

NEW JAPANESE ENCEPHALITIS VACCINE

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UN NOUVEAU VACCIN CONTRE L'ENCÉPHALITE JAPONAISE

RÉSUMÉ • Le virus de l'encéphalite japonaise (VEJ) est un flavivirus transmis par certains moustiques. L'encéphalite japonaise est la plus fréquente des encéphalites en Asie du Sud-Est, responsable d'environ 50 000 cas déclarés et 10 000 décès par an, principalement chez les enfants et les personnes âgées [Burke 1988; OMS 2006; Solomon 2003]. Parmi les individus qui développent des symptômes de l'encéphalite japonaise le taux de mortalité s'élève à 20-30%, et à peu près 50% conservent des séquelles neuropsychiatriques permanentes [Solomon 2006]. Actuellement il n'existe aucun traitement efficace contre l'encéphalite japonaise. Toute personne qui voyage ou séjourne dans les zones endémiques ou épidémiques, particulièrement en période de transmission, s'expose au risque de contracter la maladie. Le personnel qui manipule le VEJ dans les laboratoires de recherche ou de l'industrie est également exposé. La fabrication du JE-VAX[®], qui est le seul vaccin autorisé aux États-Unis, a été arrêtée et les stocks encore disponibles seront épuisés mi-2008.

MOTS-CLÉS • Encéphalite japonaise - Vaccin - Cellule Vero.

ABSTRACT • Japanese encephalitis virus (JEV) is a mosquito-borne flavivirus. Japanese encephalitis is the most common encephalitis in eastern and southern Asia, with approximately 50,000 cases and 10,000 deaths reported annually, primarily in children and the elderly [Burke 1988; WHO 2006; Solomon 2003]. In symptomatic individuals who develop Japanese encephalitis (JE), 20-30% are likely to die and approximately 50% are left with permanent neuropsychiatric sequelae [Solomon 2006]. Currently, there is no treatment available for JE. Persons who plan to reside in or travel to areas where JE is endemic or epidemic, especially during the transmission season, are at risk of JEV infection. Persons who work with JEV in laboratories and in industry are also at risk. JE-VAX[®], the only licensed JEV vaccine in the US, is no longer in production, and remaining supplies will be depleted mid-2008.

KEY WORDS • Japanese Encephalitis - Vaccine - Vero cell.

Several first generation, inactivated JE vaccines have been produced by Japan, Korea, Vietnam and other national manufacturers for decades, mostly using mouse brains as a substrate for growth of the virus. More recently, Chinese manufacturers have produced inactivated and live virus vaccines, predominantly using a primary hamster cell substrate [Bista 2001, Hennessy 1996, Ohrr 2005]. However, use of these vaccines is predominantly limited to domestic supply.

The only JE vaccine in use outside Asia is the formalin-inactivated, mouse brain derived vaccine JE-VAX[®], which is currently licensed for the vaccination of travelers and military personnel against JE in the US, Canada, Israel and Australia.

IC51 is a purified inactivated vaccine, containing the JE strain SA₁₄-14-2 and manufactured by Intercell Biomedical Ltd, Livingston, U.K. This attenuated SA₁₄-14-2 vaccine strain was adapted to growth in Vero cells. The vaccine was prepared by using a purification and inactivation process consistent with current good manufacturing practices

(cGMP). The finished product does not contain thimerosal. One dose of IC51 contains 6 mcg of purified and inactivated virus adsorbed to 0.1% aluminum hydroxide. The vaccine is injected i.m. into the deltoid muscle on days 0 and 28.

A new JE vaccine with a good immunogenicity and safety profile would provide an alternative to the licensed JE vaccine, and will meet an unmet medical need when this vaccine is no longer available. IC51 does not contain stabilizers or preservatives (which may be associated with allergic responses [Georgitis 2001, Pool 2002, Sakaguchi 2000]) and is produced using a cell culture substrate in lieu of brain tissue. IC51 also has a more convenient two-dose vaccination schedule compared to the three-dose schedule of JE-VAX[®].

CLINICAL DEVELOPMENT PROGRAM

The classical approach of a field efficacy study is not possible for new JE vaccines for a number of reasons. First, a licensed vaccine was available in the U.S. in adequate supply until very recently. However, even in the absence of a licensed vaccine, the incidence of overt

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disease in travellers to JE endemic areas is too low to conduct a placebo-controlled efficacy trial in this population. In addition, in general, effective vaccines are available and recommended for populations in endemic countries precluding placebo-controlled trials in those populations. Even if trials were feasible in endemic areas, the rate may be too low to conduct a placebo-controlled trial. Thus, for assessment of IC51, comparative immunogenicity was used to infer clinical efficacy. Neutralizing antibodies are considered to be the best markers of protection against JEV and it is widely accepted that a JEV neutralizing antibody threshold of $\geq 1:10$ by PRNT50 is protective (PRNT50 is defined as the serum dilution giving a 50% reduction of plaque counts in a plaque reduction neutralization test). These assumptions are supported by non-clinical studies with IC51 and all clinical studies with IC51 have used immunogenicity (measured using PRNT) as an indicator of clinical efficacy.

CLINICAL STUDY PROGRAM

The pivotal immunogenicity study was a randomized, active-controlled, modified double-blind, phase 3 study to demonstrate non-inferiority of IC51 against JE-VAX[®] in terms of immunogenicity.

The pivotal safety study was a randomized, placebo-controlled, double-blind, phase 3 study to assess the safety and tolerability of IC51.

A supporting follow-up study investigates the persistence of immunogenicity of IC51 in subjects from the two pivotal studies up to 60 months after the first vaccination. This follow-up study is currently ongoing; 12-month data are available.

A randomized, active-controlled, single-blind phase 3 study to demonstrate the non-inferiority of IC51+HAVRIX[®] 1440 (Hepatitis A vaccine) compared to each individual vaccine.

Blinded safety data are available from two further phase 3 studies. A supporting study to compare a compressed immunization regimen of IC51 with the standard regimen, and a long-term, follow-up study to assess the persistence of immunogenicity of IC51 in subjects from the compressed immunization study up to 24 months after the first vaccination.

Across the phase 2 and 3 clinical studies 3656 subjects were exposed to IC51, 657 subjects were exposed only to placebo (intramuscularly), 456 subjects were exposed to JE-VAX[®] and 65 subjects were exposed to HAVRIX[®] 1440. The subject population for all studies included healthy volunteers aged 18 years or older. The subject population was taken from Europe, the United States of America, Australia, New Zealand or Israel. Combined safety data are also available from the phase 3 studies in the 6-month pooled safety population (N=4715, including 3558 subjects who received at least one IC51 vaccination).

IMMUNOGENICITY RESULTS

Pivotal Immunogenicity Study

• Immunogenicity at Day 56

Non-inferiority of IC51 to JE-VAX[®] was demonstrated in the pivotal immunogenicity study IC51-301, as assessed by the co-primary endpoints of SCR and GMT at Day 56. JE-VAX[®] is a licensed vaccine against JEV with proven efficacy in the field.

At Day 56, the SCR was 98% in the IC51 group versus 95% in the JE VAX[®] group, and the GMT was more than twice as high in the IC51 group (244.0) compared to the JE VAX[®] group (102.0). The SCR risk difference estimate for IC51 minus JE-VAX[®] was 1.05% (95% CI: -1.33%, 3.43%) and the GMT ratio for IC51/JE-VAX[®] was 2.33 (95% CI: 1.97, 2.75).

Since the lower 95% confidence interval (CI) limit of the SCR risk difference estimate (-1.33%) was above the pre-defined non-inferiority limit of -10%, and the lower 95% CI limit for the GMT ratio (1.97) was above the predefined limit of 1/1.5, non-inferiority of IC51 to JE-VAX[®] was demonstrated for both of the co-primary endpoints.

• Long-term Immunogenicity

The persistence of immunogenicity of IC51 was demonstrated in an ongoing study to Month 12 after vaccination. Data for the primary endpoint in this study (SCR at Month 36 after vaccination) are not yet available.

The percentage of subjects with JEV neutralizing antibody titer of $\geq 1:10$ were assessed at 2, 6 and 12 months after the first IC51 vaccination.

In total, 98.9% of subjects had seroconverted at Month 2 (95% CI: 96.06%, 99.70%). At Month 6, 95.0% of subjects had JEV neutralizing antibody titer of $\geq 1:10$ (95% CI: 90.82%, 97.36%). At Month 12, the percentage of subjects with JEV neutralizing antibody titer of $\geq 1:10$ had decreased to 83.4% (95% CI: 77.33%, 88.14%).

At Month 2, the GMT was 310.8 (95% CI: 268.76, 359.44) in the ITT population; this decreased to 83.5 (95% CI: 70.89, 98.38) at Month 6, and to 41.2 (95% CI: 34.39, 49.33) at Month 12.

The GMT decline following IC51 vaccination (3.7-fold from Day 56 to 6 months; 7.5-fold from Day 56 to 1 year) is expected after immunization with an inactivated vaccine and compares well with data from other inactivated JE vaccines.

At Month 2, the SCRs were similar between the treatment groups; 98.9% for the IC51 group and 97.6% for the JE-VAX[®] group, respectively. At Month 6, 95.0% of subjects in the IC51 group had neutralizing antibody titer of $\geq 1:10$ compared to 74.4% of subjects in the JE-VAX[®] group (risk difference estimate for IC51 minus JE-VAX[®] 17.81%, 95% CI: 6.75%, 28.86%).

At Month 2, GMT was more than three times higher in the IC51 group (310.8) than in the JE-VAX[®] group (99.5)

(GMT ratio estimate [IC51/JE-VAX®]: 2.36, 95% CI: 1.79, 3.11). GMTs decreased in both treatment groups by Month 6, but still remained more than twice as high in the IC51 group (83.5) than in the JE-VAX® group (34.1) (GMT ratio estimate: 2.26, 95% CI: 1.61, 3.17).

VACCINE -VACCINE INTERACTIONS

This Phase 3 trial investigated the immunogenicity and safety of co-administered IC51 with another typical travellers vaccine, HAVRIX® 1440 (Hepatitis A Vaccine, Inactivated).

This was approached by demonstration of non-inferiority of co-administered IC51 + HAVRIX® vs. IC51 + placebo vs. Havrix® + placebo in terms of GMT for anti JEV neutralizing antibody at Day 56 and HAV antibody at day 28.

Immune response was assessed by determination of PRNT50 for JEV antibodies and anti HAV (Hepatitis A Virus) antibodies 4 weeks after the last vaccination. SCR was defined by percentage of subjects with $\geq 1:10$ anti-JEV antibody titer (PRNT); and anti HAV antibodies ≥ 20 mIU/mL.

GMT for anti-JEV neutralizing antibodies at Day 56 was 202.7 for subjects treated with IC51+HAVRIX®, and 192.2 for subjects receiving IC51+placebo.

At Day 28 GMT for anti-HAV antibody (as measured using ELISA) was 150.3 mIU for IC51 + HAVRIX® group and 124.0 mIU for HAVRIX® + placebo group.

Co-vaccination of IC51 and HAVRIX® was demonstrated to be non-inferior to each individual vaccine in terms of GMT for anti-JEV neutralizing antibody at Day 56 and GMT for anti-HAV (Hepatitis A virus) antibody at Day 28. For both comparisons non-inferiority was demonstrated, as the lower bound of the 95% CI for the GMT ratio was greater than the predefined non-inferiority margin of 0.5 (0.8).

SAFETY OF THE NEW VACCINE

All clinical studies reported adverse events following immunization (AEFIs). In the pivotal safety study the primary safety endpoints were the rates of serious adverse events (SAEs) and medically attended AEFIs at Day 56.

Tolerability was assessed in all phase 3 studies in which treatment was administered. Subjects were asked to record in a diary the occurrence of specific symptoms for a total of 7 consecutive days after each vaccination, starting with the day of vaccination (Days 0 to 6). The local symptoms recorded were pain, itching, tenderness, hardening, swelling and redness. The systemic symptoms recorded were headache, muscle pain, fever, flu-like symptoms, nausea, vomiting, rash and excessive fatigue.

The assessments were recorded once daily into a subject diary. The subjects were also asked to report any other AEFIs at each visit. Local and systemic tolerability symptoms recorded in the subject diary were analyzed separately

and systemic symptoms were also recorded as AEFIs. In the concomitant vaccination study, systemic tolerability was assessed by a general question and all systemic tolerability symptoms were recorded as AEs rather than in separate tolerability summaries.

Two grading scales were used for the assessment of local tolerability; one of them was based on the FDA/CBER draft Guidance for Industry «Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials». The grading scales were not reconciled and give complementary information.

Particular emphasis is given to the pivotal safety study and 6-month pooled safety population.

Local tolerability symptoms were more common after Vaccination 1 than after Vaccination 2. Over the 7-day period following the first and second vaccinations (Days 0 to 6 and Days 28 to 34, respectively), local symptoms were reported by 48.5% and 32.6% of subjects, respectively, in the IC51 group, and in 47.7% and 32.2% of subjects, respectively, in the placebo group. There was no statistically significant difference between the two groups in the incidence of any local tolerability symptom over the 7-day period following either vaccination, with the exception of tenderness after the second vaccination (IC51: 22.5% of subjects; placebo: 18.1%; $p=0.0193$).

Within each 7-day period, local symptoms were most commonly reported on Day 0 after vaccination.

POOLED SAFETY ANALYSIS: 6 MONTHS SAFETY POPULATION

In the 6-month pooled safety analysis, AEFIs were summarized up to 6 months after the first vaccination and tolerability (recorded in subject diaries) was summarized for Days 0 to 6 after each vaccination. Safety data were generally analyzed descriptively.

In general, local tolerability of IC51 was comparable to placebo, and appeared to be more favorable compared with JE-VAX®, particularly with regard to itching, hardening, swelling and redness.

Local tolerability for the 7-day period after vaccination is also presented by vaccination (Vaccination 1=Day 0 or Vaccination 2=Day 28) and for any vaccination.

The incidence of local symptoms within 7 days after Vaccination 1 was comparable between IC51, placebo and JE-VAX® (47.9%, 47.6% and 45.7%, respectively). After the Vaccination 2, the incidence of local symptoms within 7 days was lower in the IC51 and placebo groups (29.8% and 33.7%, respectively) compared to the JE-VAX® group (42.0%).

Within 7 days after Vaccination 1, the most common symptoms were tenderness and pain. JE-VAX® was associated with a higher incidence of itching, hardening, swelling and redness (11.7%, 8.8%, 7.8%, and 15.6%, respectively) compared with IC51 (2.3%, 5.5%, 3.2%, and 6.3%, respectively) For this same time period, IC51 was associated with a higher incidence of pain and tenderness compared with JE-VAX®.

Within 7 days after the Vaccination 2, the most common symptoms were again tenderness and pain in the IC51 and placebo groups, plus redness in the JE-VAX[®] group. As was seen after the Vaccination 1, JE-VAX[®] was associated with a higher incidence of itching, hardening, swelling and redness (13.6%, 13.4%, 11.5%, and 20.5%, respectively) compared with IC51 (1.5%, 4.1%, 2.4%, and 4.5%, respectively); these symptoms were more common after Vaccination 2 compared to Vaccination 1 for the JE-VAX[®] group, possibly as three vaccinations had been administered by this time point.

The incidence of severe local tolerability symptoms in IC51 recipients (3.2%) was similar to placebo recipients (3.1%) and slightly lower than that reported in JE-VAX[®] recipients (13.8%). This difference was predominantly due to the higher incidence of severe hardening, swelling and redness in the JE-VAX[®] group (5.2%, 5.4%, and 10.8%, respectively) compared with the IC51 group (1.4%, 1.0%, and 1.0 %, respectively).

Severe local tolerability for the 7-day period after vaccination is also presented by vaccination (Vaccination 1=Day 0 or Vaccination 2=Day 28) and for any vaccination. The incidence of severe local symptoms within 7 days of vaccination was generally low in the IC51 and placebo groups, and slightly higher in the JE-VAX[®] group (Day 0: 2.5%, 2.0% and 5.8%; Day 28: 1.3%, 1.3% and 10.5%, respectively). The severe local tolerability profile was similar between IC51 and placebo for all symptoms. In contrast, after the Vaccination 1, a higher percentage of subjects in the JE-VAX[®] group reported severe symptoms of redness (3.9%) compared with IC51 (0.7%). After the Vaccination 2, a higher percentage of subjects in the JE-VAX[®] group reported severe hardening, swelling and redness (4.5%, 4.5%, and 8.4%, respectively) compared with IC51 (0.6%, 0.4%, and 0.5%, respectively).

CONCLUSIONS

IC51 is safe and well-tolerated, with a safety profile comparable to placebo.

The local tolerability of IC51 was similar to placebo, and appears to be favorable to JE-VAX[®], particularly with regard to itching, hardening, swelling and redness. The systemic tolerability profile of IC51 was similar to placebo and JE-VAX[®].

The most common adverse events following immunization reported in IC51 vaccinees (headache, myalgia, influenza-like illness and fatigue) occurred at rates similar to that observed in JE-VAX[®] recipients in IC51-301; these rates are consistent with the JE-VAX[®] literature. The observed incidence of sensitivity/allergic reactions in IC51 recipients was comparable to placebo.

Serious adverse events were rare and no treatment-related SAEs were reported. One death was reported (lung adenocarcinoma metastatic) in an IC51 recipient and this was considered unrelated to study medication.

Concomitant administration of IC51 with inactivated HAV vaccine (HAVRIX[®]) did not detrimentally affect the safety profile of either vaccine.

The safety profile of IC51 was broadly consistent across different IC51 batches.

The data presented indicate that the risk-benefit ratio for IC51 is favorable for the intended population of healthy adults. IC51 demonstrates good immunogenicity against JEV and licensure is sought for immunization of persons intending to reside in or travel to at-risk areas and those working with JEV. IC51 has a safety profile that is comparable to placebo and no safety issues emerged during the clinical development.

REFERENCES

- Burke DS, Leake CJ. Japanese encephalitis. Monath TP ed. Arboviruses: Epidemiology and Ecology. Vol III. Boca Raton, FL: CRC Press; 1988; 63-92.
- No authors listed. Japanese encephalitis vaccines. Wkly Epidemiol Rec. 2006; 81 : 331-40.
- Solomon T, Ni H, Beasley WC, Ekkelenkamp M, Cardosa MJ, Barrett AD. Origin and evolution of *Japanese encephalitis* virus in southeast Asia. *J Virol* 2003; 77 : 3091-8.
- Georgitis JW, Fasano MB. Allergenic components of vaccines and avoidance of vaccine-related adverse events. *Curr Allergy Rep* 2001; 1 : 11-7.
- Bista MB, Banerjee MK, Shin SH, Tandan JB, Kim MH, Sohn YM, et al. Efficacy of single-dose SA 14-14-2 vaccine against Japanese encephalitis: a case control study. *Lancet* 2001; 358 : 791-5.
- Hennessy S, Liu Z, Tsai TF, Strom BL, Wan CM, Liu HL et al. Effectiveness of live-attenuated *Japanese encephalitis* vaccine (SA14-14-2): a case-control study. *Lancet* 1996; 347 : 1583-6.
- Ohrr H, Tandan JB, Sohn YM, Shin SH, Pradhan DP, Halstead SB. Effect of single dose of SA 14-14-2 vaccine 1 year after immunisation in Nepalese children with Japanese encephalitis: a case-control study. *Lancet* 2005; 366 : 1375-8.
- Solomon T. Control of Japanese encephalitis-within our grasps? *N Engl J Med* 2006; 355 : 869-71.
- Pool V, Braun MM, Kelso JM, Mootrey G, Chen RT, Yunginger JW et al. Prevalence of anti-gelatin IgE antibodies in people with anaphylaxis after measles-mumps rubella vaccine in the United States. *Pediatrics* 2002; 110 : e71.
- Sakaguchi M, Inouye S. IgE sensitization to gelatin: the probable role of gelatin-containing diphtheria-tetanus-acellular pertussis (DTaP) vaccines. *Vaccine* 2000; 18 : 2055-8
- Schuller E, Jilma B, Voicu V, Golor G, Kollaritsch H, Kaltenböck A et al. Long-Term Immunogenicity of the New Vero Cell-Derived, Inactivated Japanese Encephalitis Virus Vaccine IC51. 6 and 12 Month Results of a Multicenter Follow-Up Phase 3 Study. *Vaccine* 2008; 26 : 4382-6.
- Tauber E, Kollaritsch H, von Sonnenburg F, Lademann M, Jilma B, Firbas C, Jelinek T, Beckett C, Knobloch J, McBride WJ, Schuller E, Kaltenböck A, Sun W, Lyons A. Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial of the Safety and Tolerability of IC51, an Inactivated Japanese Encephalitis Vaccine. *J Infect Dis* 2008; 198 : 493-9.
- Tauber E, Kollaritsch H, Korinek M, Rendi-Wagner P, Jilma B, Firbas C, Schranz S, Jong E, Klingler A, Dewasthaly S, Klade CS. 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.