT=geometric mean titer; n=number of subjects with data; N=number of subjects in group; NA=not applicable; PRNT50=Serum dilution giving a 50% reduction of plaque counts in a plaque reduction neutralization test; SD=standard deviation. Observed values used.

¹ GMTs with CIs for single batches calculated descriptively.

² Estimate for GMT ratios with CI (from analysis of variance with factors center and batch).

Source: Original BLA 125280, 2.7.3 – Summary of Clinical Efficacy, p.37

In terms of SCR, by predefined statistical parameters (for equivalence to be demonstrated, the SCR difference estimates had to be less than 3% in magnitude and all 95%CI's had to include 0 at day 56 in the PP population), Batch A, B, and D met criteria for equivalence. (See Table 26).

Table 26. Immunogenicity (SCR) at Day 56, Per Protocol Population

Parameter	Estimate %	95% CI %
SCR		
IC51 Batch A, N=198	97.97	94.90, 99.21 ¹
IC51 Batch B, N=202	99.01	96.46, 99.73 ¹
IC51 Batch D, N=200	96.50	92.95, 98.29 ¹
Difference of SCRs²		
IC51 Batch A-Batch B	-1.25	-3.65, 1.15
IC51 Batch A-Batch D	1.43	-1.86, 4.71
IC51 Batch B-Batch D	2.65	-0.29, 5.60
Difference of SCRs³		
IC51 Batch A-Batch B	-1.04	-3.44, 1.36
IC51 Batch A-Batch D	1.47	-1.75, 4.69
IC51 Batch B-Batch D	2.51	-0.38, 5.40

Abbreviations: CI=confidence interval, N=number of subjects in group; SCR=seroconversion rate.

Observed values used.

¹ CI for SCR calculated according to Wilson's method recommended by Altman.

² Mantel-Haenszel type risk difference estimate for seroconversion with 95% CI, stratified by center.

³ Risk difference estimate for seroconversion with 95% CI without adjustment by center.

%=percentage of subjects based on number of observed values.

Source: Original BLA 125280, 2.7.3 – Summary of Clinical Efficacy, p.39

Results/Conclusions:

The three study lots produced for the phase III studies were all adequately immunogenic, but they failed to meet criteria for equivalence, with Batch B inducing higher GMT's than Batch A and Batch D.

Clinical Reviewer's Note: A CBER statistician reviewed the data submitted for this study and concurs with the stated conclusions.

Clinical Reviewer's Note: Demonstration of manufacturing consistency is a critical component of licensure. As noted, the study lots evaluated in IC51-309 did not meet clinical criteria for equivalence. However, IC51-310 (see below), the study of three commercial lots which was submitted during the BLA review process, demonstrated equivalence in a more stringent test (fewer subjects were enrolled, yet statistical criteria were similar to those used in IC51-309). The reviewer considered the study of the commercial lots to be definitive. Please see the CBER statistics and CBER CMC review for more details.

9.2.2.5 Study IC51-310

This was a multicenter, double blind, randomized, controlled phase 3 study to demonstrate equivalence between three commercial batches of IC51. The batch numbers were: IC51/07E/006A (Batch A), IC51/07E/007A (Batch B), IC51/07F/008A (Batch C). The 389 subjects were enrolled and randomized 1:1:1 into the following groups:

Batch A: IC51 6 mcg i.m. injection (0.5 mL) on Day 0 (Visit 1) and Day 28 (Visit 2) with a vaccine produced from commercial IC51 batch IC51/07E/006A. (N=124 in the PP population)

Batch B: IC51 6 mcg i.m. injection (0.5 mL) on Day 0 (Visit 1) and Day 28 (Visit 2) with a vaccine produced from commercial IC51 batch IC51/07E/007A. (N=121 in the PP population)
Batch C: IC51 6 mcg i.m. injection (0.5 mL) on Day 0 (Visit 1) and Day 28 (Visit 2) with a vaccine produced from commercial IC51 batch IC51/07F/008A. (N=119 in the PP population)

In terms of GMT, by predefined statistical parameters (for equivalence to be demonstrated, the 95%CI for the GMT ratio had to fall between 0.5 and 2 at day 56 in the PP population), all three batches met criteria for equivalence. (See Table 27).

Table 27. Immunogenicity (GMT) at Day 56, Per Protocol Population

	p-value	Estimate	95% CI
GMT¹			
IC51 Batch A		160.80	[133.51, 193.66]
IC51 Batch B		188.21	[163.77, 216.29]
IC51 Batch C		168.43	[136.20, 208.29]
Ratios of GMTs^{2,3}			
IC51 Batch A/Batch B		0.8534	[0.6630, 1.0984]
IC51 Batch A/Batch C		0.9570	[0.7426, 1.2333]
IC51 Batch B/Batch C		1.1214	[0.8689, 1.4474]
Ratios of GMTs⁴			
IC51 Batch A/Batch B		0.8524	[0.6612, 1.0987]
IC51 Batch A/Batch C		0.9634	[0.7464, 1.2437]
IC51 Batch B/Batch C		1.1303	[0.8743, 1.4614]
Batch × Center Interaction	0.9093		

CI=confidence interval; GMT=geometric mean titer; ANOVA=analysis of variance.

¹GMT and CIs for single batches are descriptive.

²Estimate for GMT ratios with CI (from ANOVA with factors center and batch).

³Primary efficacy comparison.

⁴Estimate for GMT ratios with CI (from ANOVA with factors center and batch), including a center × batch interaction.

Source: Original BLA 125280, 5.3.5.1.3 – Study Report IC51-310, p.64

In terms of SCR, by predefined statistical parameters (for equivalence to be demonstrated, the SCR difference estimates had to be less than 3% in magnitude and all 95%CI's had to include 1 at day 56 in the PP population), Batch A, B, and C met criteria for equivalence. (See Table 28).

Table 28. Immunogenicity (SCR) at Day 56, Per Protocol Population

	Estimate	95% CI
SCR		
IC51 Batch A	98.39%	[94.31%, 99.56%] ¹
IC51 Batch B	100.00%	[96.92%, 100.00%] ¹
IC51 Batch C	97.48%	[92.85%, 99.14%] ¹
Difference of SCR²		
IC51 Batch A–Batch B	-1.62%	[-3.84%, 0.59%]
IC51 Batch A–Batch C	0.81%	[-2.77%, 4.40%]
IC51 Batch B–Batch C	2.50%	[-0.26%, 5.26%]
Difference of SCR³		
IC51 Batch A–Batch B	-1.61%	[-3.83%, 0.60%]
IC51 Batch A–Batch C	0.91%	[-2.68%, 4.49%]
IC51 Batch B–Batch C	2.52%	[-0.30%, 5.34%]

%=percentage of subjects based on number of observed values; CI=confidence interval,

SCR=seroconversion rate.

¹CI for SCR calculated according to Wilson's method recommended by Altman.

²Mantel-Haenszel type risk difference estimator for seroconversion with 95% CI, stratified by center.

³Risk difference estimator for seroconversion with 95% CI without adjustment by center.

Source: Original BLA 125280, 5.3.5.1.3 – Study Report IC51-310, p.65

Results/Conclusions:

The three commercial batches used in this study were all adequately immunogenic, and they met criteria for equivalence.

Clinical Reviewer's Note: A CBER statistician reviewed the data submitted for this study and concurs with the stated conclusions.

9.2.3 Immunogenicity Stratified by Demographic Variables

A post-hoc analysis was performed on immunogenicity data stratified by gender, ethnicity, and age. The analysis was limited to the dataset from IC51-301, because this was the only study that included an active control.

9.2.3.1 Immunogenicity Stratified by Gender

SCR's and GMT's were uniformly high in each subpopulation (stratified by gender) taken from the PP population at day 56. See Table 29. There were no clinically significant differences in SCR or GMT between the groups.

Table 29. SCR and GMT at Day 56 After Primary Vaccination in the PP Population Stratified by Gender

Gender	SCR n (%)		GMT	
	IC51	JE-VAX	IC51	JE-VAX
Male, N=285	128 (96.2%)	139 (91.4%)	226.1	94.4
Female, N=450	224 (96.6%)	208 (95.4%)	254.3	107.6

N=number of subjects in group.

Adapted from: original BLA 125280, 5.3.5.3.27 – Integrated Summary of Efficacy, p.63

9.2.3.2 Immunogenicity Stratified by Ethnicity

SCR's and GMT's were uniformly high in each subpopulation (stratified by ethnicity) taken from the PP population at day 56. (See Table 30). There were no clinically significant differences in SCR or GMT between the groups.

Table 30. SCR and GMT at Day 56 After Primary Vaccination in the PP Population Stratified by Ethnicity

Race	SCR n (%)		GMT	
	IC51	JE-VAX	IC51	JE-VAX
Caucasian, N=604	284 (96.3%)	293 (94.8%)	234.2	100.0
Black, N=84	43 (97.7%)	34 (85.0%)	324.2	114.8
Asian and other, N=47	25 (96.2%)	20 (95.2%)	235.4	109.9

N=number of subjects in group.

Adapted from: original BLA 125280, 5.3.5.3.27 – Integrated Summary of Efficacy, p.64

9.2.3.3 Immunogenicity Stratified by Age

The effect of age on the immune response to IC51 and JE VAX® was assessed in subjects over >65 years of age (N = 24 for IC51; N=19 for JE-VAX) compared with those ≤65 years of age (N = 341 for IC51; N=351 for JE-VAX). In subjects >65 years of age, IC51 was similar to JE-VAX at Day 56 in terms of SCR's (95.8% versus 89.5%, respectively) and GMT's (255.2 versus 96.8, respectively). (See Table 31). In addition, within the IC51 group, there were no significant differences between subjects ≤65 years of age versus those >65 years of age in terms of Day 56 SCR's (96.5% versus 95.8%, respectively) or GMT's (242.8 versus 255.2, respectively).

Table 31. SCR and GMT at Day 56 After Primary Vaccination in the PP Population Stratified by Age

Age	SCR n (%)		GMT	
	IC51	JE-VAX	IC51	JE-VAX
≤65, N=692	329 (96.5%)	330 (94%)	242.8	102.3
>65, N=43	23 (95.8%)	17 (89.5%)	255.2	96.8

N=number of subjects in group.

Adapted from: original BLA 125280, 5.3.5.3.27 – Integrated Summary of Efficacy, p.61

9.2.4 Clinical Data to Support Manufacturing Consistency

Studies IC51-309 and IC51-310 were conducted to examine immunogenicity in 3 different study and commercial batches, respectively. In study IC51-309, the three study lots failed to meet criteria for equivalence, whereas in study IC51-310, the commercial lots met those criteria. See Section 9.2.2 for summaries of the studies. A CBER statistician reviewed both studies in detail and concurred with the immunogenicity conclusions.

Clinical Reviewer Comment: Because the manufacturing process underwent several technical changes between the production of the study lots and the commercial lots, CBER places primary emphasis on the clinical data from the commercial lots, which were studied in IC51-310, and met criteria for equivalence.

9.2.5 Duration of Immunity

The sponsor reports that two studies are underway investigating the duration of immunity after primary vaccination and the timing and efficacy of a booster dose.

IC51-303

The protocol for the immunogenicity section of Study IC51-303 calls for long-term follow-up (up to 24 months) of a subset of the subjects who completed Studies IC51-301 and IC51-302 per protocol. The subset was comprised of all the subjects who completed the IC51-301 and -302 protocols at four of the study sites in Europe (two in Austria, one in Germany, and one in Romania). Immunogenicity data was made available in an interim study report. It included 6 month SCR's on subjects who received IC51 (181 subjects – SCR 95%) or JE-VAX (82 subjects – SCR 74%) and 12 months SCR's on the IC51 group (181 subjects – SCR 83%). See Appendix 1 for a summary of IC51-303 interim analysis.

Clinical Reviewer Comment: The reviewer noted in Section 8.1.5.2.2 that the use of SA 14-14-2 as the input virus in the PRNT assay introduces bias towards IC51 (produced from the homologous strain) compared to JE-VAX (produced from Nakayama strain) in terms of GMT's. In a study report (5.3.1.4 – Neutralization of JE: Interstrain Comparison), the sponsor documents that SCR's were not affected by input virus. However, the sera tested were from IC51-301 study subjects, so the time frame was not longer than 56 days after 1st vaccination. In longer term studies, when GMT's of subjects fall closer to the titer of $\geq 1:10$ definition of SCR, it is possible that the input virus bias documented for GMT's could extend to SCR's. The reviewer thus interpreted long term SCR comparisons of IC51 versus JE-VAX cautiously.

IC51-305

This study will follow subjects originally enrolled and treated in Study IC51-304. A booster dose will be given to subjects who are PRNT negative at 6 months or 12 months. See Appendix 1 for a brief summary of the protocol. No results were made available in support of licensure.

Clinical Reviewer's Note: Because data was not submitted to permit analysis of the timing and/or efficacy of booster dosing, no guidance on this will be published in the product insert.

9.3 Effectiveness (Immunogenicity) Conclusions

IC51 appears to be adequately immunogenic at the 6 mcg dose, administered i.m. on day 0 and day 28. IC51 met non-inferiority criteria compared to the only currently U.S.-licensed JE vaccine, JE-VAX. Given the strength of the data supporting JE-neutralizing serum antibodies as a surrogate for efficacy, and considering the immunogenicity data on IC51 submitted to the BLA, it is reasonable to conclude that IC51 will be efficacious in the prevention of disease caused by Japanese encephalitis virus.

The vaccine lots produced for commercial release meet criteria for immunogenicity equivalence.

Immunogenicity data is limited in populations of special interest, particularly geriatric and certain ethnic populations. However, immunogenicity does not appear to be compromised when stratified by gender, ethnicity, or age. There is also no evidence that any decline in immunogenicity with advancing age is out of proportion to the natural waning of the immune response with age.

PRNT50 titers are slightly higher early after vaccinating with an initial dose of 12 mcg. However, the reviewer does not consider these differences to be clinically significant. The higher SCR's achieved on Days 10 and 28 compared to the 6 mcg dose are reversed 7 days after the repeat 6 mcg dose on Day 28 called for in the established regimen. In addition, even on Days 10 and 28 after the 12 mcg dose, SCR's are relatively low. Travelers attempting to achieve rapid protection should be cautioned that before completing the proposed regimen (particularly before day 35), their risk, as measured by seroconversion, remains relatively high, and that if they receive only one dose, protection may wane rapidly.

More data is needed to define the duration of immunity after the primary vaccination series and to determine the timing and efficacy of a booster dose.

10 Overview of Safety across Trials

10.1 Safety Database

The safety population from the phase III studies submitted to the BLA was pooled to form a database of 4715 subjects. All subjects were monitored for safety up to Day 56 (28 days after the second vaccination), and 91.5% (4313/4715) were followed out to 6 months. This database is referred to herein as the pooled 6 month safety population.

10.1.1 Studies Included in the Safety Analysis

Studies IC51-301, IC51-302, IC51-304, IC51-308, and IC51-309 were included in this analysis.

10.1.2 Treatment Group Allocation

Each subject who received at least one dose of a treatment was included in the safety population for that treatment. The comparator groups were included to provide data on background rates of AE's and to validate the observed safety profile. Table 32 is the number of subjects allocated to each treatment group by study. Table 33 is the total number in each treatment group.

Table 32. Number of Subjects in Pooled 6 Month Safety Population by Study Protocol

<u>IC51-301</u>	
IC51:	428
JE-VAX:	435
<u>IC51-302</u>	
IC51:	1993
Placebo:	657
<u>IC51-304</u>	
IC51:	374
<u>IC51-308</u>	
IC51 + HAVRIX:	62
(grouped with IC51 subjects for purposes of analysis)	
IC51 + Placebo:	65
(grouped with IC51 subjects for purposes of analysis)	
HAVRIX + Placebo:	65
(grouped as HAVRIX subjects for purposes of analysis)	
<u>IC51-309</u>	
IC51	636

Total:	4715

Table 33. Number of Subjects in Each Treatment Group in the Pooled 6 Month Safety Population

IC51	JE-VAX	HAVRIX	Placebo
3558	435	65	657

10.1.3 Exposure and Time of Follow-up

Of the 3558 subjects that were assigned to the IC51 group (3482 [97.9%] of these received two IC51 vaccinations). Of the 435 subjects assigned to the JE-VAX group, (403 [92.6%] received the three vaccination regimen), 65 received one HAVRIX® vaccination, and of the 657 assigned to placebo (645 [98.2%] received two vaccinations). Placebo was a PBS solution containing 0.1% aluminum hydroxide as an adjuvant.

Overall, 4313/4715 subjects (91.5%) completed a 6-month visit.

10.2 Safety Assessment Methods

The definition of the safety analysis population (those subjects who were entered in the study and received at least one study treatment) was identical in all of the studies. All AE's were coded using Medical Dictionary for Regulatory Activities (MedDRA).

The methods for observing, recording, and analyzing AE's, systemic tolerability, local tolerability, laboratory parameters, etc., were the same across studies. See Section 8.1.3.3.2 for details.

10.3 Significant Events

10.3.1 Deaths

One death occurred in the 6 month pooled safety database. The subject was a 70 year old Caucasian female who was enrolled in study IC51-301, was randomized to receive IC51, and was vaccinated on 1/17/06 and 2/17/06. Her concomitant medications included vitamin E,

vitamin C, calcium, fish oil, ferrous sulphate, B complex, acetylsalicylic acid, atenolol, oxycontin, protonix, dilantin, aspirin, phenergan, flagyl, daily multivitamin, calcium carbonate, epogen and percocet. On 3/27/06, she was diagnosed with adenocarcinoma of the lung, metastatic to the brain and liver. She underwent surgery and was treated with dexamethasone and tarceva postoperatively. She died on -(b)(6)-. The event was assessed as unrelated to the study drug by the Investigator.

10.3.2 Serious AE's (SAE's)

Overall, the rate of SAE's was low. In the 6 month pooled safety population, the number of subjects that experienced a SAE was 38/3558 (1.1%) in the IC51 group, 3/435 (0.7%) in the JE-VAX group, 0/65 (0%) in the HAVRIX group, and 13/657 (2%) in the placebo group. No SAE's were assessed by the Investigator as probably or possibly related to study medication.

Clinical Reviewer's Comment: The case histories from each of the subjects in the IC51 group who experienced an SAE were reviewed. The reviewer concurs that in each case the SAE was unlikely related to study treatment. However, considering that the currently licensed JE vaccine, JE-VAX, has been linked to cases of encephalitis and delayed hypersensitivity with serious sequelae, two of the SAE's, "dermatomyositis" and "central nervous system inflammation" were of particular interest. The clinical information made available in those two cases is summarized – the dermatomyositis case under "8.2.5.3.1 Adverse Events, Serious Adverse Events", and the central nervous system inflammation event below. These studies, including the pooled datasets, were not powered to determine whether SAE's such as these occurred with a frequency significantly higher than the background rate expected for this population. Post-marketing studies and the pharmacovigilance plan were designed to detect a doubling or tripling in rare adverse events.

Subject 3201-112 – "Central nervous system inflammation"

Subject 3201-112, a 22 year old Caucasian female with a medical history significant only for allergy to nickel, was randomized to IC51 and vaccinated on 02 November 2005 and 30 November 2005. Concomitant medication included meliane. Vaccination history included tick borne encephalitis in 1999 and 2003, and typhus, hepatitis B, meningococcus, diphtheria, polio and tetanus, rabies, cholera, yellow fever and influenza in 2005. At the final study visit on 27 December 2005, the subject complained of a mild headache. On 09 January 2006, she visited the study center again and reported ocular fixation difficulties which had started on 06 January 2006. The subject was referred to a neurologist on 11 January 2006. MRI showed a small, focal signal enhancement of about 3 mm in the region of the left crus cerebri, and blood tests showed no relevant abnormalities. Her symptoms failed to improve and she subsequently had a lumbar puncture which showed the following:

- 18 cells per μ l (no differential provided).
- increased IgG (4.42) and IgM (0.29).
- glucose 71mg/dl (reference 76-119).
- elevated IgM and IgG with oligoclonal bands.

The case history provided by the sponsor indicates that during the subject's clinical course, she was given two different diagnoses – "multiple sclerosis" and "suspected neuroborreliosis". With regard to the CSF analysis, either diagnosis is possible.

"CSF oligoclonal gamma globulin bands occur in association with a number of viral infections. The associated antibodies are often directed against viral proteins. Oligoclonal bands occur commonly in certain noninfectious neurologic diseases (e.g., multiple sclerosis) and may be found in nonviral infections (e.g., neurosyphilis, Lyme neuroborreliosis)."

The information provided was not sufficient to determine the final diagnosis. CBER was satisfied that the sponsor performed due diligence in attempting to obtain follow-up on this case.

10.3.3 Withdrawals Due to Study Medication

In the pooled 6 month safety population, the incidence of AE's leading to study withdrawal was similar across groups: IC51 group, 0.8%; JE-VAX group, 1.8%; Placebo group, 0.8%. Analysis by SOC revealed no significant differences between the groups.

10.4 Other Safety Findings

10.4.1 Analysis of Treatment Emergent Adverse Events (TEAE)

10.4.1.1 Overview of TEAE's

An overview of TEAE's in the 6 month pooled safety population, with subset analysis, is given in Table 34.

Table 34. Overview of TEAE's in 6 Month Pooled Safety Population

Category	IC51 N=3558		JE-VAX® N=435		HAVRIX® N=65		Placebo N=657	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects:								
With at least one TEAE	2282	(64.1)	279	(64.1)	31	(47.7)	402	(61.2)
With at least one severe TEAE	207	(5.8)	19	(4.4)	3	(4.6)	42	(6.4)
With at least one serious TEAE	38	(1.1)	3	(0.7)	0	(0.0)	13	(2.0)
With at least one related TEAE ¹	1362	(38.3)	149	(34.3)	12	(18.5)	255	(38.8)
With at least one medically attended TEAE ²	668	(19.4)	36	(10.7)	11	(16.9)	129	(19.6)
With at least one TEAE leading to withdrawal	27	(0.8)	8	(1.8)	0	(0.0)	5	(0.8)
Who died	1	(<0.1)	0	(0.0)	0	(0.0)	0	(0.0)

¹ Events with a causality reported as probable or possible or with a missing classification were considered related to study medication.

² Medically attended TEAEs were not collected during study IC51-304 and IC51-301 (in which JE-VAX® was administered) but were collected during follow-on study IC51-303. Therefore the JE-VAX® column represents medically attended TEAEs collected from Month 2 to Month 6. All subjects in the pooled 6-month safety population receiving JE-VAX® originate from study IC51-301.

Abbreviations: N=number of subjects in group; n=number of subjects with event; %=percentage of subjects based on number of subjects in the group; TEAE=treatment-emergent adverse event.

Source: Original BLA 125280, 2.7.4 – Summary of Clinical Safety, p.44

10.4.1.2 TEAE's of Special Interest

Clinical Reviewer's Note: The hypersensitivity reactions linked to JE-VAX are thought to be caused by the -(b)(4)- gelatin used as a --(b)(4)-- in production of the vaccine. Although IC51 does not contain any gelatin as an excipient, monitoring for hypersensitivity reactions continues to be an important component of vaccine development and post-marketing surveillance. To investigate the possibility of a hypersensitivity-related safety signal, a group of MedDRA preferred terms associated with allergy and hypersensitivity were identified and used to perform a post-hoc analysis on the 6 month pooled safety population.

The MedDRA terms used for analysis of hypersensitivity events included: rash, dermatitis, erythema, pruritis, urticaria, hypersensitivity, flushing, conjunctivitis, dyspnea, hypotension, circulatory collapse, wheezing, and eye pruritis.

The rate of allergy/hypersensitivity associated events was similar across groups: IC51: 125/3558 (3.5% [95%CI 2.9, 4.2]), JE-VAX: 24/435 (5.5% [95%CI 3.6, 8.1]), Placebo: 24/657 (3.7% [95%CI 2.4, 5.4]).

10.4.1.3 Serious TEAE's that were Treatment-Related

No serious TEAE's in the 6 month pooled safety population were assessed as being probably or possibly related to study drug.

10.4.2 Local Tolerability

Local tolerability was assessed by two different sets of criteria (see Section 8.1.3.3.2.3). In the 6 month pooled safety population, local reactogenicity was assessed by the sponsor's criteria. Generally, the results were the same as those reported in studies IC51-301 and IC51-302: there was a trend toward higher rates of local symptoms in the JE-VAX vaccinated subjects, particularly in terms of hardening, swelling, and redness. Table 35 displays the percentages of subjects experiencing local tolerability symptoms (any symptom and severe symptoms) during the first 7 days after the first and second vaccinations.

Table 35. Local Tolerability in the 6 Month Pooled Safety Population during the 7 Days After First and Last Vaccination

	IC51	JE-VAX	Placebo
Any symptom (any severity)	1191/3532 (54%)	261/427 (61%)	366/652 (56%)
Any symptom (severe)	112/3532 (3.2%)	59/427 (13.8%)	20/652 (3.1%)

Adapted from: Original BLA 125280, 5.3.5.3.28 – Integrated Summary of Safety, p.57-58

Clinical Reviewer's Note: Because the route of administration for IC51 and JE-VAX are different (intramuscular versus subcutaneous, respectively), assessments of local tolerability are not directly comparable. For example, induration or erythema might be more readily apparent to the subject after subcutaneous injection because the reaction is closer to the surface of the skin. However, it was noted that scores for pain and tenderness in these datasets were similar for IC51 and JE-VAX. Regardless of whether the route of administration makes a difference, IC51 does appear to produce fewer severe local symptoms than JE-VAX.

10.4.3 Laboratory Findings

Laboratory parameters were not collected in follow-up study IC51-303. Therefore, they were not analyzed in the pooled 6 month safety population.

10.4.4 Product / Demographic Interactions

In the TEAE analysis performed on subsets of the 6 month pooled safety population, there was no evidence of differences in the safety profile of IC51 in subjects stratified by age, gender, or ethnicity. However, data on age and ethnicity should be interpreted with caution because of the low number of subjects ≥65 years old (161 out of 4715 (3.4%) in the 6 month pooled safety

population) and subjects of any ethnicity other than Caucasian (Asian: 66/4715 (1.4%); Black: 208/4715 (4.4%); Other (136/4715 (2.9%).

10.4.5 Product / Product Interactions

One study in the BLA addressed concomitant treatment with another vaccine. In study IC51-308, safety and immunogenicity were assessed for co-administration of IC51 and the Hepatitis A vaccine, HAVRIX versus each vaccine administered alone. This study was reviewed in depth in Section 8.3.

10.4.6 Clinical Data to Support Manufacturing Consistency – Safety Analysis

Studies IC51-309 and IC51-310 investigated three different study and commercial batches, respectively, for consistency in terms of immunogenicity and safety. The studies are briefly summarized in Appendix 1. There was no evidence that the safety profile was significantly different from one batch to the next within either study.

CBER performed a post-hoc analysis comparing TEAE's in with the study batches (IC51-309) to those with the commercial batches (IC51-310). It was found that in the category of subjects who experienced a severe TEAE there was an excess in the IC51-310 data compared to the IC51-309 data (10.8% versus 4.4%, respectively) that reached statistical significance. However, considering the fact that the percentage of subjects who experienced any TEAE was similar (59.4% versus 60.5% in IC51-309 and 310, respectively) and the percentage who experienced a treatment-related TEAE was identical (35.4%) and that the two studies were performed at different times and in two slightly different subject populations, CBER determined that the difference was not clinically important.

10.4.7 Human Reproduction

Pregnancy was an exclusion criteria for each of the studies submitted to the BLA. In addition, female subjects were required to commit to the use of reliable contraception during the study period. Very few subjects conceived during the 56 day vaccination regimen or during the follow-up period in the long term studies. In several of these cases, data on pregnancy outcomes was not yet available for submission to the BLA.

Therefore, no definitive conclusions can be reached regarding the safety of IC51 in pregnancy and/or lactation. See Section 4.2 for a summary of reproductive/developmental toxicology animals studies conducted during preclinical vaccine development.

10.4.8 Person to Person Transmission

Not applicable. The virus in the vaccine is attenuated and formalin-inactivated. In addition, humans are a dead-end host even for wild-type JE virus. There is no evidence for human to human transmission.

10.4.9 Post-marketing Surveillance

Commitments for post-marketing studies and surveillance are documented in detail in the Summary Basis for Regulatory Approval (SRBA) published at the time licensure was granted. The clinical reviewer concurs with the recommendations as stated in the SRBA letter.

10.5 Safety Conclusions

In general, IC51 appears to have an acceptable safety profile in a healthy, adult population.

There is no evidence that IC51 causes serious neurological or hypersensitivity adverse events similar to those attributed to JE-VAX. However, this issue requires further monitoring because the studies in support of licensure were not powered to detect rare events.

There is no evidence that safety is compromised in a geriatric population. However, the number of treated subjects aged >65 was too small to make definitive conclusions about safety in this population.

IC51 appears to be relatively well-tolerated, in terms of local reactogenicity. The local tolerability profile compares favorably to that of JE-VAX.

Co-administration of another traveler's vaccine, the Hepatitis A vaccine, HAVRIX, did not appear to compromise the IC51 safety profile. If given concomitantly, the two vaccines should not be given in the same arm.

11 Additional Clinical Issues

11.1 Directions for Use

The prefilled syringe should be visually inspected for coarse particulate matter and discoloration before administration. If either of those conditions exists, the vaccine should not be administered. The vaccine should be well shaken before administration to obtain a homogeneous suspension. The vaccine should be administered by intramuscular injection into the deltoid muscle.

11.2 Dose Regimens and Administration

The vaccine should be administered intramuscularly as a 0.5ml dose on Days 0 and 28.

11.3 Special Populations

Safety and immunogenicity have not been established in:

- pregnant women
- nursing mothers
- immunocompromised patients
- people less than 18 years of age

Although data are limited, there is no evidence that safety or immunogenicity is compromised in geriatric populations.

11.4 Pediatrics

The Pediatric Research Equity Act (PREA) of 2003 requires that each application for licensure contain data on the safety and efficacy of the product in relevant pediatric subpopulations. The sponsor was granted deferred submission of pediatric data, which is acceptable when "the product is ready for approval in adults before studies in pediatric patients are complete" (21 CFR 601.27(b)(1)).

Under PREA, the sponsor is obligated to conduct post-marketing studies to investigate the safety and efficacy of IC51 in a pediatric population. During the BLA review, the sponsor requested a partial waiver for infants <1 year of age. At the time, CBER recommended denial of the waiver request. Subsequently, the sponsor investigated the feasibility of performing studies in subjects in this age group. In a memo that included documentation of discussions with officials at the State Department, the CDC, the U.S. Army, a consortium of travel clinics (----- (b)(4) -----), and several clinical research organizations (----- (b)(4) -----)

-----), the Applicant determined that studies in the age group 0 to 12 months would be impracticable due to the obstacles they would likely encounter. The most significant of those obstacles is summarized as follows:

- Very few U.S. or European families travel to remote areas of Asia for at least 4 weeks (the scenario for which the ACIP currently recommends JE vaccination) with children less than one year of age.
- Non-travelers in non-endemic countries could not expect any potential benefit from a JE vaccine; therefore, conducting a study in a non-traveler pediatric population would not be ethically justifiable.
- JE vaccines are generally given starting at one year of age in JE-endemic countries; this practice is consistent with WHO recommendations.
- Maternally derived JE-neutralizing antibodies are common in infants born in endemic areas and would be expected to interfere with immunogenicity studies.

After further internal review and discussions with the sponsor, CBER agreed to grant a partial waiver for children less than one year of age because necessary studies would be impracticable.

The post-marketing pediatric development plan agreed to at the time of approval includes vaccination of ~2100 subjects ≤17 years of age. Table 36 displays the number of subjects to be recruited and the age stratification planned for each study.

Table 36. Subjects in the pediatric development program for IC51, per study, age stratum and treatment group.

	IC51-321		IC51-323		IC51-322	Total Number of Subjects
Total Number of Subjects in Study	488		1550		100	2138
Treatment Group	IC51	Jence-Vac	IC51	HAV	IC51	
Total Number of Subjects in Treatment Group	234+20	234	1150	400	100	1504 / 634
Subjects in Age Group ≥6 months – <1 year	20		100	50	not specified	120 / 50
Subjects in Age Group ≥1 year - ≤ 3 years	117	117	475	160	not specified	592 / 277
Subjects in Age Group ≥ 3 - ≤ 17 years	117	117	575	190	not specified	692 / 307

Source: Original BLA - Pediatric Phase 3 Development Plan for the Japanese Encephalitis Vaccine IC51, p.3/28.

The sponsor plans to conduct the pivotal immunogenicity and safety trials (IC51-321 and -323, respectively) in a country in which JE is endemic. CBER concurs with this plan because a study in a non-endemic region would not be expected to confer any possible benefit on the pediatric study subjects and would therefore be considered unethical. In addition, it is clear that recruiting and obtaining follow-up data on a significant number of pediatric subjects expected to travel from non-endemic to endemic areas would be impracticable. Because of similar obstacles, a study of efficacy of a booster dose in JE-naïve, non-endemic children would also be impracticable.

After evaluating the proposed pediatric development plan, CBER expressed concern that, because the sponsor planned to include subjects with pre-existing JE-neutralizing antibody in the per protocol population of the pivotal immunogenicity trial, the analysis might not be relevant to the population required to be studied under PREA (JE naïve children residing in the U.S.). To explore safety and immunogenicity in a naïve, non-endemic pediatric population, the sponsor

plans to conduct a small trial (designated IC51-322) in U.S. and European subjects aged 1-10 years who are expected to travel to endemic areas.

At the time of the approval action, the sponsor had recently completed a phase II dose finding study in 60 subjects aged 1-3 years. According to the sponsor, the data from this study, designated IC51-221, supports a dose of 3 µg (half the adult dose) in this population.

12 Conclusions

The available safety and immunogenicity data support the approval of IC51 administered intramuscularly as two 6µg doses on Days 0 and 28 for adults ≥17 years of age.

13 Recommendations

13.1 Approval Recommendations

IC51 is recommended for approval for active immunization against JEV for person 17 years of age and older at risk of exposure to JEV.

13.2 Recommendations on Post-marketing Actions

A comprehensive discussion of CBER's recommendations on post-marketing actions is contained in the approval letter for IXIARO published at the time the license was granted. The clinical reviewer concurs with the recommendations as stated in the approval letter.

13.3 Recommendations on Request for Partial Waiver of Pediatric Studies in Infants <1 Year of Age

A partial waiver for infants <1 year of age should be granted based on the assessment that studies in this population would be impracticable. See Section 11.4 for details.

13.4 Labeling

CBER communicated with the sponsor on multiple occasions to achieve consistency with CBER's current guidance on the intent and format of package inserts. The final label was reviewed by the clinical team and by the Advertising and Promotional Labeling Branch (APLB) and found to be acceptable.

Appendix 1 – Brief Summary of Studies in the IC51 Development Program

WRAIR 763 Phase I dosing study

Type of study: Phase I dose and regimen finding, and safety

Study report submitted to the BLA: yes

Study design and type of control:

Randomized (1:1:1:1), controlled, single-center, single-blind, dose-finding, schedule-finding

Test products(s); dosage regimen; route of administration:

IC51 Grp 1: 0.4 mcg i.m. (Days 0 and 28; placebo on Day 7)

IC51 Grp 2: 0.4 mcg i.m. (Days 0, 7 and 28)

IC51 Grp 3: 2.0 mcg i.m. (Days 0 and 28; placebo on Day 7)

IC51 Grp 4: 2.0 mcg i.m. (Days 0, 7 and 28)

Booster of primary dose at Months 8-9.

Number of subjects:

Total: 25

IC51 Grp 1: 6

IC51 Grp 2: 5

IC51 Grp 3: 7

IC51 Grp 4: 7

Duration of treatment:

Treatment 4 weeks. Follow-up 4 weeks. Booster dose 8-9 months after primary vaccine, and follow-up for 30-days.

Objective(s) of the study:

Primary objective:

- To evaluate the safety and AEs of 0.4 mcg and 2.0 mcg of JE-PIV purified inactivated JE vaccine administered in 2 doses, at 0 and 28 days, and administered in 3 doses at 0, 7 and 28 days.

Secondary objective:

- To evaluate immune response to the vaccine given in 2 or 3 dose schedules.

Results / Conclusions:

- None of the dose regimens was sufficiently immunogenic, with seroconversion rates in the range of 50%.
- Three doses (Days 0, 7, and 28) did not improve immunogenicity over two doses (Days 0 and 28).
- A booster dose at 8-9 months after primary vaccination was effective, with 92% SCR in the combined groups.
- The vaccine appeared to be safe and well-tolerated.

WRAIR 815 Phase II dosing study

Type of study: Phase II dose and regimen finding, efficacy, and safety

Study report submitted to the BLA: yes

Study design and type of control:

Randomized (1:1:1:1), active-controlled, single-center, open label, dose-finding, schedule-finding

Test products(s); dosage regimen; route of administration:

IC51 Grp 1: 6 mcg i.m. (Days 0 and 28)

IC51 Grp 2: 6 mcg i.m. (Days 0, 7 and 28)

IC51 Grp 3: 12 mcg i.m. (Days 0 and 28)

IC51 Grp 4: JE-VAX 1.0ml s.c. (Days 0, 7 and 28)

Number of subjects:

Total: 92

IC51 Grp 1: 22

IC51 Grp 2: 24

IC51 Grp 3: 25

IC51 Grp 4: 21

Objective(s) of the study:

Primary objective:

- To evaluate the immune response to 6.0 mcg, and 12.0 mcg of JE-PIV, WRAIR purified inactivated Japanese encephalitis vaccine, administered in two doses, at 0 and 28 days, and 6.0 mcg administered in three doses, at 0, 14, and 28 days, and to identify any large differences in immunogenicity between the JE-PIV and JE-VAX® vaccines.

Secondary objectives:

- To evaluate the safety and reactogenicity of 6.0 mcg, and 12.0 mcg of JE-PIV WRAIR purified inactivated Japanese encephalitis vaccine administered in two doses, at 0 and 28 days and 6.0 mcg administered in three doses at 0, 14, and 28 days.
- To evaluate the persistence of serum antibodies from month 6 to month 24 after the initial vaccination.

Results / Conclusions:

- The 6ug dose at Days 0 and 28 was immunogenic, with 95% SCR at day 56, compared to 74% SCR in the JE-VAX arm.
- The 6ug dose at Days 0 and 28 was chosen as dose/regimen for development in phase III trials.
- SCR's remained high (87.5%) at Day 720 after primary vaccination with the 6ug, 2 dose regime.
- The vaccine appeared to be safe and well-tolerated.

IC51-301 Phase III Pivotal Immunogenicity Study

Type of study: Phase III immunogenicity and safety

Study report submitted to the BLA: yes

Study design and type of control:

Randomized (1:1), active-controlled, multi-center, observer-blinded

Test products(s); dosage regimen; route of administration:

IC51: 6.0 mcg i.m. (Days 0 and 28) and placebo i.m. on Day 7

JE-VAX®: 1.0 ml s.c. (Days 0, 7 and 28)

Number of subjects:

Total: 867

IC51: 430

JE-VAX: 437

Objective(s) of the study:

Primary objective:

- To demonstrate the non-inferiority of IC51 (2 x 6 mcg) compared to JE-VAX® (3 x 1.0 mL) in terms of the seroconversion rate (SCR) and geometric mean titer (GMT) at day 56; four weeks after the last vaccination.

Secondary objectives:

To compare:

- The superiority of IC51 versus JE-VAX® SCR and GMT at day 56, provided that non-inferiority has been demonstrated.
- The immunogenicity of both vaccines in regards to SCR and GMT's of the North American with the European study population.
- The immunogenicity of both vaccines in regards to SCR and GMT's in subjects older versus younger than 50 years of age.
- The safety of both vaccines regarding changes in laboratory parameters and adverse events (AE's) including local reactogenicity.

Results / Conclusions:

- The immunogenicity of a two dose regimen (days 0 and 28) of IC51 was non-inferior to the standard three dose regimen (days 0, 7, and 28) of JE-VAX.
- Superiority of IC51 versus JE-VAX for SCR was not demonstrated.
- There were no significant differences between the North American and European study populations in terms of SCR or GMT at day 56.
- There was no significant differences between subjects older versus younger than 50 years of age in terms of SCR or GMT at day 56.
- Compared to JE-VAX, IC51 had an acceptable safety profile and there was a trend toward a more favorable local tolerability profile for IC51 compared to JE-VAX.

IC51-302 Phase III Pivotal Safety Study

Type of study: Phase III safety

Study report submitted to the BLA: yes

Study design and type of control:

Randomized (3:1 IC51: placebo), placebo-controlled, multi-center, double-blind

Test products(s); dosage regimen; route of administration:

IC51: 6.0 mcg i.m. (Days 0 and 28) and placebo i.m. on Day 7

Placebo: 0.5 ml i.m. (Days 0 and 28)

Number of subjects:

Total: 2675

IC51: 2012

Placebo: 663

Objective(s) of the study:

Primary objective:

- To investigate the safety and tolerability of IC51 during a vaccination period of 28 days until 4 weeks after the last vaccination compared with an inactive control.

Secondary objectives:

- To analyze the rates of serious adverse events (SAE's) and medically attended adverse events (AEs) in individuals before and after immunization with IC51.
- To assess possible changes in laboratory parameters.

Results / Conclusions:

- IC51 appeared to be well-tolerated, with a safety and tolerability profile similar to placebo.
- The rates of serious AE's, medically attended AE's, and AE's possibly or probably related to study medication were similar in the IC51 and placebo groups.
- Laboratory data, vital signs, and physical examination results did not indicate any safety issues with similar results between the two groups.

IC51-303 Phase III Safety and Immunogenicity Follow-Up Study to IC51-301 and IC51-302

Type of study: Phase III safety and immunogenicity

Study report submitted to the BLA: yes – interim report through 24 months

Study design and type of control:

Multi-center, uncontrolled follow-up study to IC51-301 and IC51-302

Test product(s); dosage regimen; route of administration:

No treatment given (follow-up study). See studies IC51-301 and IC51-302 for treatment in preceding studies.

Definition of Analysis Populations:

Intent-to-Treat (ITT) Population

The ITT analysis population was defined as all subjects who were enrolled into this study, were planned to participate in the long-term immunogenicity part, and received IC51 in the respective preceding study.

Intent-to-Treat (ITT2) Population

The ITT2 analysis population was defined as all subjects who were enrolled into this study, were planned to participate in the long-term immunogenicity part, received IC51 in the respective preceding study, and had a positive PRNT result at Visit 1.

Intent-to-Treat (ITT3) Population

The ITT3 population contained the 181 IC51 recipients from the ITT population plus 82 JE-VAX® recipients and 35 placebo recipients.

Six Month Safety Population

The six month safety population comprised all subjects who were enrolled in this study. All analyses based on the six month safety population were carried out using the actual treatment received. The six month safety population was used for the safety analysis following the six month visit (Visit 2).

Long-Term Safety Population

The long-term safety population is identical to the ITT2 population. The long-term safety population will be used for the safety analysis following the 12 month visit (Visit 3) and the 24 months visit (Visit 4). These will be included in a separate report.

Number of subjects:

6-month safety population

IC51: 2283

JE-VAX®: 338

Placebo: 637

6-month ITT3 immunogenicity analysis

IC51: 181

JE-VAX®: 82

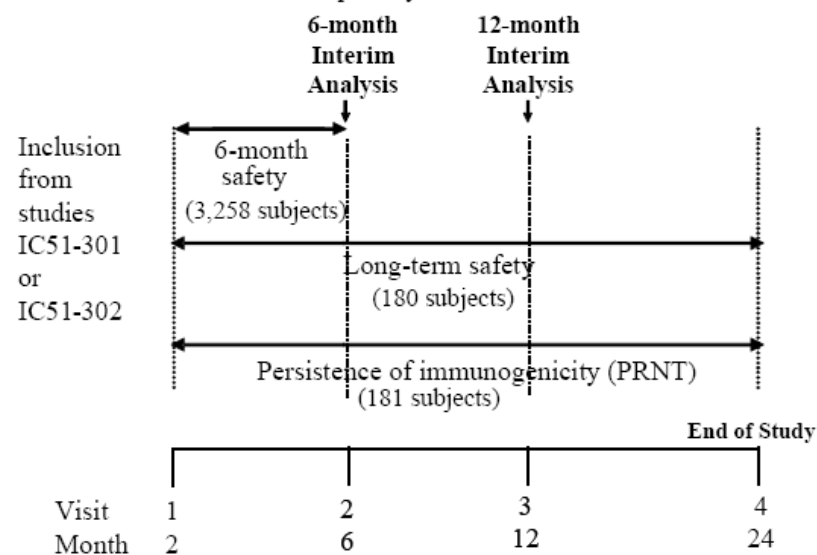
Placebo: 35

12-month ITT immunogenicity analysis

IC51: 181

All subjects who completed IC51-301 and IC51-302 were to complete the 6 month follow-up to assess long-term safety. Thereafter, only the subset of subjects enrolled in the immunogenicity part of the study, and who received IC51 in the preceding studies IC51-301 or IC51-302, were to continue to the 12-month and 24-month assessments of immunogenicity and safety. See Figure 2 for timeline.

Figure 2. Timeline for Study IC51-303



Source: Original BLA 125280, 5.3.5.1.3 IC51-303 – Clinical Study Report – 6 Month Interim Analysis, p.44

Duration of treatment:

Up to 24 months. Interim reports submitted to the BLA assessed safety and immunogenicity up to 12 months.

Objective(s) of the study:

- To investigate the immunogenicity of IC51 in subjects 24 months after the first vaccination.
- To investigate the frequency of vaccination-related adverse events (AEs) during the study period.

Results / Conclusions:

- SCR's at 6 months (ITT3 population) were significantly higher in the IC51 group (172/181, 95%) compared to the JE-VAX group (61/82, 74%) with a risk difference estimate of 17.8 (95%CI, 6.8, 28.9).
- SCR's remained relatively high (83.4%) for the IC51 group (ITT population) at 12 months.

- GMT's were higher in the IC51 group compared to the JE-VAX group, but both decreased markedly over time (month 2 – IC51: 310.8, JE-VAX: 99.5; month 6 – IC51: 83.5, JE-VAX: 34.1; month 12 – IC51: 41.2, JE-VAX – data not available).
- No safety concerns were apparent in the 2-6 month follow-up period (6 month safety population) after vaccination with IC51.

IC51-304 Comparison of Rapid Immunization with Standard Regimen for IC51

Type of study: Phase III immunogenicity and safety

Study report submitted to the BLA: yes

Study design and type of control:

Multicenter, observer-blinded, randomized, parallel study

Test product(s); dosage regimen; route of administration:

Group A: IC51 6 mcg i.m. at Days 0 and 28 (2x6 mcg);

Group B: IC51 12 mcg i.m. at Day 0 (1x12 mcg);

Group C: IC51 6 mcg i.m. at Day 0 (1x6 mcg).

Number of subjects:

Total: 374

Group A: 125

Group B: 124

Group C: 125

Objective(s) of the study:

Primary:

- To demonstrate non-inferiority of IC51 1x12 mcg vs. IC51 2x6 mcg in terms of seroconversion rates at Day 56 after the first vaccination.

Secondary:

- To analyze the immunogenicity of a rapid-immunization, single-vaccination scheme IC51 1x12 mcg vs. IC51 1x6 mcg and the standard vaccination scheme IC51 2x6 mcg vs. IC51 1x6 mcg in terms of superiority of the seroconversion rate at 10, 28, 35 and 56 Days after the first vaccination.
- To compare Geometric Mean Antibody Titers (GMTs) of all regimens.
- To confirm the safety profile of IC51.

Results / Conclusions:

- Non-inferiority of IC51 1x12 mcg vs. IC51 2x6 mcg in terms of GMT and SCR rates was not demonstrated at Day 56 ($p > 0.99$) after the first vaccination; conversely, the IC51 2x6 mcg dose was found to be superior to the IC51 1x12 mcg and 1x6 mcg doses on Day 56.
- The objective of improving rapid immunogenicity was partially successful in that the 1x12 mcg dose was superior the 6 mcg dose in terms of SCR's on days 10 and 28 (day 10: 55% vs. 26% and day 28: 64% vs. 43%, respectively). However, SCR rates in the 1x12 mcg group on day 35 (57%) were low compared to those achieved in the 2x6 mcg group (98%). Indeed, superiority was reversed at day 35 and thereafter.
- IC51 appeared to be safe and well-tolerated. There were no significant differences between any of the groups in terms of TEAE's and tolerability profiles.

IC51-305 Phase III Safety and Immunogenicity Follow-Up Study to IC51-304

Type of study: Phase III immunogenicity and safety

Study design and type of control:

Multicenter, open label, follow-up study to IC51-304

Test products(s); dosage regimen; route of administration:

Initial treatment in IC51-304, as follows:

Group A: IC51 6 mcg i.m. at Days 0 and 28 (2x6 mcg);

Group B: IC51 12 mcg i.m. at Day 0 (1x12 mcg);

Group C: IC51 6 mcg i.m. at Day 0 (1x6 mcg).

Follow-up treatment in IC51-305, as follows:

IC51: 6.0 mcg i.m. (Month 11) if PRNT-negative at Month 6

IC51: 6.0 mcg i.m. (Month 23) if PRNT-negative at Month 12

Number of subjects:

Total: 356

Data are blinded so group numbers are not known.

Duration of treatment:

Up to 24 months.

Objective(s) of the study:

Primary objective:

- To determine long-term persistence of immunogenicity of IC51 (2 x 6 mcg, 1 x 12 mcg or 1 x 6 mcg) in terms of SCR in subjects 24 months after the primary vaccination.

Secondary objectives:

- To determine immunogenicity of a booster dose of IC51.
- To compare the GMT of both regimes.
- To confirm the safety profile of IC51.

Results / Conclusions:

Study is ongoing. Clinical study report not available.

IC51-308 Phase III Safety and Immunogenicity Follow-Up Study to IC51-304

Type of study: Phase III immunogenicity and safety

Study design and type of control:

Randomized, controlled, multi-center, single-blind study

Test products(s); dosage regimen; route of administration:

IC51 6.0 mcg i.m. (Days 0 and 28) and placebo i.m. on Day 0

HAVRIX® 1.0 ml i.m. (Day 0) and placebo i.m. on Days 0 and 28

IC51 6.0 mcg i.m. (Days 0 and 28) and HAVRIX® 1.0 ml i.m. (Day 0)

Number of subjects:

Total: 192

IC51: 65

HAVRIX®: 65

IC51 + HAVRIX®: 62

Duration of treatment:

Up to 26 weeks.

Objective(s) of the study:

Primary objective:

- To demonstrate the non-inferiority of IC51 (2 x 6 mcg) + HAVRIX® 1440 (Hepatitis A Vaccine, Inactivated) as compared to IC51 (2 x 6 mcg) + placebo in terms of the geometric mean titer (GMT) at Day 56, and IC51 (2 x 6 mcg) + HAVRIX® 1440 as compared to HAVRIX® 1440 + placebo in terms of the GMT at Day 28; 4 weeks after the last vaccination.

Secondary objectives:

To compare:

- The seroconversion rate (SCR) of the combined vaccination vs. IC51 + placebo at Day 56 and the combined vaccination versus (vs.) HAVRIX® 1440 + placebo at Day 28.
- The immunogenicity of the combined vaccination vs. IC51 + placebo at Day 28, and the combined vaccination vs. HAVRIX® 1440 + placebo at Day 56 in terms of the GMT and SCR for anti-JEV antibody titer (plaque reduction neutralization testing, PRNT)/HAV antibodies.
- The safety and tolerability of the combined vaccination vs. IC51 + placebo and HAVRIX® 1440 + placebo up to 6 months after the first vaccination.

Results / Conclusions:

- Non-inferiority in terms of GMT, of the co-administration of IC51 + HAVRIX® vs. IC51 + placebo and HAVRIX® + placebo was demonstrated for anti-JEV neutralizing antibody at Day 56 and HAV antibody at Day 28.
- The secondary analysis for SCR confirmed non-inferiority at day 28 for HAV antibody and day 56 for anti-JEV neutralizing antibody.
- Co-administration of IC51 + HAVRIX did not result in an unfavorable safety profile. TEAE's, laboratory data, vital signs and physical examination results were similar across the groups.
- Local tolerability was somewhat compromised by co-administration of the two vaccines compared to administration IC51 alone or HAVRIX alone.

IC51-309 Phase III Equivalency Study of Three Study Batches of IC51

Type of study: Phase III immunogenicity and safety

Study design and type of control:

Randomized, controlled, multi-center, double blind study

Test products(s); dosage regimen; route of administration:

IC51 Batch A: 6.0 mcg i.m. (Days 0 and 28)

IC51 Batch B: 6.0 mcg i.m. (Days 0 and 28)

IC51 Batch D: 6.0 mcg i.m. (Days 0 and 28)

Number of subjects:

Total: 636

Batch A: 212

Batch B: 213

Batch D: 211

Duration of treatment:

Up to 28 weeks.

Objective(s) of the study:

Primary objective:

- To demonstrate equivalence of three IC51 batches in terms of Geometric Mean Titers (GMTs) for anti-Japanese Encephalitis Virus (JEV) neutralizing antibody.

Secondary objectives:

- To assess the seroconversion rates (SCRs) of three IC51 batches.
- To investigate the safety of three IC51 batches during a vaccination period of 28 days until six months after the first vaccination.
- To investigate tolerability of three IC51 batches during a vaccination period of 28 days until four weeks after the last vaccination.
- To analyze the rates of serious adverse events (SAEs) and medically attended adverse events (AEs) in individuals after immunization with IC51.
- To assess possible changes in laboratory parameters.

Results / Conclusions:

- Criteria for equivalence was not met for the three batches. GMT's were significantly higher for Batch B compared to both to Batch A and to Batch D.
- GMT's and SCR's were high for all three batches and were in the ranges observed in previous studies.
- None of the batches had an unfavorable safety profile. TEAE's, laboratory data, vital signs and physical examination results were similar across the groups.
- All three batches had similar local and systemic tolerability profiles.

IC51-310 Phase III Equivalency Study of Three Commercial Batches of IC51

Type of study: Phase III immunogenicity and safety

Study design and type of control:

Randomized, controlled, multi-center, double blind study

Test product(s); dosage regimen; route of administration:

IC51 Batch A: 6.0 mcg i.m. (Days 0 and 28)

IC51 Batch B: 6.0 mcg i.m. (Days 0 and 28)

IC51 Batch C: 6.0 mcg i.m. (Days 0 and 28)

Number of subjects:

Total: 389

Batch A: 131

Batch B: 129

Batch C: 129

Duration of treatment:

Up to 10 weeks.

Objective(s) of the study:

Primary objective:

- To demonstrate equivalence of three commercial IC51 batches in terms of Geometric Mean Titers (GMTs) for anti-Japanese Encephalitis Virus (JEV) neutralizing antibody.

Secondary objectives:

- To assess the seroconversion rates (SCRs) of three commercial IC51 batches.
- To investigate the safety of three commercial IC51 batches during a period of 56 days after the first vaccination.

- To investigate the tolerability of three commercial IC51 batches during a period of 56 days after the first vaccination.
- To analyze the rates of serious adverse events (SAEs) and medically attended adverse events (AEs) in individuals after immunization with IC51.
- To assess possible changes in laboratory parameters.

Results / Conclusions:

- Criteria for equivalence was met for the GMT's and SCR's from the three batches.
- GMT's and SCR's were high for all three batches and were in the ranges observed in previous studies.
- None of the batches had an unfavorable safety profile. TEAE's, laboratory data, vital signs and physical examination results were similar across the groups.
- All three batches had similar local and systemic tolerability profiles.

IC51-311 Phase III Long-Term Safety and Immunogenicity Follow-Up to Study IC51-309

Type of study: Phase III immunogenicity and safety

Study design and type of control:
Uncontrolled, open label study

Test products(s); dosage regimen; route of administration:
Initial randomization and treatment as per IC51-309. Subjects will be given a 6 mcg i.m. booster vaccination with IC51 approximately 15 months after the primary immunization in an unblended fashion.

Number of subjects:
Total: ~200

Duration of treatment:
Subjects will be followed for 12 months after booster vaccination.

Objective(s) of the study:
Primary:

- To assess the effect of a booster vaccination on immunogenicity of IC51 in terms of seroconversion rate (SCR) at Month 12 after the booster vaccination (Month 27 after primary immunization).

Secondary:

- To assess the effect of a booster vaccination on immunogenicity of IC51 in terms of SCR at Day28 and Month 6 after the booster vaccination (Months 16 and 21 after primary immunization).
- To assess the effect of a booster vaccination on immunogenicity of IC51 in terms of geometric mean titer (GMT) for anti-Japanese Encephalitis virus (JEV) neutralizing antibodies at Day 28, Month 6 and Month 12 after the booster vaccination (Months 16, 21 and 27 after primary immunization).
- To investigate tolerability of a booster vaccination until Day 28 after the booster vaccination.
- To analyze the rates of serious adverse events (SAEs) and medically attended adverse events (AEs) in individuals after a booster vaccination with IC51.
- To assess changes in laboratory parameters.

Results / Conclusions:

Study is ongoing. Clinical study report not available.