Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial of the Safety and Tolerability of IC51, an Inactivated Japanese Encephalitis Vaccine

E. Tauber,[1] H. Kollaritsch,[2] F. von Sonnenburg,[4] M. Lademann,[5] B. Jilma,[3] C. Firbas,[3] T. Jelinek,[6] C. Beckett,[8] J. Knobloch,[7] W. J. H. McBride,[10] E. Schuller,[1] A. Kaltenböck,[1] W. Sun,[9] and A. Lyons[9]

[1]Intercell AG, Campus Vienna Biocenter 6, and [2]Institute of Specific Prophylaxis and Tropical Medicine at the Center for Physiology and Pathophysiology and [3]Department of Clinical Pharmacology, Medical University Vienna, Vienna, Austria; [4]Department of Infectious Diseases and Tropical Medicine, University of Munich, Munich, [5]Department of Tropical Medicine, University of Rostock, Rostock, [6]Berlin Center for Travel and Tropical Medicine, Berlin, and [7]Institute of Tropical Medicine, University of Tübingen, Tübingen, Germany; [8]Viral and Rickettsial Diseases Department, Naval Medical Research Center, and [9]Division of Virus Diseases, Walter Reed Army Institute of Research, Silver Spring, Maryland; [10]School of Medicine, James Cook University, Cairns Base Hospital, Cairns, Australia

Background. Japanese encephalitis (JE) is the most important mosquito-borne viral encephalitis and has a high case fatality rate. It is caused by Japanese encephalitis virus. Improved vaccines are urgently needed for residents in countries of endemicity, travelers, and the military. The aim of the present trial was to evaluate the safety and tolerability of IC51, Intercell's Vero cell–derived, purified, inactivated JE vaccine.

Methods. This was a randomized (3:1), double-blind, placebo-controlled, multicenter phase 3 trial. Healthy subjects were randomized to receive 2 doses of IC51 ($n = 2012$) or placebo ($n = 663$) at a 4-week interval. Adverse events following immunization (AEFI) were documented over a period of 2 months.

Results. The rate of severe AEFI was similar in the IC51 group (0.5%) and the placebo group (0.9%). The rate of medically attended AEFI and all AEFI was also similar in the IC51 group and the placebo group. The same applied for all adverse events, including local and systemic tolerability. Importantly, there were no signs of acute allergic reactions.

Conclusion. The Intercell JE vaccine IC51 had a safety profile similar to that of placebo. These data, together with the immunogenicity data from a recent phase 3 trial, form the basis of application for licensure of this vaccine.

Trial registration. ClinicalTrials.gov identifier: NCT00605058.

Japanese encephalitis (JE), a mosquito-borne arboviral infectious disease, is the leading cause of viral encephalitis in Asia [1]. The mortality rate is high, from 15% to 40%, and a high incidence of sequelae is recorded after recovery [2–5]. Because no antiviral treatment is available once the disease is acquired, prevention of infection is particularly important. Vaccination against infection with Japanese encephalitis virus (JEV), which exists as only one serotype [6], provides an effective protective measure, especially in combination with mosquito control and prevention of mosquito bites by use of repellent agents and protective clothing. The US Advisory Committee on Immunization Practices recommends immunization against JE for travelers to Asian countries in which the disease is endemic, especially if they carry a high risk of exposure by visiting rural areas and spending considerable time outdoors [1].

For many years, JE-VAX was used as the primary vaccine against JE in countries such as the United States and Australia. However, serious adverse reactions have restricted the immunization recommendations for this vaccine [7]. The principal vaccine-associated adverse reactions of concern are hypersensitivity reactions, including generalized urticaria and angioedema, which may lead to anaphylaxis in severe cases. Because these

Received 19 October 2007; accepted 3 March 2008; electronically published 27 June 2008.

Potential conflicts of interest: E.T., E.S., and A.K. are employees of Intercell AG, which sponsored this clinical trial. All other institutions received compensation for the conduct of this trial.

Financial support: Intercell AG.

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, the Department of Defense, or the US government.

Reprints or correspondence: Dr. Bernd Jilma, Dept. of Clinical Pharmacology, Medical University of Austria, Waehringerguertel 18-20, Vienna 1090, Austria (Bernd.Jilma@meduniwien.ac.at); or, Arthur G. Lyons, Dept. of Virus Diseases, Div. of Communicable Diseases and Immunology, Walter Reed Army Institute of Research, 503 Robert Grant Ave., Silver Spring, MD 20910 (arthur.lyons@na.amedd.army.mil).

The Journal of Infectious Diseases 2008; 198:493–9

0022-1899/2008/19804-0007$15.00
DOI: 10.1086/590116

hypersensitivity reactions often have a delayed onset after vaccination [8], the labeling for JE-VAX advises vaccinees to remain in areas where they have ready access to medical care for 10 days after receiving a dose of JE-VAX [9]. Gelatin stabilizers as contained in the JE-VAX formulation have been reported to cause severe hypersensitivity adverse effects such as anaphylaxis [10]. In addition, the mouse brain origin of the vaccine has raised concerns about possible vaccine-related neurologic adverse effects, although the content of neural tissue in the vaccine is minimized by purification and the concentration of myelin basic protein has been shown to be below the limit of detection (<2 ng/mL) [11–13]. Because of these issues, an expert committee recommended the establishment of guidelines for the development of second-generation JE vaccines and supported the evaluation of new JE vaccines by national regulatory agencies in a meeting sponsored by the World Health Organization (WHO) [14]. Safety concerns after the occurrence of a single case of disseminated encephalomyelitis have also led to the suspension of routine vaccination using the mouse brain–derived, inactivated JE vaccine in Japan in May 2005, even though a causal relationship between JE-VAX vaccination and the event was not demonstrated [15]. Eventually, JE-VAX production by the Japanese manufacturer was halted.

A new purified, inactivated JE virus vaccine, IC51, has been developed, which is manufactured in a Vero cell culture substrate [16, 17] in lieu of mouse brain tissue and without the bovine gelatin stabilizers and thimerosal that were present in JE-VAX. The safety and efficacy of IC51 have already been evaluated in 867 subjects in a randomized, controlled phase 3 trial [18]. A 2-dose schedule of IC51 was compared with JE-VAX given in the recommended 3-dose schedule. The safety profile of IC51 proved to be comparable to that of JE-VAX, and its local tolerability was superior to the licensed vaccine. The seroconversion rate of IC51 was 98%, compared with 95% for JE-VAX, on day 56, and geometric mean titers were 2-fold higher for IC51. Although this observed difference in geometric mean titers could partially be due to the use of the same JEV strain for vaccine production and immunization in the case of IC51 (JEV strain SA14-14-2 for both) as opposed to 2 different strains (Nakayama and SA14-14-2) in the case of JE-VAX, these results showed that IC51 is both immunogenic and safe. However, large-scale safety results for this vaccine were still required. The present study was designed to provide reliable information on rarer adverse events that might be related to vaccination with IC51.

METHODS

Study design. This trial was a randomized, placebo-controlled, double-blind study to distinguish between adverse reactions related and unrelated to the vaccine. Randomization (IC51 to placebo, 3:1) was stratified by center, with a total of 39 centers in Australia, Austria, Germany, Israel, New Zealand, Romania, and the United States. The trial was performed from October 2005 to March 2006. An interactive voice-response service was used to randomly allocate subjects to treatment groups. The protocol was approved by all of the institutional review boards of the study sites, by the US Food and Drug Administration, by the competent authorities in Europe, and by the regulatory authorities in Australia and New Zealand. Written informed consent was obtained from all participants before enrolment.

Table 1. Demographic characteristics: safety population.

Parameter	IC51 (n = 1993)	Placebo (n = 657)
Age		
No. with available data	1993	657
Median (range), years	29 (18–86)	28 (18–76)
Weight		
No. with available data	1992	657
Median (range), kg	72 (39–172)	72 (44–147)
Sex, no. (%)		
Male	905 (45)	279 (42)
Female	1088 (55)	378 (58)
Race, no. (%)		
White	1837 (92)	593 (90)
Asian	33 (2)	16 (2)
Black	66 (3)	25 (4)
Other	57 (3)	23 (4)

Study population. The study population consisted of healthy male and female subjects aged at least 18 years. Inclusion criteria were as follows: provision of written informed consent by the subject, and female subjects had to be of nonchildbearing potential or to have a negative urine pregnancy test result before each vaccination. Exclusion criteria comprised the following: previous JE vaccination; use of any investigational or nonregistered drug or vaccine other than the study vaccine during the study period or within 30 days preceding the first dose of the test vaccine; administration of chronic immunosuppressants or other immune-modifying drugs within 6 months of vaccination; and a history of severe hypersensitivity reactions to any component of the JE vaccine.

Demographics. Demographic data were comparable between groups (table 1). The flow of patients is depicted in figure 1. The safety population comprised 2650 subjects, 1993 in the IC51 group and 657 in the placebo group. The proportion of white subjects was highest in Europe (98%, compared with 89% in Australia and 77% in the United States). There was a lower proportion of subjects of African descent in Australia (0%) and Europe (0.5%) than in the United States (13%).

Study objectives. The primary end point was to investigate the rate of serious adverse events following immunization (SAEFI) and medically attended AEFI as a subgroup of all AEFI from the first dose up to 4 weeks after the last vaccination (day 56), compared with that after administration of placebo. Medi-

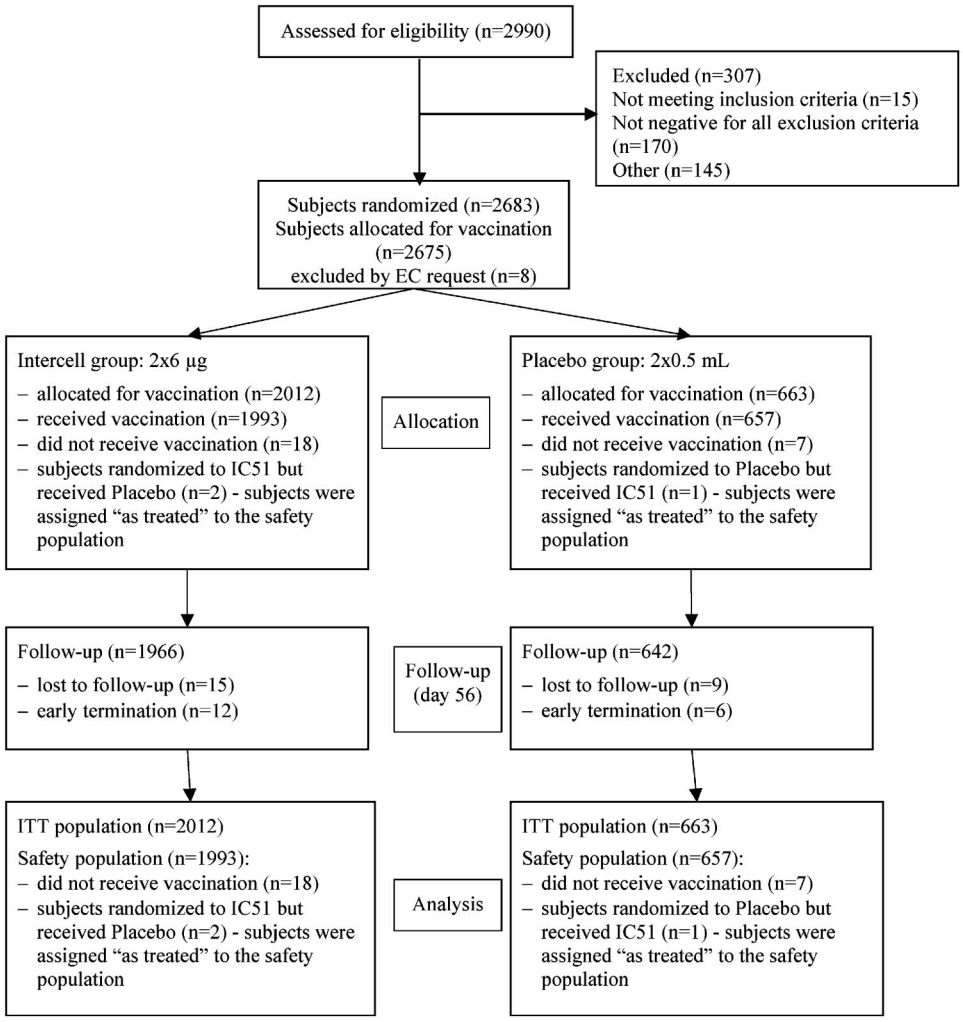

Figure 1. Patient flow. EC, institutional ethics committee in Berlin.

cally attended AEFI were all adverse events for which a subject sought medical care (i.e., visited a doctor's office, an emergency service, or a hospital) and did not self-medicate only.

Secondary objectives included the evaluation of safety laboratory parameters (hematology, serum chemistry, and urinalysis) and the intensity, kind, and duration of local AEFI. Subjects maintained a daily diary for 7 days after each injection. The presence or absence of pain, itching, tenderness, hardening, redness, and swelling were recorded, and dimensions of the hardness, swelling, and redness were measured when present. The presence of the following systemic symptoms was also recorded: headache, muscle pain, fever, flu-like symptoms, nausea, vomiting, rash, and excessive fatigue. Subjects were examined on days 28 and 56, when their diaries were collected and information on any other adverse events was recorded.

Intensity grades were applied to local injection-site redness, swelling, and fever, which were classified as mild-moderate or severe according to WHO definitions. For a standardized approach, the National Cancer Institute common toxicity criteria for adverse events (version 3.0; 2003) were used as a clinical and laboratory adverse event grading scale for assessments of toxicity.

Study vaccine and placebo. The Intercell JE vaccine IC51 is a purified, inactivated JEV vaccine strain. Clinical lots ICB05/501 and ICB05/502 were developed and manufactured by Intercell Biomedical (Livingston, Scotland). The attenuated SA14-14-2 vaccine strain, adapted to primary canine kidney cells [19], was further passaged in Vero cells [16, 17]. This vaccine is prepared by using a purification and inactivation process consistent with current good manufacturing practices.

The finished product contains aluminum hydroxide as adjuvant and was administered intramuscularly (im) as a single dose in syringes. A single dose of IC51 contained 6 μg of purified virus adsorbed to 0.1% aluminum hydroxide in 0.5 mL. The placebo was a PBS solution (0.5 mL) containing 0.1% aluminum hydroxide as an adjuvant. A label covered the entire body of the syringe, to keep both the users and the vaccinees blinded to the study product. There were no visual differences between syringes with vaccine or placebo.

Table 2. Serious adverse events following immunization (SAEFI) for the total study period: safety population.

System organ class, preferred term	No. (%) IC51 (*n*=1993)	Placebo (*n* = 657)
Any SAEFI	10 (0.5)	6 (0.9)
Cardiac disorders	0 (0)	1 (0.2)
Acute coronary syndrome	0 (0)	1 (0.2)
Gastrointestinal disorders	1 (0.1)	1 (0.2)
Proctalgia	0 (0)	1 (0.2)
Rectal hemorrhage	1 (0.1)	0 (0)
General disorders and administration site conditions	1 (0.1)	0 (0)
Chest pain	1 (0.1)	0 (0)
Infections and infestations	2 (0.1)	2 (0.3)
Abscess limb	1 (0.1)	0 (0)
Appendicitis	1 (0.1)	2 (0.3)
Injury, poisoning, and procedural complications	3 (0.2)	0 (0)
Face injury	1 (0.1)	0 (0)
Facial bones fracture	1 (0.1)	0 (0)
Ulna fracture	1 (0.1)	0 (0)
Renal and urinary disorders	0 (0)	1 (0.2)
Calculus urinary	0 (0)	1 (0.2)
Reproductive system and breast disorders	2 (0.1)	0 (0)
Adnexa uteri pain	1 (0.1)	0 (0)
Ovarian cyst rupture	1 (0.1)	0 (0)
Ovarian torsion	1 (0.1)	0 (0)
Skin and subcutaneous tissue disorders	1 (0.1)	0 (0)
Dermatomyositis	1 (0.1)	0 (0)
Vascular disorders	0 (0)	1 (0.2)
Circulatory collapse	0 (0)	1 (0.2)

Subjects assigned to IC51 received 6 μg im in 0.5 mL on days 0 and 28. Subjects assigned to placebo received the PBS solution containing 0.1% aluminum hydroxide in 0.5 mL administered im with 2 injections on days 0 and 28. Subjects returned for follow-up 56 days after the initial inoculation.

Statistics. The sample size of this study was determined to fulfill regulatory prerequisites for submitting all clinical trial data for licensure application. A sample size of 2010 subjects in the IC51 group results in a power of 86.6% to observe 1 or more adverse events with an anticipated incidence rate of 0.1%. Additionally, the randomized comparison of 2010 vs. 663 subjects would allow for a power of 80% to detect a difference in event rates of 2.8% (vaccine) vs. 1.0% (placebo) by a 2-sided χ^2 test without continuity correction and at a significance level of 5%.

RESULTS

The primary objective of this study was to compare the rate of SAEFI and medically attended AEFI between the vaccine and placebo groups up to 4 weeks after the last vaccination (day 56). The frequency of SAEFI for the total study period is summarized in table 2. There were a total of 16 subjects who experienced SAEFI during the total study period, 10 (0.5%) in the vaccine group and 6 (0.9%) in the placebo group. SAEFI occurred in 0.3% of subjects overall in any system organ class (SOC). Only appendicitis ($n = 2$) occurred in >1 subject. None of the SAEFI was considered to be related to study vaccination. A total of 17 subjects, 12 (0.6%) in the IC51 group and 5 (0.8%) in the placebo group, terminated the study prematurely due to treatment-emergent adverse events. Only 2 of those events in the IC51 group were severe in intensity (gastroenteritis and rash), and 8 of them (headache [2 events], influenza-like illness, allergic dermatitis, injection site pain, nausea, fatigue, and rash) were considered to be at least possibly related to study treatment. In the placebo group, 3 treatment-emergent adverse events were severe in intensity (nuchal rigidity, migraine, and acute coronary syndrome), and 1 (nuchal rigidity) had a possible relationship to study treatment. No deaths occurred during this study.

The overall frequency of AEFI requiring medical attention was similar between the 2 groups (12.7% for IC51 and 12.2% for placebo) (table 3), and none of the individual differences between IC51 and placebo was statistically significant or clinically relevant. The most common SOC for medically attended AEFI was infections and infestations (4.9% and 4.1% for IC51 and placebo, respectively). All other SOCs were detected in <2% of subjects overall. As expected, the most common AEFI requiring medical attention were headache (0.9% and 1.1% for IC51 and

Table 3. Medically attended adverse events following immunization (AEFI) for the total study period: safety population.

System organ class, preferred term	No. (%) IC51 (*n* = 1993)	Placebo (*n* = 657)
Any AEFI	254 (12.7)	80 (12.2)
General disorders and administration site conditions	28 (1.4)	11 (1.7)
Fatigue	4 (0.2)	5 (0.8)
Influenza-like illness	19 (1.0)	6 (0.9)
Pyrexia	5 (0.3)	3 (0.5)
Infections and infestations	98 (4.9)	27 (4.1)
Bronchitis	10 (0.5)	0 (0)
Cystitis	6 (0.3)	1 (0.2)
Nasopharyngitis	11 (0.6)	3 (0.5)
Sinusitis	9 (0.5)	2 (0.3)
Upper respiratory tract infection	7 (0.4)	2 (0.3)
Urinary tract infection	11 (0.6)	3 (0.5)
Musculoskeletal and connective tissue disorders	22 (1.1)	6 (0.9)
Myalgia	8 (0.4)	1 (0.2)
Nervous system disorders	32 (1.6)	11 (1.7)
Headache	18 (0.9)	7 (1.1)

Table 4. Frequency of common adverse events following immunization (AEFI) for the total study period: safety population.

System organ class, preferred term	No. (%) IC51 (n = 1993)	No. (%) Placebo (n = 657)
Any AEFI	1173 (58.9)	372 (56.6)
Gastrointestinal disorders	200 (10.0)	62 (9.4)
Diarrhoea	31 (1.7)	7 (1.1)
Nausea	131 (6.6)	49 (7.5)
Vomiting	27 (1.4)	11 (1.7)
General disorders and administration site conditions	444 (22.3)	151 (23.0)
Fatigue	227 (11.4)	77 (11.7)
Influenza-like illness	248 (12.4)	78 (11.9)
Pyrexia	64 (3.2)	20 (3.0)
Infections and infestations	276 (13.8)	87 (13.2)
Nasopharyngitis	94 (4.7)	26 (4.0)
Rhinitis	29 (1.5)	9 (1.4)
Upper respiratory tract infection	33 (1.7)	13 (2.0)
Injury, poisoning, and procedural complications	44 (2.2)	9 (1.4)
Investigations	40 (2.0)	12 (1.8)
Musculoskeletal and connective tissue disorders	359 (18.0)	120 (18.3)
Back pain	25 (1.3)	7 (1.1)
Myalgia	311 (15.6)	102 (15.5)
Nervous system disorders	585 (29.4)	181 (27.5)
Headache	559 (28.0)	173 (26.3)
Respiratory, thoracic, and mediastinal disorders	83 (4.2)	30 (4.6)
Cough	23 (1.2)	8 (1.2)
Pharyngolaryngeal pain	32 (1.6)	9 (1.4)
Skin and subcutaneous tissue disorders	53 (2.7)	20 (3.0)
Rash	26 (1.3)	10 (1.5)

placebo, respectively) and influenza-like illness (1.0% and 0.9%). In each group, 2% of subjects experienced medically attended AEFI that were possibly or probably related to study treatment (or missing causality). The most common medically attended AEFI considered to be treatment related were headache (0.4% for IC51 and 0.3% for placebo) and influenza-like illness (0.3% in each group).

Any AEFI was seen in 58.9% of subjects in the IC51 group and in 56.6% of subjects in the placebo group (table 4). The most common AEFI reported were headache (28.0% and 26.3% for IC51 and placebo, respectively), myalgia, influenza-like illness, and fatigue. The intensity of AEFI was classified as mild in 34% of subjects in both groups. Moderate AEFI occurred in 20% of subjects in the IC51 group and 17% of subjects in the placebo group. AEFI were graded as severe in 5% of both groups.

AEFI that were classified as possibly or probably related to study treatment (total number, including AEFI with or without medical attention) occurred in 39% of subjects in both groups. The most common treatment-related AEFI were headache (21.5% and 20% of subjects for IC51 and placebo, respectively), myalgia (14% for both IC51 and placebo), fatigue (9% for IC51 and 10% for placebo) and influenza-like illness (9% for both IC51 and placebo).

The local tolerability profiles as reported in the subject diaries were comparable between the IC51 and placebo groups, although, on day 1 after both vaccinations, the incidence of all symptoms tended to be slightly higher in the IC51 group than in the placebo group, with the exception of itching after the first and second vaccinations as well as hardening, swelling, and redness after the second vaccination (table 5). Local symptoms were most common immediately after vaccination and decreased over time in both treatment groups.

Two cases of urticaria were noted during the study: 1 case of generalized urticaria (affecting the face, breast, arms, and abdomen) in the IC51 group, which occurred 8 days after the second vaccination, and 1 case of localized urticaria on both inner thighs 6 days after the second vaccination in the placebo group. Only the event in the placebo group was considered to be possibly related to study medication, whereas the event in the IC51 group was assessed as being unlikely related to vaccination. This case of urticaria in the IC51 group was of moderate intensity; it was treated with cetirizine hydrochloride (Zyrtec) and resolved after 3 days. Angioedema was not observed.

Table 5. Subject diary local tolerability 1 day after vaccination: safety population.

Symptom reported, vaccination	No. (%) IC51 (n = 1993)	No. (%) Placebo (n = 657)
Pain		
First	369 (18.5)	102 (15.5)
Second	210 (10.5)	62 (9.4)
Itching		
First	15 (0.8)	11 (1.7)
Second	15 (0.8)	8 (1.2)
Tenderness		
First	414 (20.8)	114 (17.4)
Second	295 (14.8)	79 (12.0)
Hardening		
First	55 (2.8)	24 (3.7)
Second	49 (2.5)	12 (1.8)
Swelling		
First	24 (1.2)	14 (2.1)
Second	28 (1.4)	3 (0.5)
Redness		
First	65 (3.3)	23 (3.5)
Second	58 (2.9)	10 (1.5)

Review of laboratory data, vital signs, and results of physical examination did not indicate any differences between the 2 groups.

DISCUSSION

JE is a major health threat in countries of endemicity in Southeast Asia. The currently licensed vaccines for the prevention of JEV infection in people living in or traveling to those countries are mainly derived from mouse brain. Although effective, their use has been hampered due to a suboptimal safety profile after the most widely used JE vaccine, JE-VAX, had been used for several years. Serious hypersensitivity reactions—mainly urticaria and angioedema [8,9,20–25]—have been reported, and the concern that rare neurologic side effects might be associated with the mouse brain-derived vaccines has been raised [7]. Cases of neurological events, such as encephalitis, encephalopathy, seizures, and peripheral neuropathy [20–22], have been reported after vaccination with JE-VAX. Although these neurological events occurred very rarely (1 in 2.3 million vaccinees) [26], they were of particular concern to physicians. In a study conducted by the Centers for Disease Control and Prevention, hives and facial swelling were reported in 0.2% and 0.1% of JE-VAX vaccinees, respectively [9]. Furthermore, 3 vaccine recipients developed respiratory distress, and in several other cases distress or collapse caused by hypotension resulted in hospitalization. Eventually, these safety issues led to cessation of JE-VAX production by the Japanese manufacturer.

An alternative vaccine using the live attenuated vaccine strain SA14-14-2 [27–29] has been produced in China for several years now and is widely used in China, India, and Nepal. Despite good experiences in these countries, broader international use and licensure has been difficult because of issues concerning the vaccine's manufacturing process. Thus, an alternative vaccine with noninferior safety and immunogenicity profiles and perhaps a favorable dosing schedule is urgently needed.

The Intercell JE vaccine IC51 is designed to satisfy these needs. It was derived using Vero cells as substrate and employing procedures that had been used extensively in the development of other viral vaccines. Its efficacy has clearly been shown to be at least noninferior to that of JE-VAX in a previous phase 3 study [18], and, instead of the inconvenient JE-VAX immunization schedule of 3 vaccinations over 1 month, only 2 doses of IC51 were required to induce a comparative protective neutralizing antibody response. The overall IC51 safety profile was excellent in that previous study, with an incidence of local tolerability events lower than for JE-VAX.

The present double-blind, randomized, placebo-controlled trial was a safety study designed to investigate possible rare adverse events with an incidence of 0.1% that could be related to vaccination with IC51. The low adverse event profile observed previously for the vaccine [18] was confirmed in this study. The test vaccine demonstrated a safety and tolerability profile similar to that of placebo. SAEFI occurred rarely in both groups. These SAEFI were events that also occur in the general population. Thus, none of these SAEFI was considered to be related to either IC51 or placebo. Also, analysis of medically attended AEFIs did not reveal any rare events. The most commonly observed treatment-related adverse events were headache, myalgia, fatigue, and influenza-like illness, which are typical for the cold and flu season in the Northern Hemisphere, when this trial was performed; hence, the similar distribution observed between IC51 and placebo. Analysis of laboratory data and vital signs did not indicate any safety issues in comparison with placebo. The local tolerability profile as reported in the subject diaries was similar between IC51 and placebo.

Of note is the low incidence of allergic reactions observed in this study. Only a single case of urticaria occurred among 1993 subjects receiving IC51, which was well below the hypersensitivity reaction rate (including generalized urticaria and angioedema) reported for JE-VAX (62 per 10,000 vaccinees) [30]. The observed event occurred 8 days after the second vaccination; although this is what is typically seen for vaccine-induced urticaria, the event was considered to be unlikely related to study treatment by the investigator. Given that there was also 1 case of possibly related urticaria in the placebo group 6 days after the second vaccination, IC51 was not inferior to placebo in the incidence of hypersensitivity events. The lack of thimerosal and gelatin in the vaccine preparation provides a possible explanation for the low number of such reactions, compared with that for JE-VAX. However, a direct comparison of the frequency of adverse events with that in previous trials of SA14-14-2–based vaccines is difficult because of differences in the assessment of AEFI and the still-limited number of subjects in the present trial. Very rare adverse events according to the WHO definition (<1: 10,000) are detectable only in large postlicensure surveillance studies. However, the present randomized, controlled clinical safety trial had a very positive outcome, with a safety and tolerability profile for IC51 similar to that for placebo. These data, together with the immunogenicity data from the pivotal comparative phase 3 trial conducted recently [18], are encouraging. The results suggest that IC51 can be considered a good candidate for replacing the currently used JE vaccine and can form the basis of application for licensure of this vaccine.

Acknowledgments

We are indebted to all trial sites, to all the staff members performing the trial, and to all the participating subjects.

References

1. Advisory Committee on Immunization Practices. Prevention and control of influenza: part I, vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep **1993**; 42(RR-6):1–14.

2. Simpson T, Meiklejohn G. Sequelae of Japanese B encephalitis. Am J Trop Med Hyg **1947**; 27:727–31.
3. Oya A, Kurane I. Japanese encephalitis for a reference to international travelers. J Travel Med **2007**; 14:259–68.
4. Solomon T, Vaughn DW. Pathogenesis and clinical features of Japanese encephalitis and West Nile virus infections. Curr Top Microbiol Immunol **2002**; 267:171–94.
5. Solomon T. Control of Japanese encephalitis—within our grasp? N Engl J Med **2006**; 355:869–71.
6. Tsarev SA, Sanders ML, Vaughn DW, Innis BL. Phylogenetic analysis suggests only one serotype of Japanese encephalitis virus. Vaccine **2000**; 18(Suppl 2):36–43.
7. Centers for Disease Control and Prevention. Travelers' health: yellow book. Chapter 4. Prevention of specific infectious diseases: Japanese encephalitis. **2007**. Available at: http://wwwn.cdc.gov/travel/yellowBookCh4-JapaneseEncephalitis.aspx. Accessed 11 January 2008.
8. Berg SW, Mitchell BS, Hanson RK, et al. Systemic reactions in U.S. Marine Corps personnel who received Japanese encephalitis vaccine. Clin Infect Dis **1997**; 24:265–6.
9. Summary of product characteristics: JE-VAX.
10. Kamin W, Staubach P, Klär-Hlawatsch B, Erdnüss F, Knuf M. Anaphylaxis after vaccination due to hypersensitivity to gelatin. Klin Padiatr **2006**; 218:92–4.
11. Robinson HC, Russell ML, Csokonay WM. Japanese encephalitis vaccine and adverse effects among travellers. Can Dis Wkly Rep **1991**; 17: 173–4, 7.
12. World Health Organization. WHO report of the bi-regional meeting on Japanese encephalitis (WHO SEA/WPR and PATHs JE Project). Bangkok, Thailand. **2005**.
13. RxList: the Internet drug index. San Clemente. Je-Vax. Available at: http://www.rxlist.com/cgi/generic/jevax.htm. Accessed 10 January 2008.
14. Tsai TF. New initiatives for the control of Japanese encephalitis by vaccination: minutes of a WHO/CVI meeting, Bangkok, Thailand, 13–15 October 1998. Vaccine **2000**; 18(Suppl 2):1–25.
15. Global Advisory Committee on Vaccine Safety, 9–10 June 2005. Wkly Epidemiol Rec **2005**; 80(28):242–8. Available at: http://www.who.int/wer/2005/wer8028.pdf. Accessed 11 January 2008.
16. Srivastava AK, Putnak JR, Lee SH, Hong SP, Moon SB, Barvir DA, et al. A purified inactivated Japanese encephalitis virus vaccine made in Vero cells. Vaccine **2001**; 19:4557–65.
17. Lyons A, Kanesa-thasan N, Kuschner RA, et al. A phase 2 study of a purified, inactivated virus vaccine to prevent Japanese encephalitis. Vaccine **2007**; 25:3445–53.
18. Tauber E, Kollaritsch H, Korinek M, et al. Safety and immunogenicity of a Vero-cell-derived, inactivated Japanese encephalitis vaccine: a non-inferiority, phase III, randomised controlled trial. Lancet **2007**; 370:1847–53.
19. Eckels KH, Yu YX, Dubois DR, Marchette NJ, Trent DW, Johnson AJ. Japanese encephalitis virus live-attenuated vaccine, Chinese strain SA14-14-2; adaptation to primary canine kidney cell cultures and preparation of a vaccine for human use. Vaccine **1988**; 6:513–8.
20. Plesner AM, Ronne T. Allergic mucocutaneous reactions to Japanese encephalitis vaccine. Vaccine **1997**; 15:1239–43.
21. Plesner A, Ronne T, Wachmann H. Case-control study of allergic reactions to Japanese encephalitis vaccine. Vaccine **2000**; 18:1830–6.
22. Takahashi H, Pool V, Tsai TF, Chen RT. Adverse events after Japanese encephalitis vaccination: review of post-marketing surveillance data from Japan and the United States. The VAERS Working Group. Vaccine **2000**; 18:2963–9.
23. Andersen MM, Ronne T. Side-effects with Japanese encephalitis vaccine. Lancet **1991**; 337:1044.
24. Ruff TA, Eisen D, Fuller A, Kass R. Adverse reactions to Japanese encephalitis vaccine. Lancet **1991**; 338:881–2.
25. Sakaguchi M, Inouye S. Two patterns of systemic immediate-type reactions to Japanese encephalitis vaccines. Vaccine **1998**; 16:68–9.
26. Ohtaki E, Murakami Y, Komori H, Yamashita Y, Matsuishi T. Acute disseminated enceahalomyelitis after Japanese B encephalitis vaccination. Pediatr Neurol **1992**; 8:137–9.
27. Hennessy S, Liu Z, Tsai TF, et al. Effectiveness of live-attenuated Japanese encephalitis vaccine (SA14-14-2): a case-control study. Lancet **1996**; 347:1583–6.
28. Liu ZL, Hennessy S, Strom BL, et al. Short-term safety of live attenuated Japanese encephalitis vaccine (SA14–14-2): results of a randomized trial with 26,239 subjects. J Infect Dis **1997**; 176:1366–9.
29. Sohn YM, Park MS, Rho HO, Chandler LJ, Shope RE, Tsai TF. Primary and booster immune responses to SA14–14-2 Japanese encephalitis vaccine in Korean infants. Vaccine **1999**; 17:2259–64.
30. Centers for Disease Control and Prevention. Inactivated Japanese encephalitis virus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep **1993**; 42(RR-1):1–15.