Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Japanese Encephalitis Chimeric Virus

Proprietary Product Name: Imojev

Sponsor: Sanofi Pasteur Pty Ltd

November 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity (NCE)
Decision:	Approved
Date of Decision:	16 August 2010
Active ingredient(s):	Japanese Encephalitis Chimeric Virus
Product Name(s):	Imojev Japanese Encephalitis Vaccine (live, attenuated); ChimeriVax-JE); JE-CV
Sponsor's Name and Address:	Sanofi Pasteur Pty Ltd Locked Bag 2227, North Ryde, BC 1670
Dose form(s):	Freeze-dried powder for injection and a 0.4% sodium chloride diluent for reconstitution in a single dose presentation.
Strength(s):	4.0 – 5.8 log plaque forming units (PFU) of live, attenuated, recombinant JE virus per dose (0.5 mL)
Container(s):	Single dose vial.
Pack size(s):	A pack of 1 powder vial and 1 diluent vial, 1 syringe and 2 needles.
Approved Therapeutic use:	The prophylaxis of Japanese encephalitis caused by the Japanese encephalitis virus, in individuals from 12 months of age and over.
Route(s) of administration:	Subcutaneous injection (SC)
Dosage:	Single dose of 0.5 mL
ARTG number(s):	162215

Product Background

Japanese encephalitis (JE) is a mosquito-borne flavivirus infection which is considered a disease of major public health importance because of its high epidemic potential, high case-fatality rate, and severity of sequelae among survivors. JE occurs in much of Asia including India, Southeast Asia, and China, and in more recent years there have been outbreaks on Torres Strait islands and in north Queensland. Expatriates and children living in endemic areas as well as travellers and military personnel deployed overseas are at risk of contracting the disease. JE virus (the causative agent) is an enveloped, positive strand RNA virus. The natural reservoir for JE virus is typically pigs and wading birds, and the virus can be passed to humans living in proximity to these animals by culicine mosquitoes. Most human infections are asymptomatic, with estimates of the symptomatic to asymptomatic ratio varying in different populations from 1:25 to 1:1000. The disease is typically an acute neurological illness that has a high fatality rate and a high prevalence of neurological sequelae in survivors (The Australian Immunisation Handbook, 9th edition). Vaccination is the most effective approach to JE disease control.

Imojev is a live, attenuated, JE virus vaccine belonging to the pharmacotherapeutic group of encephalitis vaccines (J07BA). The vaccine virus (also referred to in this application as ChimeriVax-JE or JE-CV) was constructed via recombinant DNA technology using two well characterised, live attenuated vaccine viruses (see *II Quality findings. Drug substance.* for more details).

A number of JE vaccines are available (many locally produced in Asia), disadvantages of these include reactogenicity, and need for multiple doses. The currently licensed JE vaccines in use include inactivated mouse brain derived vaccines (MBDV)s, inactivated cell-derived vaccines, and live attenuated vaccines. Inactivated MBDV JE vaccines are the historical standard-of-care for JE vaccination. An increasing number of allergic reactions related to the repeated doses of the MBDV necessary are being noted (thought to be related to the development of anti-gelatin antibodies[1]). Worldwide, there are several types of JE vaccines currently in use. Inactivated mouse brain-derived JE vaccines (MBDVs) use either the Nakayama or Beijing-1 JE strain grown in and purified from mouse brain, inactivated with formalin, and they generally require a primary immunization of two or three doses for an adequate antibody response, with recommended boosters after 2 years to maintain long-term immunity. Je-Vax is a MBDV manufactured in Japan and licensed in the USA and Australia, which was used as a comparator in the JE-CV clinical development.

Other current alternatives include an inactivated cell-derived JE vaccine. Such a vaccine based on the P3 strain, grown in primary hamster kidney (PHK) cells, was developed in China. This vaccine requires two initial doses (administered on Days 0 and 7) as well as multiple boosters. An inactivated JE vaccine based on strain SA14-14-2 produced in Vero cells has been recently licensed in Europe, Australia and New Zealand (Intercell, Vienna, Austria), and is administered in a two-dose schedule. SA14-14-2, the only live attenuated JE vaccine currently licensed (in China, India, Nepal, the Republic of Korea, and Sri Lanka), is based on the SA14 strain that has been attenuated through serial cell culture passages and is grown in PHK cells. This vaccine requires two doses (given between 3 months and one year apart). The live attenuated JE vaccine grown in primary hamster kidney (PHK) cells has previously been available only in China. In the last few years, several Asian countries introduced the SA14-14-2 vaccine for mass vaccination campaigns. The proposed JE chimeric virus vaccine was developed to provide a single-dose vaccine for those persons at risk for contracting JE. Imojev potentially provides some advantages relative to previous vaccines, including a broader and longer-lasting immunity, the requirement for a single inoculation, and the lack of adjuvant-induced toxicities.

Regulatory Status

As of date, no marketing authorisation has been granted for Imojev in any country. An application was submitted in Thailand in June 2009.

[1] Sakaguchi M, Yoshida M, Kuroda W *et al*. (1997). Systemic immediate-type reactions to gelatin included
in Japanese encephalitis vaccines. Vaccine 15:121-2.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

The JE-CV drug substance is a sterile aqueous concentrated suspension of purified live attenuated JE-CV viral particles in histidine, potassium glutamate, Human Serum Albumin (HSA), and sodium chloride (NaCl).

The virus was obtained via recombinant DNA technology and is based on two well-characterised live attenuated vaccine viruses, the yellow fever (YF) 17D vaccine virus and the JE SA14-14-2 vaccine virus. The vaccine virus was constructed by inserting RNA encoding the prM and E structural proteins of the JE SA14-14-2 virus into the genome of YF 17D virus. The YF 17D virus provides the replication engine. The antigen responsible for induction of neutralizing antibodies is the E protein, while the M protein is needed to ensure to the correct conformation of E.

JE-CV virus is propagated in Vero cells grown in serum-free conditions using a seed lot system. It is purified and then formulated in a stabiliser constituted of lactose, mannitol, histidine, glutamic acid, human serum albumin and salts. The JE-CV formulation is then freeze-dried. It contains between 4.0 and 5.8 log plaque forming units (PFU) of JE-CV virus per dose.

Manufacture

The drug substance is manufactured in cultures of a continuous cell line of African green monkey kidney (Vero) cells grown on microcarriers under serum-free (SF), antibiotic free conditions in an industrial-scale bioreactor. The manufacturing process includes the following successive steps:

- Culture of Vero cells, viral inoculation and propagation, followed by virus harvest;
- Downstream purification and filtration;
- Filling in aliquots and storage.

Preparation of starting materials for the production of the drug substance that is, viral bank system, cell bank system, purification and final filtration steps were described, including process description for cell amplification and seed recovery and viral propagation.

Source, history and generation and development of the JE-CV viral vaccine strain (YF 17D Parent virus and JE SA14-14-2 Parent virus) were described. Acambis has developed JE-CV manufactured in Vero cells. The cell banking system was developed starting from Vero cells and cultivated in serum free and antibiotic free culture media. The Vero WCBs were prepared from American Type Culture Collection (ATCC) source. Details of the source, manufacturing, characterisation and testing of cell banks were provided. Cell banking processes are satisfactory. All viral safety issues have been addressed, including use of animal-derived excipients, supplements in the cell banking.

Once sterile filtration step is completed, aliquots of the final filtered drug substance are filled into sterile Polyethylene Terephthalate Copolyester (PETG) bottles. Upon completion, the drug substance is transferred to storage at ≤-60°C. The drug substance is shipped from the manufacturing site to the Drug Product (DP) manufacturing site according to Federal regulations, State regulations, the International Air Transport Association, and Department of Transportation, using a validated shipping combination of containers.

Specifications

The proposed specifications, which control identity, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use, were included in the current Australian submission. The following tests are included in the specifications of drug substance; Sterility, Potency, Residual DNA, Safety Test - Infant Mouse Neurovirulence and Identity. The Identity test is set to ensure that the expected mutation specific of JE-CV and attenuating mutations in the SA14-14-2 E gene are present. Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under real time/stressed conditions to characterise the stability/degradation profile of the substance and to establish a shelf life.

The proposed shelf life is 60 months when stored at≤ –60°C.

The test results of the stability study performed on the drug substance under real-time/real-temperature conditions (≤-60°C for 60 months) for up to 48 months were provided.

The sterility tests show no growth on T0 for the three lots tested. The drug substance meets the established specifications for potency at the time points evaluated. All results are within the range of variability of test, no tendency is observed, supporting a good stability of the drug substance.

The applicant commits to completing the ongoing real-time/real-temperature stability study (≤-60°C for 60 months). Stability data will be provided when the 60 month data are available.

Drug Product

Formulation(s)

Imojev contains between 4.0 and 5.8 log plaque forming units (PFU) of live, attenuated, recombinant JE virus per dose (0.5 mL). It is formulated in a stabiliser constituted of lactose, mannitol, histidine, glutamic acid, human serum albumin and salts (sodium chloride and potassium hydroxide). No adjuvant or antimicrobial preservative is added.

The Drug Product is a lyophilised powder for reconstitution of formulated Drug Substance, and intended for subcutaneous administration. It is a white to creamy white homogeneous lyophilised cake. It is supplied in a 3 mL Type I glass vial, closed with a halo-butyl siliconised rubber stopper and an aluminium flip-off cap, in a protective tray also containing a vial with 0.4% NaCl diluent. The protective tray, in turn, is packaged

in an outer cardboard box. The pack is stated to contain a powder vial, a diluent vial, a syringe and two needles. The DP is reconstituted with 0.5 mL of diluent and then forms a colourless to amber suspension. The product is a single-dose presentation and must be stored between +2°C and +8°C.

Manufacture

The manufacturing of the drug product consists of the following successive steps:

Blending of drug substance/excipients and Sterile Filtration.

Aseptic filling and lyophilisation, Stoppering and Crimping; Inspection, and Labelling and Secondary Packaging.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product have been evaluated.

The sponsor has agreed to reduce the Endotoxin content specification to 5 IU/dose for the drug product. Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Post reconstitution stability studies were also carried out at +5°C ± 3°C and +25°C ± 2°C on three batches. All parameters are tested using the same methods as used at batch release specifications.

Based on the stability data currently available, the applicant requests a shelf life of three years for vaccine storage at +5°C ± 3°C, and the proposed shelf-life for the NaCl diluent is 48 months at +5°C ± 3°C.

Results available from stability studies for long term conditions to date at 12 months time point all comply with the acceptance criteria. No unexpected trends were observed. The sponsor has provided further updates for stability data of validation batches up to 24 months and clinical batches up to18 months at +5°C ± 3°C. The results comply with the specifications. No unexpected trends were observed in accelerated stability studies. Post reconstitution stability studies performed on three batches with NaCl diluent were completed. All the results are satisfactory and show no significant evolution, in particular in terms of potency levels that remain stable within the variability of the method.

Real time stability studies of Imojev vaccine are incomplete*; the company has been asked to provide the TGA with real- time results of stability studies up to 36 months when available for all six batches.*

Sanofi Pasteur is committed to continue the ongoing stability studies and stability data will be provided once all studies are completed

Quality Summary and Conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data (as applicable) submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

The sponsor has responded to questions raised by TGA regarding sterility, endotoxin and container safety and the answers were *found to be satisfactory*.

The sponsor has also responded to issues raised by the TGA regarding viral safety issues and the answers were *found to be satisfactory*.

Issues of concern

There are no outstanding issues regarding the Manufacture and Quality Control including Viral Safety Aspects of Imojev vaccine. However a number of deficiencies and other issues requiring resolution before the product could be recommended for approval were identified during the evaluation and in response to these the sponsor has committed to provide validation of sterility and validation of Mycoplasma testing on viral harvest and control cells before the marketing of the final product, that is, sale of the product in Australia. In addition, the sponsor has committed to provide results of the integrity testing of the container closure system at the end of stability studies and to complete the on-going stability studies and provide the stability data.

III. Nonclinical Findings

Introduction

The nonclinical submission in support of Imojev consisted of well-conducted, generally-GLP-compliant studies examining immunogenicity, protective efficacy, safety pharmacology and single-dose toxicity. The nonclinical references cited in this part of the document are listed at the end of the AusPAR under *References*.

Pharmacology

Primary pharmacodynamics

The immunogenicity and protective efficacy of JE-CV virus was evaluated in three studies using rhesus (*Macaca mulatta*) or cynomolgus (*Macaca fascicularis*) monkeys.

The two studies using rhesus monkeys examined the induction of viraemia and seroconversion following SC injection of different viral loads. In one of these studies, the response to challenge with wild-type (w.t.) JE virus, following inoculation with JE-CV, was tested. Inoculation with 2.0, 3.0, 4.0, or 5.0 $\log_{10}$ plaque forming units (PFU) of JE-CV (n = 4/group) produced a brief, low-level viraemia in all 16 monkeys tested. The mean peak viraemia (1.7-2.1 $\log_{10}$ PFU/mL) and mean duration (1.8-2.3 days) were similar in all dose groups. However, the onset of viraemia was earlier in animals given a higher viral dose. All 16 monkeys showed seroconversion. The kinetics of the neutralising antibody response were viral dose dependent, with monkeys receiving 4 or 5 $\log_{10}$ PFU showing detectable neutralising antibodies on day 6 or 7 after inoculation, while monkeys receiving 2 or 3 $\log_{10}$ PFU developed antibodies on days 8-10. High antibody titres in serum were achieved in all groups by day 30 post-immunisation. There was no statistically significant difference in mean antibody titre between the dose

groups. The 4 monkeys that received 5 $\log_{10}$ PFU of JE-CV virus were also tested for neutralising antibodies to heterologous (w.t.) JE viruses. Antibody titres to the homologous viral strain (that is, the vaccine) were ≥ 4-fold higher than to heterologous strains. Two monkeys with the lowest homologous antibody titres had no detectable antibodies (at a serum dilution of 1:20) against JE virus Korea, JKT-1724 (Indonesia), or P-20778 (India). However, all monkeys developed antibodies to the w.t. virus used for challenge (see below).

All immunised monkeys and two sham-immunised controls were challenged on day 52 post-immunisation by intracerebral inoculation of 5.2 $\log_{10}$ PFU of w.t. IC-37 JE virus. Note that intracerebral inoculation provides a severe test of effective immunity, and that the natural route of infection by mosquito bite resembles experimental SC inoculation. The 16 immunised monkeys showed no signs of illness, whereas the two sham-immunised controls developed severe encephalitis and were euthanised on Day 11 after inoculation. None of the immunised monkeys developed viraemia, whereas both controls did. Only three of the 16 immunised monkeys failed to show a greater than 2-fold increase in serum antibody titre after viral challenge. Two of the three non-responders were the only monkeys that showed no signs of subclinical encephalitis at necropsy (30 days after w.t. viral challenge). The other immunised monkeys that had been challenged with w.t. virus showed some residual histopathological changes in brain, and sham-immunised controls showed severe pathological changes. Prior to w.t. viral challenge, only one monkey showed (a low level of) neutralising antibodies in CSF. However, at necropsy, most monkeys showed high levels of neutralising antibodies in CSF. The only exceptions were the sham-immunised controls and the two immunised monkeys that showed no histopathological changes in brain. The second rhesus monkey study involved inoculation at 3, 4, or 5 $\log_{10}$ PFU of JE-CV (n = 4/group). As with the above study, there were no adverse events and all monkeys showed a brief, low-level viraemia and underwent seroconversion. Mean antibody titres did not differ significantly between the three groups.

Similar to the above studies, 5 of 5 cynomolgus monkeys showed no adverse effects following SC inoculation with 4.0 $\log_{10}$ PFU of JE-CV and developed a brief, low-level viraemia, followed by seroconversion.

The above studies demonstrated rapid induction of immunogenicity by JE-CV in two monkey species at doses that were within or well below the anticipated human dose range (comparing a 3.0 kg monkey with a 70 kg human and assuming kg to m^2 conversion factors of 12 and 37, respectively, a monkey given 2 $\log_{10}$ PFU of JE-CV is receiving about a 13-fold lower dose, on a PFU/m^2 basis, than a human given the minimum expected dose of JE-CV). JE-CV induced production of high titres of specific neutralising antibodies in both species. The immune response elicited by JE-CV in rhesus monkeys was shown to be effective in protecting against intracerebral challenge with w.t. JE virus. A limitation of the immunological studies was the lack of investigation of response duration, and mnemonic response. The effect of prior YF vaccination was not studied in animals, but was in humans.

Secondary pharmacodynamics

Studies of this type were not performed as potential undesirable pharmacological activities of the vaccine were not identified. This decision is consistent with European Medicines Agency (EMA) vaccine guideline (CPMP/SWP/465/95, 1997).

Safety pharmacology

Since w.t. JE and YF viruses are neurotropic, the characterisation of the attenuation of JE-CV focused on testing for neurovirulence. This involved intracerebral inoculation of mice and monkeys with JE-CV. (Note that intracerebral inoculation provides a stringent test of viral attenuation.)

ICR[2] mice inoculated with 0.1, 1.0, 2.0, or 3.0 $\log_{10}$ PFU of JE-CV showed no illness or death during a 3-week follow-up period. In contrast, the LD_{50} in ICR mice for yellow fever 17D virus (one of the parents of JE-CV) was 1.67 $\log_{10}$ PFU. The result suggests considerable attenuation of JE-CV neurovirulence as compared with one of its parents.

Neurovirulence of master seed and working batches of JE-CV was compared with that of YF 17D virus in both rhesus and cynomolgus monkeys. The monkey species and methods used conformed to the requirements of the World Health Organization for the testing of YF vaccines. (Note that YF 17D virus has been used in humans for 60 years as a live, attenuated vaccine strain and has an excellent record for safety and effectiveness.) Rhesus monkeys received 4.37-4.79 $\log_{10}$ PFU of YF 17D, 4.57-5.93 $\log_{10}$ PFU of master seed JE-CV, or 5.89-6.22 $\log_{10}$ PFU of working batch JE-CV (that is, inoculations were within or slightly above the anticipated human dose range). During a 30-day follow-up period, all vaccinated animals survived and showed no clinical signs. Most of the JE-CV-inoculated monkeys developed a low level viraemia that lasted for around three days and had mean peak titres of 2.3 (master seed) and 2.6 (working batch) $\log_{10}$ PFU/mL. These titres were somewhat lower than that found for YF 17D-inoculated animals (mean = 3.0 $\log_{10}$ PFU/mL) and were within World Health Organization (WHO) specifications for YF vaccines. All monkeys in the three inoculated groups showed seroconversion and produced high titres of JE virus-specific neutralising antibody. There were no gross necropsy or histopathological findings in various organs that could be attributed to inoculation in any of the groups. The severity of lesions in both "target" (substantia nigra) and "discriminator" (basal ganglia and thalamus of brain and grey matter of spinal cord) areas of the CNS was quantified. A significant fraction of JE-CV-inoculated monkeys showed no lesions. Those lesions found were of low intensity. The scoring indicated that the lesions induced by JE-CV were no worse than those induced by YF 17D.

The format of the above study was repeated using cynomolgus monkeys that received an intracerebral injection of ~4.7 $\log_{10}$ PFU of YF 17D, ~ 5 $\log_{10}$ PFU of master seed JE-CV, or ~ 5 $\log_{10}$ PFU of working batch JE-CV (that is, inoculations were within the anticipated human dose range). No vaccine-related changes in clinical signs or other vital parameters were observed during a 30-day follow-up period. Lymphoid hyperplasia was noted in the spleen, but was considered an expected response to vaccination. Viraemia followed a similar course to that described for the above study

[2] Institute for Cancer Research (ICR)

and was comparable in YF 17D and JE-CV inoculated animals. Viral titres were well within WHO specifications for YF vaccines. Histological examination of the central nervous system (CNS) of inoculated monkeys showed that lesions were mostly of minimal severity, with occasional moderate severity lesions (these involved mild inflammation without substantial involvement of neurons), and that lesion scores were significantly lower in both groups of JE-CV-inoculated as compared with YF 17D-inoculated animals.

In summary, safety pharmacology studies in mice and two species of monkey suggested that JE-CV has a neurovirulence that is comparable to or lower than that of the YF 17D virus, which is not neurovirulent in man. Hence, even in the unlikely event that the virus could escape the host immune response and cross the blood brain barrier to infect the brain parenchyma, it would not cause pathology or clinical symptoms.

Pharmacokinetics

Pharmacokinetic studies were not performed with JE-CV. The EMA Vaccine Guideline (CPMP/SWP/465/95, 1997) suggests that such studies are not normally necessary.

Toxicology

Single-dose toxicity

Cynomolgus monkeys (2-4 years old) were given a single SC inoculation of JE-CV and observed for up to 21 days prior to necropsy. The viral dose (5.2 $\log_{10}$ PFU) was within the range proposed for human use (for monkeys with bodyweights of ~3.2 kg). Both sexes were examined and the numbers of animals tested were appropriate. There were no premature deaths, adverse clinical signs, injection site reactions, vaccine-related changes in body weight or body temperature, ophthalmic findings, or changes in serum chemistry, haematology, coagulation, or urinalysis parameters. There were no JE-CV-related macroscopic alterations. Microscopic alterations were limited to localised, minimal to moderate mononuclear and/or mixed cell infiltrates at the injection site in 5 of 10 JE-CV inoculated animals on Day 4. The latter finding appeared to resolve as only a single control group animal exhibited neutrophilic inflammation associated with subcutaneous haemorrhage at the injection site, secondary to the injection process, on Day 22. All inoculated monkeys had seroconverted by day 22.

In summary, no significant toxicological findings were identified in male or female cynomolgus monkeys during a 21-day test period after SC injection of JE-CV vaccine.

Repeat-dose toxicity

No repeat-dose toxicity studies were performed as the vaccine is intended for delivery as a single dose.

Biodistribution and genetic stability

Studies with cynomolgus monkeys showed that JE-CV was restricted to the inoculation site on day 4 and all monkeys were negative on day 22 post inoculation. All urine, faeces, injection site swabs, and saliva samples were negative for JE-CV on both Days 4 and 22. Thus, there was no viral shedding.

A major concern for the production of live attenuated viral vaccines is that the attenuated phenotype may revert upon serial passaging *in vivo* or in cell culture. Such

concerns appear minimal in the case of JE-CV due to the number of mutations required for reversion and the relatively high fidelity of the RNA polymerase encoded by JE-CV (error rate of around 1.9×10^{-7} to 2.3×10^{-7} per nucleotide (Pugachev *et al*. 2004). Consistent with such predictions, JE-CV showed no genetic drift *in vivo*, as sequences encoding the structural proteins prM, M, and E isolated from inoculated monkeys were identical to the sequences present in the virus vaccine lot used for their immunisation.

Genotoxicity and carcinogenicity

No genotoxicity or carcinogenicity studies were performed with JE-CV. This is consistent with the EMA Vaccine Guideline (CPMP/SWP/465/95, 1997).

Local tolerance

Local tolerance was assessed in the single-dose toxicity study (see above). Effects seen were expected consequences of viral inoculation.

Adjuvant

Imojev does not contain adjuvants or antimicrobial preservatives.

Reproductive toxicity

In the primary nonclinical evaluation of Imojev, possible reproductive toxicity of JE-CV was not examined in animal studies and it was considered that vaccination with Imojev is contraindicated in pregnant and lactating women.

A secondary nonclinical report evaluated reproductive and developmental toxicity data relevant to Imojev vaccine, with the emphasis on developmental toxicity. Additional paediatric data were submitted for Imojev, hence the nonclinical data supporting paediatric use were also assessed in this secondary report. All other Imojev nonclinical data were considered in the primary evaluation (see above).

All references quoted in the secondary evaluation (of *Reproductive toxicity* and *Paediatric Use*) of the nonclinical report can be found in Appendix 1.

Live-attenuated virus vaccines are registered for measles, mumps and rubella (MMR), varicella zoster, yellow fever (YF), and rotavirus (not indicated in adults). All live-attenuated virus vaccines recommended for women of childbearing age are contraindicated in pregnancy, although in the case of disease outbreaks, YF vaccine "may be administered to pregnant women after the assessment of the risk related to the epidemiological context." (Stamaril Product Information). The registered live virus vaccines lack nonclinical developmental toxicity studies, as a consequence of a long history of clinical development and use. None of the live virus vaccines have been conclusively demonstrated to pose a risk to the developing foetus (NHMRC, 2009), but the prevention and management of inadvertent pregnancy are still problematic (Chang *et al.*, 2008, Dempsey *et al.*, 2009).

Regulatory background

Several new regulatory guidelines have been issued during the development of Imojev, as outlined below.

EMA

The 1997 European Medicines Evaluation Agency (EMEA; now EMA) Guidance "Preclinical Pharmacological and Toxicological Testing of Vaccines" (CPMP/SWP/465/95) states: "Some existing vaccines, although safe for use in women who are not pregnant, may cause foetal infection resulting in malformations or abortions in women who are pregnant. Documentation on clinical and/or epidemiological data on exposure to the infectious agent or related vaccines during pregnancy should be provided, and may be sufficient to evaluate the risk. In other cases, the availability of appropriate animal models should be considered."

In 2009, the EMEA issued a draft guideline (EMEA/CHMP/VWP/141697/2009) for live recombinant viral vectored vaccines. Although a draft, the guideline is relevant and refers to YF virus as an example of a vaccine vector under investigation. It extends the previous vaccine guideline and states "The need for reproductive toxicity studies is mainly dependent on the potential use of the vaccine during pregnancy. Consideration should be given to available clinical and/or epidemiological data on infection by the virus upon which the vector is based; however, a change in tropism brought about by the heterologous antigen may cause unknown and unexpected effects on the foetus. When required, the study design should reflect the application of the vaccine during the most sensitive period."

"Reproductive studies should also be considered if biodistribution studies suggest replication in reproductive organs."

WHO

The WHO issued guidelines for nonclinical evaluation of vaccines in 2005, including live attenuated vaccines, with similar recommendations to the EMEA.

USA FDA

In 2006 the FDA issued the Guidance for Industry "Considerations for developmental toxicity studies for preventive and therapeutic vaccines for infectious disease indications" (not adopted by the TGA). It noted that many registered vaccines, unless specifically intended for use in pregnant women, lacked developmental toxicity studies and had limited clinical pregnancy data at the time of registration. The guidance notes increasing concern with regard to unintended exposure to vaccines due to inadvertent pregnancy.

The Guidance states "Until recently, few licensed vaccines have been tested for developmental toxicity in animals prior to their use in humans. However, for the reasons listed above, we, FDA, recommend that you address during the investigational new drug (IND) studies the risk versus the benefits of immunization programs for pregnant women and/or females of childbearing potential by performing developmental toxicity studies in animal models."

"Developmental toxicity studies are usually not necessary for vaccines indicated for immunization during childhood. However, for vaccines indicated for adolescents and adults and for vaccines that are indicated or may have the potential to be indicated for immunization of pregnant women, we recommend that you consider developmental toxicity studies."

Females of childbearing potential: … For these products, we recommend that you include data from developmental toxicity studies with the initial Biologic License Application (BLA) submission, regardless of whether such studies have been submitted earlier to the IND."

Parent wild-type viruses

Wild-type JEV

JE infection in humans results in symptomatic illness in only about 1 in 250 infections. After an infectious mosquito bite a period of viraemia distributes the virus to secondary sites of replication. Infection of the brain probably occurs from the blood through the vascular endothelium. The virus localizes in a number of specific brain regions and causes neuron apoptosis, which may result in permanent neurological disability or death.

There is very limited published information regarding the potential for human transplacental infection with flaviviruses. In areas endemic for JE, infection in women of childbearing age may be limited due to acquisition of immunity in childhood, and high infant mortality and lack of surveillance may limit detection (Tsai, 2006). There are 2 reports of transplacental JEV infection in pregnancy during a JE epidemic in Uttar Pradesh, India (Chaturvedi *et al.*, 1980, Mathur *et al.*, 1985). In total the 2 studies reported 9 cases of JE in pregnancy, resulting in 4 spontaneous abortions (~8-22 weeks gestation) and isolation of JEV from the foetal liver, brain and placenta in 1 case (~22 weeks gestation), and the placenta in a second case (~8 weeks gestation). Neither study reported any foetal malformations. The spontaneous abortions occurred during or shortly after the encephalitis, with symptoms of pyrexia and convulsions, which might have been contributing or causative factors. No human data regarding transplacental infection during subclinical JEV infection were available.

In animals, there are published reports of stillborn and moribund newborn piglets, and dead ("mummified") foetuses, with CNS malformations and liver and spleen necrosis, during JE epidemics as early as the 1940s (Burns, 1950). The infected sows were generally asymptomatic, but had JE neutralizing antibodies. Experimental intravenous (IV) inoculation of pregnant pigs with JEV resulted in sporadic foetal infection and deaths, with hydrocephalus, more commonly after infection in early gestation (Shimizu *et al.*, 1954). There are also several brief reports of degenerative effects in the seminiferous epithelium of pigs naturally infected with JEV (cited in Straw *et al.*, 2006).

In mice, transplacental infection with JEV has been reported by Fujisaki *et al.* (1976, 1977, 1982, and 1983) and Mathur *et al.* (1981). Fujisaka *et al.* (1976) found that the rate of foetal infection was dependent on the mouse and virus strains, and the gestational age, but not on the level of viraemia. Neither group reported foetal malformations, but Mathur *et al.* (1981) reported abortions and stillbirths, and later cited unpublished observations of "smallness, runting and hydrocephaly" in infected mice (Mathur *et al.*, 1986b). *Fujisaki et al.* (1976) did not report abortions or stillbirths. Latent transplacental infection in mice was also reported by Mathur *et al.* (1982, 1986a).

In summary, transplacental infection with JEV has been reported in pigs and mice, with clear evidence of teratogenicity in pigs, and there are 2 single reports of transplacental infection in humans.

Wild-type YFV

YFV infection in humans is marked by an initial period of viraemia, and "viscerotropic" infection of the liver, spleen, heart and kidneys. The ensuing haemorrhagic disease may be fatal. The virus may also be "neurotropic", causing encephalitis. Spontaneous abortion, stillbirth, and congenital malformation have not been observed after yellow fever epidemics (Plotkin *et al.*, 2008). No information regarding transplacental infection with YFV in animals was available.

Parent vaccines

JE vaccine

The only licensed live-attenuated JE vaccine (SA14-14-2 strain) has been used in China since 1989, and is also licensed for use in India, Nepal, the Republic of Korea, and Sri Lanka. It is prepared from primary hamster kidney cell cultures. The vaccine is recommended for use in adults and children, but is contraindicated in pregnancy. No information was available regarding exposure in inadvertent pregnancy.

YF vaccine

Live attenuated YF vaccines are derived from the 17D strain, with 2 substrains, 17DD (Brazil) and 17D-204 (all other manufacturers), and have been registered since the 1940s. The YF 17D vaccine is registered in the USA (YF-Vax), and Australia (Stamaril) as a "grandfathered" product, for use in adults and children over 6 months of age. The vaccine, which contain a minimum of 3 $\log_{10}$ mouse 50% lethal dose (LD_{50})/dose, retains some neurovirulence, and should not be administered to infants <6 months of age due to an increased risk of encephalitis.

A number of studies have investigated YF vaccine exposure during inadvertent pregnancy (Tsai *et al.*, 1993; Nasidi *et al.*, 1993; Nishioka *et al.*, 1998; Robert *et al.*, 1999; Suzano *et al.*, 2006; Cavalcanti *et al.*, 2007). The studies have reported several hundred pregnancies, mainly during mass immunization campaigns. The studies reported rates of abortion, stillbirths and major foetal malformations within normal population ranges. One study during a mass YF vaccination campaign in Trinidad reported transplacental infection in 1/41 pregnancies, as detected by virus-specific immunoglobulin type M (IgM) in a cord sample (Tsai *et al.*, 1993), but another study in Brazil failed to detect specific IgM in 341 exposed infants, at 3 months of age (Suzano *et al.*, 2006). It is noted that measurement of IgM is unlikely to detect transplacental infection early in gestation.

The clinical evaluator was asked to comment further on clinical pharmacovigilance for YF and JE parent vaccines.

Imojev vaccine

Imojev is a live-attenuated chimeric virus in which the RNA sequences encoding the premembrane and envelope structural proteins of the attenuated YF 17D vaccine strain

are replaced with those of the attenuated JE SA14-14-2 vaccine strain. The E protein mediates attachment to cell receptors and membrane fusion. It is a major determinant of neurovirulence and neuroinvasiveness in mice, and contains the main neutralizing antibody epitopes.

Nonclinical studies showed that Imojev was less neurovirulent than YF vaccine in adult monkeys and young mice. Imojev passed the WHO test for neurovirulence in adult rhesus monkeys, based on the requirements for YF vaccine. In 3-4-week old mice, an intracerebral dose of 10^4 PFU of parent YF vaccine virus resulted in 100% mortality, whereas no mortality was observed with the JE/YF chimeric virus at a dose up to 10^6 PFU. The parent JEV SA14-14-2 strain also lacked neurovirulence in 3-4-week old mice, and the JE/YF chimeric virus also showed a lack of neuroinvasiveness after an intraperitoneal (IP) dose of 10^6 PFU in 3-week old mice (Chambers *et al*, 1999).

Imojev elicited a low, transient viraemia in cynomolgus and rhesus monkeys, and adult humans, similar to YF vaccine. The occurrence of viraemia demonstrates the replication competence of the chimeric virus, and potential to reach the maternal placenta, *in vivo*.

A biodistribution study in which adult cynomolgus monkeys were administered a human dose of Imojev only detected virus in the SC injection site and sera in some monkeys. Virus was not detected in the monkey testes or ovary, suggesting a lack of a direct reproductive risk. The virus biodistribution was not investigated in young animals.

Imojev vaccine virus was not shed in injection site swabs, urine, faeces or saliva. Viremia and shedding were not investigated in young animals, where they might be more extensive. Vaccine virus transmission from vaccinated contacts to unvaccinated pregnant women would constitute a risk if there was a foetal risk. The clinical evaluator was asked to comment on the potential for virus transmission from vaccinated to unvaccinated subjects.

Sponsor response

The sponsor stated that nonclinical developmental toxicity studies have not been performed with Imojev for the following reasons.

(i) Imojev will be contraindicated in pregnancy, as are all live attenuated vaccines, and there are repeated warning statements in the Imojev Product Information.

(ii) Clinical information in pregnancy is too limited to reliably predict the effect of exposure, hence Imojev is contraindicated in all trimesters.

(iii) Imojev vaccine virus is highly attenuated, due to the attenuation of both parent vaccines, and additional attenuation due to the chimerisation process.

(iv) Viremia in humans following Imojev injection is low and transient, and similar in magnitude and duration to YF-Vax. Similar observations were made in monkeys, where virus was only detected at the injection site, and not in any organs, including the reproductive system. The potential risk for Imojev to infect the foetus was thus considered low.

(v) There are no validated models for developmental and reproductive toxicity studies with live attenuated vaccines.

(vi) All reported cases of inadvertent administration of Imojev in pregnancy would be captured through routine pharmacovigilance, followed up until the outcome is known, and provided in 6-month Periodic Safety Update Reports (PSURs) to regulatory authorities.

The sponsor has indicated that a nonclinical developmental and reproductive toxicity study is planned, in accordance with regulatory guidelines on nonclinical safety of vaccines. Ongoing investigations aim to select a relevant species, to permit assessment of vaccine components, immune response and viral replication.

Paediatric use

Imojev was submitted as a rolling submission, with later additional clinical paediatric studies, as it is proposed for use in infants≥1 year of age. No nonclinical studies were conducted specifically to address toxicity in young animals, although it is well established that JE, YF and other flaviviruses are more neurovirulent and neuroinvasive in infant mice. The greater neurovirulence might arise from the lack of a blood brain barrier, and greater intrinsic susceptibility of the immature nervous system (Ogata *et al.*, 1991). Viremia may also be more prolonged in infants. The only nonclinical data in young animals were neurovirulence tests in 7-8 day old mice, which showed that JE/YF chimeric virus was significantly less neurovirulent than the parent YF vaccine virus. Although reassuring, the mouse studies were limited with regard to the route of administration (intracerebral), and toxicological parameters investigated. The evidence supporting safety in children will therefore rely largely on clinical data.

Overall conclusions

There are reports of teratogenicity in pigs, and transplacental infection in pigs and mice with wild-type JEV, a parent virus to Imojev. The highly attenuated virulence and low viraemia of Imojev are likely to lessen a potential developmental risk, however toxicity has only been investigated in postnatal animals, and the possibility remains that the foetus is more sensitive. The available reports for YF vaccine have not indicated a developmental risk, however the E protein in YF vaccine has been substituted in Imojev with the corresponding E protein from an attenuated JEV strain, with the potential to alter cell tropism and transplacental infection. It is concluded that the available data are not sufficient to fully assess the potential reproductive and developmental toxicity of Imojev.

Nonclinical data in young animals were limited to neurovirulence studies in mice, hence approval of paediatric use will depend largely on clinical data.

Nonclinical Summary

- JE-CV was immunogenic in rhesus and cynomolgus monkeys, as evidenced by the production of high titre, JE-CV specific antibodies. All immunised monkeys showed protection against intracerebral challenge by w.t. JE virus.
- The attenuation of JE-CV was tested by intracerebral inoculation of mice and rhesus and cynomolgus monkeys. In all three species, it was found that the neurovirulence of JE-CV was comparable to or lower than that of the parental YF 17D virus (YF 17D is known to lack neurovirulence in man).

- No significant toxicological findings were identified in male or female cynomolgus monkeys during a 21-day test period after a single SC injection of the full human dose of JE-CV vaccine.
- The biodistribution of JE-CV was restricted to the inoculation site on Day 4 and all monkeys were negative on Day 22 post inoculation. There was no viral shedding from inoculated monkeys.
- JE-CV was stable under *in vivo* conditions as evidenced by no or few changes in DNA sequence in virus isolated from infected monkeys.
- Repeat-dose toxicity studies were not performed as the vaccine is intended for delivery as a single dose.
- No genotoxicity or carcinogenicity studies were performed. This is consistent with the nonclinical vaccine guidelines.
- Local tolerance was assessed in monkeys given a single dose of vaccine. Effects seen were expected consequences of viral inoculation.
  A reproductive and developmental (DART) toxicity study was not submitted for Imojev, however a study is planned by the sponsor. Additional paediatric data were submitted for Imojev, hence nonclinical data supporting paediatric use were also assessed.
- Human data regarding transplacental infection with flaviviruses are very limited. In JE endemic areas, infection in women of childbearing age may be limited by acquisition of immunity in childhood. There are two published reports of transplacental JEV infection and spontaneous abortion in pregnancy, but no reports of foetal malformations. After YF epidemics, spontaneous abortions, stillbirths and foetal abnormalities have not been observed in humans.
- In pigs, high incidences of stillborn and moribund piglets, and dead foetuses, with CNS malformations, and liver and spleen necrosis, have been observed in JE epidemics since the 1940s. Infected sows were generally asymptomatic. Similar observations were made after an IV dose of JEV in pregnant pigs. Transplacental JEV infection has been reported after an intravenous (IV), SC or IP dose in mice, with some abortions and stillbirths reported after an IP dose.
- The live-attenuated JEV (SA14-14-2 strain) vaccine, licensed in China, is contraindicated in pregnancy. No information regarding exposure in pregnancy was available. Published studies of YF (17D strain) vaccination during inadvertent pregnancy have reported rates of abortion, stillbirths and major foetal malformations within normal population ranges. One study during a mass YF vaccination campaign reported transplacental infection in 1/41 pregnancies, as detected by virus-specific IgM in a cord sample, but another study failed to detect specific IgM in 341 infants exposed *in utero*, at 3 months of age postpartum.
- There are no data regarding the potential for transplacental infection with Imojev vaccine in animals or humans. Imojev vaccine was significantly less neurovirulent than YF vaccine after intracerebral administration in young mice and adult monkeys. Pregnancy was an exclusion criterion in all Imojev clinical trials. Three pregnancies were reported, culminating in 2 voluntary, elective abortions, and 1 healthy delivery, 363 days after vaccination.

- Imojev vaccine produces a low, transient viraemia in monkeys and humans, similar to YF vaccine. A biodistribution study in monkeys only detected Imojev virus in the SC injection site and sera in some monkeys. Virus was not detected in the monkey testes or ovary, nor was it shed in injection site swabs, urine, faeces or saliva.

Conclusions and recommendations

It is likely that the high attenuation and low viraemia of Imojev vaccine would mitigate against a potential developmental risk, but the risk cannot be fully assessed from the available data. Registration is not supported in women of childbearing age in the absence of a reproductive and developmental toxicity study. However, prevention of inadvertent pregnancy and its management are clinical concerns, and clinical advice was also sought on this issue. Nonclinical data raised no objections to registration in adult males, and women without childbearing potential. Registration for use in children will depend largely on adequate clinical data, as supporting nonclinical data in young animals were limited.

IV. Clinical Findings

Introduction

This application includes data from nine clinical studies in adult populations in the USA and Australia including a Phase I/II study and also two pivotal paediatric Phase III studies of safety and of efficacy. A total of 3476 healthy adult subjects were involved in the nine JE-CV clinical studies in adults and 1500 children and toddlers. Of the adult subjects, 2486 subjects were randomly assigned to receive one dose of JE-CV. A total of 2136 subjects were randomized to the lyophilized formulation and 350 subjects were randomly assigned to the liquid formulation of JE-CV. Populations for efficacy assessments (using a serological correlate of protection) included 375 subjects who received JE-CV in studies H-040-008 (per protocol (PP) population) and H-040-009 (efficacy population). The earlier studies provided data for dose finding, proof of concept, immunogenicity and safety data and there are two pivotal Phase II/III studies that provide efficacy data. JE-CV was administered subcutaneously in at least one group of subjects as the liquid formulation in studies H-040-001, H-040-003, H-040-005, and H-040-006, or as the lyophilized (or freeze dried) formulation in studies H-040-007, H-040-008, H-040-009, and H-040-010. H-040-002 was a study without JE-CV administration to assess the memory immune response.

Clinical and biological safety was assessed in all the eight clinical studies in which JE-CV was administered. Study H-040-010 was a pivotal safety study which aimed to compare the safety of JE-CV versus placebo in a large number of subjects. An additional submission of data from two paediatric trials was also included in this application to extend the licensing to include the use of this vaccine in children and toddlers from 12 months of age. This includes a final report on Study JEC02 (which includes safety data from a 6 month follow up) and an interim report on Study JEC01 (containing immunogenicity and safety data up to 6 months as well). JEC01 is a Phase II, controlled Study of the Safety and Immunogenicity of ChimeriVax-Japanese Encephalitis Vaccine in Thai Toddlers, and Children and JEC02 is a Phase III study examining Lot-to-lot Consistency, Bridging, and Safety Trial of ChimeriVax Japanese Encephalitis Vaccine in Toddlers in Thailand and the Philippines. In total, 1400 toddlers

and children from 12 months to 5 years were vaccinated with a single dose of JE-CV (both naïve and immune). In the paediatric studies, the primary objective of JEC02 study was to demonstrate that three industrial lots of JE-CV produced in Thailand at commercial scale induced the same immune response, in terms of post-vaccination seroconversion rate, after a single vaccination. The secondary objective of JEC02 was to demonstrate the bioequivalence of JE-CV lots from Thailand with a JE-CV lot produced in the USA. In addition, safety was assessed up to 28 days after vaccination, which enlarged the safety database in paediatric populations and in particular in Asia. A total of 1 100 subjects were to be included and randomized to receive a single dose of JE-CV either from a lot from Thailand or from USA. In addition, 100 subjects were planned to be included and randomized to receive a single dose of hepatitis A vaccine, which was the control vaccine used in the study. A licensed hepatitis A vaccine was considered as a control for safety. All subjects receiving JE-CV were to be assessed for immune response 28 days after vaccine administration, and all subjects included in the study were to be assessed for clinical safety during the 28 days following vaccination.

Safety results up to 6 months after vaccination have been evalauted. Safety was monitored as immediate adverse events (AEs) (within 30 minutes after vaccination), solicited injection site and systemic reactions within 7 and 14 days post-vaccination, respectively, and unsolicited AEs in the 28-day period after vaccination. Serious adverse events (SAEs) were monitored for the 6 months following vaccination. A total of 1 200 subjects were included in the study: 899 were enrolled in the lot-to-lot consistency comparison and were randomized to receive one of the three different industrial lots of JE-CV from Thailand and 199 were enrolled in the JE-CV (USA lot) group. The Hepatitis A control group included 102 subjects.

Pharmacokinetics

No new data were submitted with the current Australian submission.

Drug Interactions

No new data were submitted with the current Australian submission.

Pharmacodynamics

The clinical pharmacology program in an adult population consisted of five Phase I/II studies:

H-040-001, H-040-003, H-040-005, H-040-006, and H-040-007, were all randomized, double-blind studies. Doses between 1.8 $\log_{10}$ PFU/0.5-mL dose and 5.8 $\log_{10}$ PFU/0.5-mL dose (liquid formulation) were tested in studies H-040-001 and H-040-003. Based on immunogenicity and safety results a dose of 3.8 $\log_{10}$ PFU/0.5-mL was deemed appropriate for studies H-040-005 and H-040-006.

Repeated administration of JE-CV was evaluated in two studies. Administration of a second dose 28 days after the first JE-CV dose was assessed in study H-040-003 to determine the benefit of more than one dose of the vaccine. H-040-005 evaluated the administration of a second dose at Month 6 after the first JE-CV vaccination.

The development of the lyophilized formulation started with a dose-ranging study (H-040-007) testing doses between 3.0 $\log_{10}$ PFU/0.5 mL dose and 5.0 $\log_{10}$ PFU/0.5-mL

dose. Based on immunogenicity and safety results, a dose with a lower potency limit of 4.0 log_{10} PFU/0.5-mL dose was chosen.

Post-vaccinal viraemia was investigated in nonclinical and early clinical studies for the assessment of safety, and also as a measure of the bioavailability and replicative ability of the vaccine virus (Table 1).

Table 1: Viremia occurrence following a single administration of JE-CV, presented by formulation across studies H-040-001, H-040-003 and H-040-007 (Safety population).

Formulation	Liquid							Lyophilized		
Study	H-040-001*		H-040-003					H-040-007		
Dose of JE-CV (log_{10} PFU/0.5 mL)	4.0	5.0	1.8	2.8	3.8	4.8	5.8	3.0	4.0	5.0
N	6	6	11	11	11	33	10	32	32	32
Number of viremic subjects (%)	5 (83)	5 (83)	9 (82)	11 (100)	9 (82)	22 (67)	5 (50)	14 (43.8)	17 (53.1)	9 (28.1)
Mean peak viremia (PFU/mL)	25.0	13.3	18.2	40.9	16.4	13.0	7.0	4.4	6.6	3.4
Range of peak viremia (PFU/mL)	0 to 80	0 to 40	0 to 50	0 to 220	0 to 50	0 to 40	0 to 20	0 to 10	0 to 30	0 to 20
Mean duration (days)	2.3	1.7	2.2	2.7	1.4	1.6	0.9	0.7	1.4	0.6
Range of duration (days)	0 to 4	0 to 3	0 to 5	1 to 6	0 to 3	0 to 5	0 to 4	0 to 3	0 to 7	0 to 11

*Data are quoted for subjects not immune to YF at baseline in study H-040-001 (that is, results for 12 subjects not displayed). No viraemia was observed in the 202 subjects in study H-040-005; therefore this study is not presented in this table.

Viremia was assessed in 302 subjects vaccinated subcutaneously with the liquid formulation (studies H-040-001, H-040-003, and H-040-005) and 96 subjects vaccinated subcutaneously with the lyophilized formulation (study H-040-007). The designs of these studies varied with regard to flavivirus immunity in the study population (immune or non-immune to YF at baseline), dosages of vaccine (1.8 to 5.8 log_{10} PFU/0.5-mL dose), time points after vaccination for measuring viraemia (Days 2 to 11 in study H-040-001, Days 1 to 8 in study H-040-003, and Days 1 to 14 in study H-040-007), and number of vaccinations (single or repeated administrations). Study H-040-005 measured viraemia at Days 14 and 42 after vaccination with JE-CV.

No viraemia was detected at either of these time points, indicating that any viraemia after vaccination had ceased within 2 weeks of JE-CV administration. The results of studies H-040-001, H-040-003, and H-040-007 showed that viraemia was observed up to 11 days after JE-CV administration, with 50% to 100% of subjects (liquid formulation) and 28% to 53% of subjects (lyophilized formulation) experiencing viraemia on at least one day. The data showed a trend for peak viraemia to occur around Day 4 to Day 6 after a single dose of JE-CV. The number of viremic subjects following administration with the lyophilized formulation of JE-CV (study H-040-007) was

slightly lower than with the liquid formulation (studies H-040-001 and H-040-003). No viraemia was observed in 202 subjects 14 days after JE-CV vaccination in study H-040-005.

In the paediatric study JEC01, viraemia was assessed on Day 4 in subjects who received JE-CV at the first vaccination (Group 1 and Group 3). No child in Group 1 presented quantifiable JE-CV viraemia, while 5 toddlers (5.1%) presented with low level viraemia just over the level of quantitation (20.0 PFU/mL). Serum samples from the five toddlers with quantified viraemia were to be characterized by direct sequencing and amplification on Vero cells followed by sequencing of viral plaques. Neither of the two approaches were able to sequence the JE-CV virus, possibly due to insufficient virus concentration and/or stability.

Efficacy

In the clinical development program of JE-CV, a serological correlate of protection was used for the demonstration of efficacy. The serological correlate was based on neutralizing antibodies as recommended by the WHO[3]. WHO has identified immunological markers for evaluation and licensure of new JE vaccines. A threshold of >1:10 using the 50% plaque reduction neutralization test ($PRNT_{50}$) was accepted as evidence of protection. Additional supportive data on long-term immunological memory including T-cell response were also recommended. In the clinical development of JE-CV, protection levels were mainly assessed using the homologous virus to administered vaccine as a challenge virus in the log10 neutralization index (LNI) assay (described below under *Methods*) and $PRNT_{50}$. The immunogenicity of JE-CV was investigated through the measurement of neutralizing antibodies in seven studies (H-040-001, H-040-003, H-040-005, H-040-006, H-040-007, H040-008, and H-040-009).

Methods

This was assessed based on seroconversion rates and geometric mean titers (GMTs) in seven studies: H-040-001, H-040-003, H-040-005, H-040-006, H-040-007, H-040-008, and H-040-009. In accordance with recommendations from WHO, the clinical development of JE-CV was carried out examining the accepted threshold for seroconversion ($PRNT_{50}$ 1:10). Neutralizing antibodies were measured with different assays:

Initially the LNI assay was used in studies H-040-001 and H-040-003. This assay uses a fixed dilution of serum and various concentrations of challenge virus. Seroconversion was defined as an LNI of ≥ 0.7. As this method is not widely used and the data are limited for comparison among JE studies, it was replaced by the $PRNT_{50}$ assay in the subsequent studies.

A constant virus, serum dilution 50% plaque-reduction neutralization test ($PRNT_{50}$) was used in studies H-040-005, H-040-006, H-040-007, H-040-008, and H-040-009. It is based on a fixed amount of virus and different dilution of serum. It is the most commonly accepted test methodology for measuring functional antibodies able to

[3] World Health Organization. Guidelines on clinical evaluation of vaccines: regulatory expectations. http://www.who.int/biologicals/publications/trs/areas/vaccines/clinical_evaluation/035-101

inactivate and neutralize JE virus and a titer of 1:10 is regarded as the minimum protective level.

Different dosages were administered in study H-040-003 (liquid formulation in doses ranging from 1.8 to 5.8 $\log_{10}$ PFU/0.5 mL-dose) and study H-040-007 (lyophilized formulation in doses from 3.0 $\log_{10}$ PFU to 5.0 $\log_{10}$ PFU/0.5 mL-dose), which allowed for the selection of a potency of at least 4.0 $\log_{10}$ PFU/0.5 mL-dose for the late phase of development. Je-Vax was considered the standard-of-care JE vaccine; therefore, Je-Vax was used as the major comparator during the development of JE-CV. Four different comparators were also used in the clinical development program: MBDV (considered at the time of the development as the standard-of-care JE vaccine and represented by Je-Vax), placebo (diluent), YF-Vax (live attenuated YF 17D vaccine), and Stamaril (live attenuated YF 17D vaccine).

The assessment of the cell-mediated immune response was also included in the JE-CV development plan in study H-040-008. The clinical development of JE-CV also included an assessment of the memory immune response, as recommended by WHO. In study H-040-002 subjects who had received JE-CV at an early stage of development were administered Je-Vax to evaluate the anamnestic response to JE-CV.

Studies Evaluating Liquid Formulation of JE-CV (H-040-001, H-040-003, H-040-005, and H-040-006)

In the first proof-of-concept Phase I/II study (H-040-001), the liquid formulation of JE-CV was compared to a live attenuated YF vaccine (YF-Vax) in subjects with and without prior YF immunity (Table 2). All JE-CV vaccinated subjects seroconverted to the homologous JE-CV virus 30 days after vaccination and there were no restrictions of immunogenicity by pre-existing YF immunity. JE-CV also elicited an immune response to different wild-type JE strains. Vaccinal viraemia was measured and was detected at low levels and was of short duration in the majority of subjects. A Phase II dose-ranging study (H-040-003) established that JE-CV doses from 1.8 to 5.8 $\log_{10}$ PFU/0.5-mL dose resulted in similar seroconversion rates and safety profiles. No clinically relevant dose-effect on the level of viraemia was detected. A second dose of JE-CV administered 28 days after the first dose did not show a measurable benefit in terms of immunogenicity compared to a single dose. This study also assessed the potential interaction between JE-CV and a live-attenuated YF vaccine (YF-Vax). Prior vaccination with YF-Vax did not suppress the response to JE-CV, while JE-CV administered 30 days before YF-Vax may have reduced the YF seroconversion rate in this study. On the basis of these results, the dose of 3.8 $\log_{10}$ PFU/0.5-mL was chosen for the subsequent studies set up with the liquid formulation.

Table 2: Seroconversion rates against JE-CV homologous virus, YF 17D virus and Wild-type JE strains in Study H-040-001 (immunogenicity evaluable subjects).

Vaccine	JE-CV				YF-VAX®	
Dose (log_{10} PFU/0.5-mL)	4.0		5.0		5.0	
YF immune status at baseline	Immune (N = 6)	Non-immune (N = 6)	Immune (N = 6)	Non-immune (N = 6)	Immune (N = 6)	Non-immune (N = 6)
Seroconversion	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Day/Challenge Virus						
Day 11						
JE-CV*	1 (16.7)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)†
Day 31						
JE-CV	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	0 (0.0)	0 (0.0)
YF 17D‡	0 (0.0)	0 (0.0)	3 (50.0)	0 (0.0)	3 (50.0)	6 (100.0)
JE Wild-type (Genotype)§:						
• Beijing (III)	5 (83.5)	4 (66.7)	5 (83.3)	6 (100.0)	0 (0.0)	1 (16.7)
• P3 (III)	6 (100.0)	6 (100.0)	5 (83.3)	6 (100.0)	0 (0.0)	2 (33.3)
• Nakayama (III)	2 (33.3)	1 (16.7)	4 (66.7)	3 (50.0)	0 (0.0)	0 (0.0)

In a Phase II study (H-040-005), JE-CV was administered either in a one- or two-dose schedule (second dose given at Month 6). The immune response to wild-type strains was confirmed in this study, and assessment of viraemia showed that it was undetectable 14 days after vaccination. One dose of JE-CV demonstrated high and sustained seroconversion rates over 24 months (Table 3). Most subjects seroconverted to the homologous virus 14 days after vaccination (132 of 157 subjects, 84.1%). The seroconversion rate to the homologous virus 28 days after vaccination in baseline seronegative subjects was 98.8% (95% CI: 95.6, 99.9). Among subjects present at Month 24, 91.4% (95% CI: 81.0, 97.1) were still seropositive. The second dose showed a slight increase in the immune response, but was not deemed necessary since a single dose elicited long-term protective immune response. This study also evaluated the immune response to different wild-type JE strains after a single dose of JE-CV (Table 4). Table 5 shows the GMTs after vaccination with JE-CV in this study. Long-term persistence up to 4 years was analysed using the Kaplan-Meier estimate (Table 6) methodology. The Kaplan-Meier seroconversion estimates showed that the seroprotection provided by JE-CV vaccination was sustained for up to 48 months in over 90%. The GMTs tended to decrease up to Month 6 (142.0) and Month 12 (97.4); they then remained stable during the follow-up period from Month 12 to 48 (with a range between 87.7 and 97.4) and remained over the defined level of seroprotection up to Month 48.

Table 3: Seroconversion Rate ($PRNT_{50}$ ≥1:10) to Homologous Virus at 14 Days, 28 Days, 6 Months, 12 Months, and 24 Months After JE-CV Vaccination for Subjects who Received a Single JE-CV Vaccination in Study H-040-005 (Per Protocol Population).

Post-vaccination Timepoint	N	n Seroconverted	Seroconversion Rate (%)	95% CI*
14 days†	157	132	84.1	77.4, 89.4
28 days†	163	161	98.8	95.6, 99.9
6 months	158	153	96.8	92.8, 99.0
12 months	60	57	95.0	86.1, 99.0
24 months	58	53	91.4	81.0, 97.1

* CI is the exact 95% confidence interval for percentage of subjects seropositive to the homologous JE-CV strain. † Depending on vaccination schedule; subjects were vaccinated with JE-CV on either Day 0 or Day 28.

Table 4: Seroconversion Rate ($PRNT_{50}$ ≥1:10) to Wild-type JE Virus Strains at 6, 12, and 24 Months After JE-CV Vaccination for Subjects who Received a Single Vaccination in Study H-040-005 (Per Protocol Population)

Strains Tested	Genotype	Time point	N	n Seroconverted	Seroconversion Rate (%)	95% CI
1991, TVP-8236	I					
		Month 6	76	66	86.8	77.1; 93.5
		Month 12	60	52	86.7	75.4; 94.1
		Month 24	58	51	87.9	76.7; 95.0
B1034/8	II					
		Month 6	76	65	85.5	75.6; 92.5
		Month 12	60	47	78.3	65.8; 87.9
		Month 24	58	36	62.1	48.4; 74.5
Beijing	III					
		Month 6	76	69	90.8	81.9; 96.2
		Month 12	60	51	85.0	73.4; 92.9
		Month 24	58	42	72.4	59.1; 83.3
JKT 9092, TVP-6265	IV					
		Month 6	76	70	92.1	83.6; 97.0
		Month 12	60	49	81.7	69.6; 90.5
		Month 24	58	41	70.7	57.3; 81.9

Table 5: Antibody Geometric Mean Titers to Homologous Virus After JE-CV Vaccination Study H-040-005 (Per Protocol Population).

		Time point After First JE-CV Administration				
		28 Days	6 Months	7 Months*	12 Months	24 Months
Group A: JE-CV then diluent (N = 82)	n	82	80	49	65	57
	GMT	406.3	153.5	289.0	135.3	106.2
Group B: Diluent then JE-CV (N = 81)	n	81	78	32	63	60
	GMT	247.3	133.1	350.5	107.3	95.9
Overall (N = 163)	n	163	158	81	128	117
	GMT	317.4	143.1	311.9	120.7	100.8
Comparison Between Vaccination Groups A and B						
Ratio of geometric means*†		1.6	1.2	0.8	1.3	1.1
95% CI		1.1; 2.5	0.8; 1.7	0.5; 1.3	0.8; 1.9	0.7; 1.8

* Only subjects who received a second dose of JE-CV were assessed at Month 7.
† Ratio of geometric means of titers between vaccination order groups (Group A - B) from ANOVA mod

Table 6: Long-Term Immune Response of JE-CV in Subjects Who Received or Not a Booster Dose in H-040-005 - Kaplan-Meier Analysis (Intent-to-Treat Population).

Visit Time Point	Subjects who did not receive a booster dose					Subjects who received a booster dose at Month 6				
	N Seropositive	N Seronegative	N Censored†	Kaplan Meier Estimate*	95% confidence interval	N Seropositive	N Seronegative	N Censored†	Kaplan Meier Estimate*	95% confidence interval
Month 6	90	0	0	100.0	100.0; 100.0	98	0	0	100.0	100.0, 100.0
Month 12	77	2	11	97.5	94.0; 100.0	87	1	9‡	98.9	96.6; 100.0
Month 24	66	3	8	93.2	87.5; 99.0	78	1	8	97.6	94.3; 100.0
Month 36	54	1	11	91.5	85.0; 98.1	59	0	19	97.6	94.3; 100.0
Month 48	37	0	17	91.5	85.0; 98.1	43	0	16	97.6	94.3; 100.0

* Kaplan-Meier estimates of percentages of subjects seropositive. For subjects who missed two consecutive visits, only the data up to the missing visits were used f Kaplan-Meier estimates.
† Subjects who were lost to follow-up were censored.
‡ One additional subject was censored at the Month 7 visit.

The safety and immunogenicity of JE-CV in comparison to a live attenuated YF vaccine (Stamaril), with both vaccines administered concomitantly or sequentially (one month between) in a single-dose schedule, were evaluated in a Phase II study (H-040-006). The study was conducted in 108 healthy adult subjects, using a JE-CV dose of 3.8 $\log_{10}$ PFU/0.5-mL. A high JE seroconversion rate was observed when JE-CV was administered concomitantly with or 30 days after Stamaril vaccine, and a high YF seroconversion rate when Stamaril was administered concomitantly with or 30 days after JE-CV, as shown in Table 7. The majority of subjects (between 73.9% and 94.1%) had seroconverted to the homologous virus by 15 days after vaccination with JE-CV; 94.1% for the group receiving JE-CV first, 91.3% for the group receiving both vaccinations on the same day, and 73.9% for the group receiving Stamaril first. The seroconversion rates to the homologous virus 30 days after vaccination were between

91.3% and 100%: 100% after a single JE-CV dose (preceding Stamaril given one month later), 95.7% for co-administration of both vaccines and 91.3% when JE-CV was administered one month after Stamaril (Table 7). The seroconversion rate for all wild-type strains was greater than 60.0% for each strain when JE-CV was co-administered with or given 1 month after Stamaril and over 88.0% when JE-CV was administered alone, one month before Stamaril.

Table 7: Seroconversion rates against homologous virus and Wild-type strains 30 days after JE-CV vaccination is Study H-040-006 (PP population).

Vaccination Order	JE-CV Then STAMARIL® (N = 17)			STAMARIL® Then JE-CV (N = 23)			Co-administration* (N = 23)		
Number and % seroconverted with 95% CI	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
15 days after JE-CV									
Homologous JE-CV	16	94.1	71.3; 99.9	17	73.9	51.6, 89.8	21	91.3	72.0, 98.9
30 days after JE-CV									
Homologous JE-CV	17	100.0	80.5; 100.0	21	91.3	72.0; 98.9	22	95.7	78.1; 99.9
Wild-type strain (genotype):									
1991 TVP-8236 (I)	17	100.0	80.5; 100.0	21	91.3	72.0; 98.9	23	100.0	85.2; 100.0
B 1034/8 (II)	15	88.2	63.6; 98.5	16	69.6	47.1; 86.8	18	78.3	56.3; 92.5
Beijing (III)	16	94.1	71.3; 99.9	20	87.0	66.4; 97.2	19	82.6	61.2; 95.0
JKT 9092 TVP-6265 (IV)	15	88.2	63.6; 98.5	15	65.2	42.7; 83.6	14	60.9	38.5; 80.3

* Co- administration = Co-administration on Day 0 then diluent on Day 30 and diluent on Day 0 then co-administration on Day 30.

Studies Evaluating Lyophilized Formulation of JE-CV (H-040-007, H-040-008, H-040-009, and H-040-010)

The assessment of the lyophilized formulation in clinical studies started with a dose-ranging study (H-040-007) designed to evaluate the safety, tolerability, viraemia, and immunogenicity (to JE-CV and a panel of wild-type strains) of three doses of JE-CV (3.0, 4.0, and 5.0 $\log_{10}$ PFU/0.5-mL dose) in comparison to placebo (see Tables 8 and 9). A dose of at least 4.0 $\log_{10}$ PFU/0.5-mL dose was deemed appropriate for the subsequent phases of the development. This study also established that the lyophilized formulation provided results similar to the liquid formulation used in previous studies in terms of safety, viraemia, and immunogenicity. JE-CV in the lyophilized formulation was further assessed in a Phase II pilot study (H-040-008 on safety and immunogenicity up to 12 months), to prepare for the pivotal Phase III study H-040-009. This study compared JE-CV to Je-Vax in terms of safety and immune response to different JE strains. In addition, cell-mediated immunity was assessed by measuring the gamma-interferon (IFNγ) T-cell response. Je-Vax was compared to JE-CV in a non-inferiority design according to a recommendation of WHO.

Table 8: Seroconversion rates to homologous virus on Days 11 and 30, Months 6 and 12 after JE-CV vaccination in Study H-040-007 (PP population).

		Vaccination Group			
		Placebo	Dose of JE-CV (log_{10} PFU/0.5-mL)		
			3.0	4.0	5.0
		N=32	N=31	N=32	N=31
Day 11	n*	32	31	32	31
	Number seroconverted	0	1	10	8
	Seroconversion rate (%)	0.0	3.2	31.3	25.8
	95% CI†	0.0; 10.9	0.1; 16.7	16.1; 50.0	11.9; 44.6
Day 30	n	32	31	32	31
	Number seroconverted	1	31	30	29
	Seroconversion rate (%)	3.1	100	93.8	93.5
	95% CI	0.1; 16.2	88.8; 100.0	79.2; 99.2	78.6; 99.2
Month 6	n	32	31	30	28
	Number seroconverted	0	30	28	27
	Seroconversion rate (%)	0.0	96.8	93.3	96.4
	95% CI	0.0; 10.9	83.3; 99.9	77.9; 99.2	81.7; 99.9
Month 12	n	29	31	30	30
	Number seroconverted	0	27	26	29
	Seroconversion rate (%)	0.0	87.1	86.7	96.7
	95% CI	0.0; 11.9	70.2; 96.4	69.3; 96.2	82.8; 99.9

Comparison of seroconversion rates at Day 30	**p-value‡**
Overall vaccination difference	<0.001
5.0 log_{10} PFU - Placebo	<0.001
4.0 log_{10} PFU - Placebo	<0.001
3.0 log_{10} PFU - Placebo	<0.001
5.0 log_{10} PFU – 4.0 log_{10} PFU	1.000
5.0 log_{10} PFU – 3.0 log_{10} PFU	0.492
4.0 log_{10} PFU – 3.0 log_{10} PFU	0.492

* n = Number of evaluable subjects at each visit in each group.

† 95% CIs based on an exact binomial calculation.

‡ Based on Fisher's exact test.

Table 9: Antibody Geometric mean titres to homologous virus after JE-CV vaccination in Study H-040-007 (PP population).

	Vaccination Group			
	Placebo	Dose of JE-CV (log_{10} PFU/0.5-mL)		
		3.0	4.0	5.0
	N = 32	N = 31	N = 32	N = 31
Day 30				
n*	32	31	32	31
GMT	5.8	1829.6	2151.5	1956.5
95% CI	4.3; 7.9	916.6; 3651.9	994.1; 4656.8	913.4; 4190.9
Comparison of seroconversion rates on Day 30		**p-value†**		
Overall vaccination difference		<0.001		
Ratio of means‡ (95%CI) on Day 30				
5.0 log_{10} PFU - Placebo		358.5 (157.3; 834.3)		
4.0 log_{10} PFU - Placebo		369.7 (151.1; 904.9)		
3.0 log_{10} PFU - Placebo		316.5 (128.4; 780.2)		
5.0 log_{10} PFU - 4 log_{10} PFU		0.9 (0.4; 2.3)		
5.0 log_{10} PFU - 3 log_{10} PFU		1.1 (0.4; 2.7)		
4.0 log_{10} PFU - 3 log_{10} PFU		1.2 (0.5; 2.9)		

* n = number of evaluable subjects at each visit in each group.

† Based on ANOVA (model = vaccination, centre) between vaccination groups (least significant difference, unadjusted pairwise comparisons), back transformed for ratio of means.

Geometric Mean Antibody Titers

The GMTs observed following vaccination with the liquid formulation of JE-CV (studies H-040-005 and H-040-006) were similar to the GMTs observed following vaccination with the lyophilized formulation of JE-CV (study H-040-007). All three studies showed that JE-CV elicits an immune response 30 days after a single-dose administration.

Choice of the Dose

The dose to be evaluated during the late phase of the clinical development of JE-CV was chosen based on the two dose-ranging studies H-040-003 and H-040-007, which used liquid and lyophilized formulations of vaccine. In study H-040-003, 82 of 87 subjects (94%) who underwent primary immunization with a single injection of JE-CV at all dose levels (from 1.8 to 5.8 log_{10} PFU/0.5-mL dose) seroconverted to JE by neutralization test within 30 days. The first dose of JE-CV was found immunogenic in all dose groups and resulted in high seroconversion rates. In study H-040-007, no apparent difference between the doses administered (from 3.0 to 5.0 log_{10} PFU/0.5-mL dose) was observed. At all doses and across all clinical pharmacology studies, seroconversion rates one month after vaccination were high and more than 90% in all but one JE-CV group (the 2.8 log_{10} PFU/0.5-mL dose group in study H-040-003 where the seroconversion rate was 82%), irrespective of the formulation (lyophilized or liquid)

used, and no dose relationship was apparent. The response tended to be faster after the 3.8, 4.8, or 5.8 $\log_{10}$ PFU/0.5-mL dose in study H-040-003 and after the 4.0 $\log_{10}$ PFU/0.5-mL and 5.0 $\log_{10}$ PFU/0.5-mL dose in study H-040-007 compared to the lower doses. Thus, a dose with a lower potency limit of 4.0 $\log_{10}$ PFU/0.5-mL dose, representing the lowest tested dose with optimal results (high seroconversion rate, rapid onset of immunity, and a good safety profile of JE-CV in a single dose administration) was deemed appropriate for the Phase II study H-040-008 as well as the Phase III studies which completed the development of JE-CV in adults (H-040-009 and H-040-010).

Effect of a Second Vaccination

The repeated administration of JE-CV in an adult population was investigated in two studies where a second dose was administered 30 days after a first dose in study H-040-003 and 5 or 6 months (Month 6 visit) after a first dose in study H-040-005, respectively. In study H-040-003, five groups of subjects received two administrations 30 days apart of JE-CV at doses of 1.8 to 5.8 $\log_{10}$ PFU/0.5-mL; the same dose was given at both administrations. A first dose of JE-CV was found immunogenic in all dose-groups and resulted in high seroconversion rates. Seroconversion was shown to be in the range of 82% to 100% 14 days after the second dose and still high 30 days after the second administration (between 64% and 100%) in both groups. Administration of a second dose of JE-CV 30 days after the first dose did not significantly increase either the seroconversion rate or the mean antibody titer.

Evaluation of a Booster Dose

Half of the subjects enrolled in study H-040-005 were randomly assigned at Month 6 to two groups, one received a second dose of JE-CV (3.8 $\log_{10}$ PFU/0.5-mL) and the other did not. Overall, 161 (98.8%) of the 163 subjects seroconverted to the homologous JE-CV virus 28 days after the first vaccination. Seroconversion rates remained high at the time of booster dose, with 98.6% of subjects still seroconverted. There were four subjects who were seronegative at the time of booster; they all showed more than a 4-fold increase in neutralizing titers after the second immunization. Although there was a trend for higher seroconversion rates after the booster dose, the seroconversion rate was not statistically different between the single-dose and booster-dose groups when evaluated at 6, 12, and 24 months after vaccination. For subjects who received a single dose, the seroconversion rate was 97.4% at Month 6, 95.0% at Month 12, and 91.4% at Month 24. Subjects who received two doses had a seroconversion rate of 96.3% at Month 6, 100.0% at Month 7, 98.5% at Month 12, and 98.3% at Month 24. The GMTs remained high in the two groups at the 6-month evaluation (ITT population) and increased in the booster dose group one month after the booster. At Month 12, GMT values were 180.5 versus 97.4($p=0.0018$), and at Month 24, 137 versus 82.9 ($p=0.0249$) for the single dose and booster dose groups, respectively.

Long-term Immunity

Long-term humoral immunity was assessed 6 to 48 months after the primary single-dose immunization (studies H-040-005, H-040-006 and H-040-007) and following the administration of a booster dose 6 months after the first dose (study H-040-005). In addition, the memory immune response induced by JE-CV was evaluated in study H-

040-002 by injecting an inactivated JE vaccine to the subjects to elicit an anamnestic response.

Long-Term Immunity after a Single Dose (Primary Immunization)

Half of the subjects enrolled in study H-040-005 were followed up to 48 months after the single dose vaccination without having received a booster dose at Month 6. Among the subjects who did not receive a booster dose at Month 6, there were 98.6%, 95.0% and 91.4% of subjects (PP population) still presenting with seroconversion 6, 12 and 24 months after JE-CV vaccination, respectively. The persistence of immunity up to 48 months was evaluated with a Kaplan-Meier estimate analysis. The probability for a subject seropositive at Month 6 of remaining with a titer≥1:10 is >90% up to Month 48: 97.5% at Month 12, 93.2% at Month 24, 91.5% at Month 36, and 91.5% at Month 48. Study H-040-006 shows the persistence of the seroconversion of JE-CV recipients, irrespective of the concomitant or successive administration of a YF vaccine, up to 6 months after a single dose of JE-CV: between 81.8% and 100.0% of subjects remained seropositive for the homologous JE-CV virus; the highest seroconversion was observed in subjects who had received first JE-CV and 30 days later YF vaccine (Table 10). In study H-040-007, seroconversion rates for the homologous JE-CV virus remained high both 6 and 12 months after a single-dose primary vaccination with JE-CV whatever the dose administered; seroconversion rates ranged between 93.3% and 96.8% at 6 months, 86.7% and 96.7% at 12 months. There were no apparent differences at a given time point whatever the dose received

Table 10: Seroconversion rates to homologous virus and Wild-type strains 30 days after JE-CV vaccination is Study H-040-006 (PP population).

Vaccination Order	JE-CV Then STAMARIL® (N = 17)			STAMARIL® Then JE-CV (N = 23)			Co-administration* (N = 23)		
Number and % seroconverted with 95% CI	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
15 days after JE-CV									
Homologous JE-CV	16	94.1	71.3; 99.9	17	73.9	51.6, 89.8	21	91.3	72.0, 98.9
30 days after JE-CV									
Homologous JE-CV	17	100.0	80.5; 100.0	21	91.3	72.0; 98.9	22	95.7	78.1; 99.9
Wild-type strain (genotype):									
1991 TVP-8236 (I)	17	100.0	80.5; 100.0	21	91.3	72.0; 98.9	23	100.0	85.2; 100.0
B 1034/8 (II)	15	88.2	63.6; 98.5	16	69.6	47.1; 86.8	18	78.3	56.3; 92.5
Beijing (III)	16	94.1	71.3; 99.9	20	87.0	66.4; 97.2	19	82.6	61.2; 95.0
JKT 9092 TVP-6265 (IV)	15	88.2	63.6; 98.5	15	65.2	42.7; 83.6	14	60.9	38.5; 80.3

* Co- administration = Co-administration on Day 0 then diluent on Day 30 and diluent on Day 0 then co-administration on Day 30.

Immune Memory Evaluated by Inactivated JE Vaccine Administration

Immune memory was investigated in study H-040-002 by administering JE-CV (single dose) recipients from study H-040-001 with a second JE vaccination 6 months later using the licensed, inactivated MBDV (Je-Vax). Je-Vax was used to determine whether

subjects previously vaccinated with JE-CV would generate an anamnestic response after exposure to an inactivated JE vaccine that contains the critical surface proteins of a JE virus. The neutralizing antibody response by Day 30 was significantly greater among those subjects previously vaccinated with JE-CV (90% seroconversion) than naïve subjects (20% seroconversion) measured by LNI. The rapid memory response was shown in the JE-CV group; six of the 10 subjects who were without detectable circulating levels of protective antibody at challenge seroconverted by Day 7.

Seroconversion to Wild-type JE Strains

Data show that JE-CV produced a neutralizing antibody response to the tested wild-type strains belonging to the four main JE virus genotypes (genotypes I to IV). The $PRNT_{50}$ titers and seroconversion rates were higher against the homologous virus than against the wild-type strains. The seroconversion rates to four of the wild-type strains (1991 TVP-8236 strain [genotype I], Beijing strain [genotype III], P3 strain [genotype III], and Nakayama strain [genotype III]) were broadly similar to the seroconversion rate to the homologous JE-CV virus. The only exception was the Nakayama strain results in study H-040-001, for which less than one-half of the subjects in the 4.0 $\log_{10}$ PFU/0.5-mL dose groups met the criteria for seroconversion at Day 31. However, the seroconversion rate for the Nakayama strain in study H-040-007 was higher at all three dose levels tested (≥84%) than in study H-040-001. These differences may be due to the Nakayama virus lot used in study H-040-001. For the other two wild-type JE strains tested (B1034/8 strain [genotype II] and JKT 9092 TVP-6265 strain [genotype IV]), seroconversion rates were also high (≥78%). In study H-040-005, 28 days after a single-dose JE-CV administration, 98.8% of the subjects seroconverted to the four strains belonging to genotype I and III (1991 TVP-8236 strain and Beijing strain, respectively). Seroconversion rates were slightly lower for the two other tested wild-type strains (B1034/8 strain [genotype II] and JKT 9092 TVP-6265 [genotype IV]) 91.4% and 89.0%, respectively). Moreover, subjects who received JE-CV in a single-dose immunization schedule presented seroconversion rates between 85.5% and 92.1% at Month 6; seroconversion rates then decreased over time for the four wild-type strains and there were still between 62.1% and 87.9% seroconverted at Month 24. In study H-040-006, the seroconversion rate against the panel of four wild-type strains follow the trend observed for the homologous virus. Whatever the groups, the highest seroconversion rates were observed for the 1991 TVP-8236 strain and the Beijing strain. The results of JE wild-type testing were similar between the two formulations tested (liquid formulation in studies H-040-001, H-040-005, and H040-006; lyophilized formulation in study H-040-007). Although there were small variations in the level of seroconversion rates to the four wild-type virus strains after JE-CV vaccination in these studies, the overall seroconversion rate was high.

Interactions between JE-CV and Yellow Fever Vaccines - Effect on Response to JE-CV

In study H-040-001, half of the subjects (12 of 24 subjects) had prior immunity to YF whilst the other half did not. There was no evidence for restriction of seroconversion to JE-CV by pre-existing immunity to YF; 100% of subjects who were administered a single-dose of JE-CV seroconverted against the homologous JE virus, irrespective of their previous immunogenicity status against YF. JE neutralizing antibody titers were slightly higher in YF-immune subjects than in YF-naïve subjects, but always above the

threshold for seropositivity (LNI ≥0.7). In study H-040-003, prior vaccination with YF-Vax did not suppress response to JE-CV, as 10 of 11 subjects (91%) administered YF vaccine before JE-CV vaccination seroconverted to JE. Study H-040-006 assessed different schedules of immunization combining JE-CV and YF vaccine (Stamaril), concomitantly or successively with a 30-day interval (Table 10). Subjects who received JE-CV first (17 subjects) presented with a 94.1% seroconversion rate 15 days after the vaccination, which continued to increase up to 100.0% 30 days post-vaccination. Slightly lower seroconversion rates were observed after both 15 and 30 days post-vaccination (91.3% and 95.7%, respectively) in subjects who were administered concomitantly JE-CV and Stamaril (23 subjects). The lowest seroconversion rates were observed in subjects who received first the YF vaccination, and JE-CV (23 subjects) 30 days later (73.9% and 91.3% seroconverted 15 and 30 days after the JE-CV administration, respectively). The antibody GMTs to JE homologous virus 30 days after JE-CV vaccination were 1461.6 in subjects receiving JE-CV 30 days before Stamaril and 426.4 in subjects receiving JE-CV 30 days after Stamaril and 344.2 in subjects receiving JE-CV and Stamaril concurrently. These reductions are unlikely to be clinically relevant as GMT levels were high overall and there was no difference between vaccine groups in proportion of subjects who seroconverted to JE.

Effect on YF Response

In study H-040-001, JE-CV did not elicit anti-YF neutralizing antibodies in subjects without previous YF immunity. The 5.0 $\log_{10}$ PFU/0.5-mL JE-CV dose stimulated YF antibody responses in 3 of 6 YF-immune subjects. No YF response was seen with the 4.0 $\log_{10}$ PFU/0.5-mL dose. YF seroconversion rates were slightly reduced in study H-040-003 in subjects with prior vaccination with JE-CV. In the group of subjects with no prior exposure to JE-CV, 10 of 11 subjects seroconverted to YF within 30 days of receiving YF-Vax, whereas in the group of subjects with prior exposure to JE-CV (30 days before), 7 of 11 subjects seroconverted to YF. The numbers in this study were small and this reduction in YF seroconversion rate does not appear to be clinically significant. In study H-040-006, all the 63 subjects who received Stamaril seroconverted to YF 30 days after the administration of YF vaccine, whatever the order of the administration of the two vaccines. This larger study suggested that pre-existing YF antibodies did not reduce the ability of JE-CV to induce a JE-specific antibody and there was no clinically relevant effect of pre-existing JE immunity on the immune response to YF vaccination.

Cell mediated Immunity

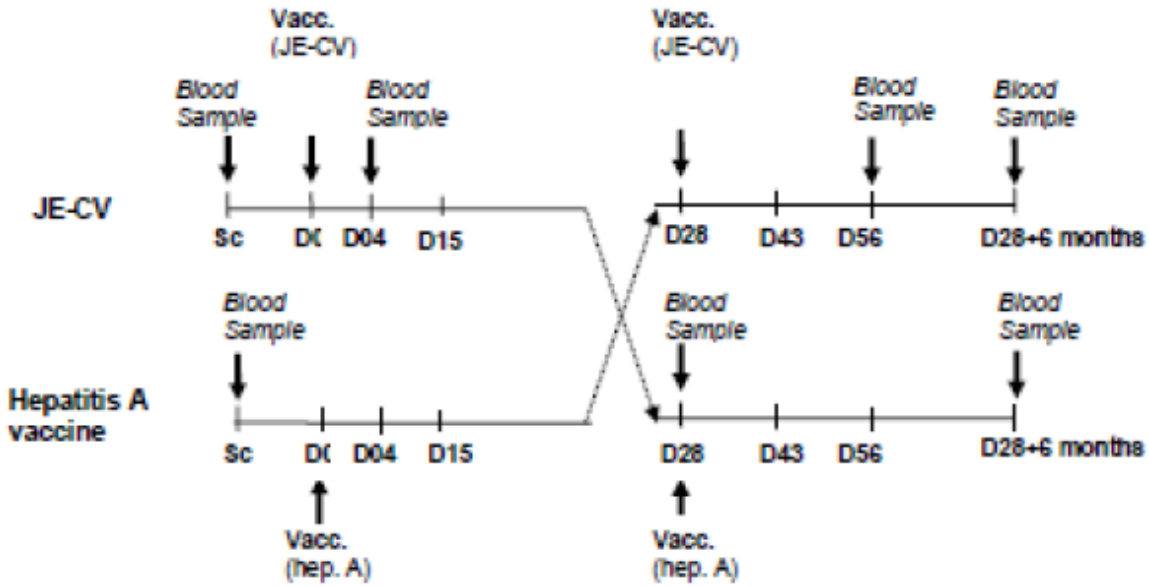
To evaluate the effect of JE-CV on the ability to elicit a memory cell-mediated immune response in vaccinated subjects, the development of T-cells able to produce IFNγ in response to peptides encompassing the JE structural proteins prM and E was evaluated by enzyme-linked immunosorbent spot (ELISPOT). Vaccination with JE-CV resulted in an increase in JE virus-specific IFNγ T-cell responses in about one third of the subjects under the conditions of this study and within the sensitivity of the assay used. The overall proportion of subjects responding in an ELISPOT assay to JE virus structural peptides encompassing the prM/M protein or first third of the JE E protein was higher in the group vaccinated with JE-CV than in the group vaccinated with Je-Vax. At 28 days after vaccination (study Day 56), 8 of 28 subjects (28.6%) vaccinated with JE-CV had a

positive response compared with 0 of 29 subjects (0.0%) vaccinated with Je-Vax. Subjects who responded to in vitro stimulation with peptides 28 days after vaccination (study Day 56) also had a response to the same peptides at Month 6. Four of six subjects evaluated who responded at Month 6 also had a detectable response to prM/M and/or E at Month 12.

Paediatric studies

JEC01 is a randomized, cross-over, open, active controlled (hepatitis A vaccine), multi-center trial conducted in Thailand. A total of 100 children and 200 toddlers were enrolled. Enrolment was sequential in the two age cohorts. The subjects received one single dose of JE-CV and one dose of hepatitis A vaccine one month apart, and receive a second dose of hepatitis A vaccine 6 months later, with a planned 5-year follow-up. The trial has a cross-over design with an active control aiming that all subjects would receive one dose of JE-CV (currently JE vaccination is recommended in the Thai immunization program). The hepatitis A vaccine was to be given as a two dose regimen, the first dose was used as a control vaccine, and the second dose will be given at the 6-month follow-up visit to complete the recommended schedule. An open design was chosen for the trial since the investigational JE-CV was administered subcutaneously whereas hepatitis A control vaccine was administered intramuscularly. Also, to limit the number of blood samples in the paediatric population, blood samples for immunogenicity and biological safety assessments 28 days after the first vaccination were only taken after injection with JE-CV (Groups 1 and 3), and not after injection with hepatitis A vaccine (Groups 2 and 4) as shown in Figure 1. Furthermore, blood samples for Day 4 viraemia and biological safety assessments were only taken in Groups 1 and 3 that received JE-CV as a first vaccination. For safety purposes the enrolment was stepwise, starting with children aged 2 to 5 years. Then when safety data obtained up to 14 days after the screening visit were found satisfactory (according to the Safety Review Committee), the younger age cohort (12 to 24 months of age) was vaccinated. For practical reasons the Month 6 follow-up visits were organized at approximately the same time-point irrespective of the group. As a consequence, the post-JE-CV vaccination time points for assessment of persistence of immune response and the period for SAE reporting differed slightly between the groups.

Figure 1: Trial Design for the Vaccination Period of JECO1



Overview of Efficacy trials

Study Design Outlines

Only studies H-040-008 and H-040-009 are considered for the efficacy evaluation. Both studies were conducted in a similar population using a similar design; a single dose of JE-CV in comparison to Je-Vax, a licensed MBDV. To maintain the study blind, the first two doses in the Je-Vax group were matched by saline placebo in the JE-CV group. The two studies had minor differences in the last administration of an investigational vaccine (at the Day 28 or 30 visit); in study H-040-008, 60 subjects received Je-Vax (in the recommended three-dose schedule on Days 0, 7 and 28) or JE-CV (on Day 28 following two placebo doses on Days 0 and 7), while in study H-040-009, 820 subjects received Je-Vax (three-dose schedule on Days 0, 7 and 30) or JE-CV on Day 30 (following two placebo doses on Days 0 and 7) and placebo, in opposite arms, on Day 30. Both studies allowed the comparison of a single-dose JE-CV administration with the recommended three-dose regimen of Je-Vax. The non-inferiority evaluation was made in a large scale Phase III study (H-040-009) assessing efficacy based on a correlate of protection in a head-to-head comparison with a standard-of-care MBDV, Je-Vax.

Study H-040-008 was a pilot Phase II study to prepare for the pivotal Phase III study H-040-009. An additional aim of study H-040-009 was to establish immunological consistency between three JE-CV lots. H-040-009 was a pivotal Phase III study performed at five centers in the USA and five centers in Australia and evaluated the safety, immunogenicity, and tolerability of JE-CV and Je-Vax. The study was conducted in a total of 820 healthy adult subjects aged 18 years or older. Subjects were assigned to two vaccine groups: 410 subjects in the JE-CV group and 410 in the Je-Vax group. The JE-CV group was comprised of three groups of 137, 135, and 138 subjects,

each receiving a different conformance lot of JE-CV. Subjects were injected subcutaneously on Days 0,7, and 30 under double-blind conditions. The primary immunogenicity endpoint was the proportion of subjects in the efficacy population who seroconverted to the respective homologous virus 30 days after completion of the immunization schedule in each vaccine group. As the only licensed JE vaccine in the countries were JE-CV was developed, Je-Vax was determined to be the most appropriate comparator for the large-scale assessment of efficacy of a new JE vaccine.

Study Sample Sizes

The sample size of the Phase II pilot study H-040-008 was defined arbitrarily to prepare the Phase III study H-040-009. Thirty subjects were included in each of the groups JE-CV and Je-Vax. The sample size of the Phase III study H-040-009 was defined according to the main statistical hypothesis to be tested, that is, in order to rule out a 5% difference in seroconversion rates in a noninferiority test. This would also allow the detection of rare AEs. A total of 410 subjects were included in each of the groups JE-CV and Je-Vax.

Study Population

Subjects planned to be enrolled for both study H-040-008, carried out in the USA, and study H-040-009, conducted in Australia and the USA, were to be in good general health, without significant medical history or clinically significant abnormal laboratory results. Subjects must have had no history of vaccination, exposure, or infection with JE, YF, or other flaviviruses as determined by subject interview. Subjects with known or suspected immunodeficiency, or those using immunosuppressive or anti-neoplastic drugs were excluded. Subjects in study H-040-008 were between the ages of 18 and 49 years (inclusive) and enrolled at one site in the USA. Study H-040-009 enrolled subjects who were at least 18 years old. A total of 880 subjects were enrolled in these two studies; 60 in study H-040-008 and 820 in study H-040-009; half of the subjects were randomized to JE-CV whilst the other half was randomized to Je-Vax. Demographic characteristics were well balanced between the vaccine groups in both studies. Since study H-040-008 was a pilot Phase II study with a limited number of subjects, the analyses were mainly descriptive. Study H-040-009 tested non-inferiority of JE-CV to Je-Vax in JE neutralizing antibody seroconversion rates. The primary population for the analysis of immunogenicity was the PP population for study H-040-008 (55 subjects) and the efficacy population for study H-040-009 (711 subjects considered). Subjects taken into account for the PP or efficacy population analyses were required to have received the investigational vaccines accordingly to the experimental plan, to have samples on the defined time-points for the assessment of the immune responses, and to be confirmed as naïve to JE at baseline. Only two of 60 subjects withdrew in study H-040-008: one in the JE-CV group because of a protocol violation and one in the Je-Vax group because of physician/investigator decision. The main reasons for withdrawal of subjects in study H-040-009 were voluntary withdrawal (18 of 820 subjects) and lost to follow-up (17 of 820 subjects). In study H-040-009, 27 subjects (6.6%) in the JE-CV group withdrew from the study before receiving JE-CV on Day 30. All subjects in the Je-Vax group received at least one dose of active vaccine. All subjects in study H-040-008 received at least one dose of active vaccine.

Seroconversion

The seroconversion assessment was based on an immune response induced either 14 days or 28 or 30 days after the completion of the vaccinations. This design allows comparing a JE-CV vaccination in a single-dose administration schedule to a Je-Vax vaccination in a three-dose regimen. Secondary endpoints included levels of neutralizing antibody titers at various time points after vaccination and comparisons of immune responses to different JE virus challenges. The main analyses were performed using the PP or efficacy populations, which included only JE-naïve subjects at baseline. In study H-040-008, seroconversion rates were summarized and compared between JE-CV and Je-Vax vaccine groups by examining the odds ratios and 95% CIs from the logistic regression model. In study H-040-009, the proportion of subjects seroconverting in the JE-CV groups and the Je-Vax group was compared using a test of non-inferiority with a delta of 5%, that is, the test intended to rule out a 5% difference in seroconversion rates between the groups. The difference and one-sided 97.5% CI in the proportion of subjects who seroconverted 30 days after completion of vaccination were constructed using exact binomial CI. The one-sided 97.5% confidence limit was obtained from the lower limit of the two-sided 95% CI. If protective antigen (PA) defined the seroconversion rate in the JE-CV group, and PD defined the seroconversion rate in the Je-Vax, then non-inferiority was established if the lower limit of the CI for PA-PD exceeded -5%.

Neutralizing Antibody Titers Post-vaccination

In study H-040-008, GMTs were summarized and compared between the JE-CV and Je-Vax vaccine groups by analysis of variance (ANOVA). In study H-040-009, the $\log_{10}$ values of the antibody titers to JE were calculated for pre-vaccination values and for all post-vaccination values using an ANOVA model. Estimates of the differences and CIs were calculated as the back transformed values obtained from the ANOVA model. Non-inferiority was established if the lower limit of the CI exceeded 0.5 (equivalent to a difference in means of the $\log_{10}$ titer being at least –0.301).

Efficacy Results

The two studies H-040-008 and H-040-009 showed high seroconversion rates and that JE-CV is as immunogenic as Je-Vax (Table 11). In both studies JE-CV and Je-Vax were compared based on $PRNT_{50}$ using the respective homologous JE viruses (JE-CV virus in the JE-CV group, Nakayama strain for the Je-Vax group). Table 11 summarizes the main rates of seroconversion 14 or 28/30 days after completion of the vaccination by PRNT. Considering the homologous JE virus 28 or 30 days post-vaccination (the JE-CV virus for the JE-CV group and the Nakayama strain for the Je-Vax group), H-040-008 demonstrated that the seroconversion rates were significantly different in the two groups and H-040-009 demonstrated that the seroconversion rates were as high for JE-CV as for Je-Vax. The seroconversion rates were 100% and 99.1% for JE-CV in studies H-040-008 and H-040-009, respectively and 80.8% and 74.8% for Je-Vax in studies H-040-008 and H-040-009, respectively (see Table 11).

Table 11: Seroconversion rates to JE viruses by $PRNT_{50}$ and by vaccine group (H-040-008 PP population and H-040-009 Efficacy population).

	H-040-008				H-040-009			
Timepoint Post Last Immunization	14 days (Day 42)		28 days (Day 56)		14 days (Day 44)		30 days (Day 60)	
$PRNT_{50}$ Challenge Virus	JE-CV (N=29)	JE-VAX® (N=26)	JE-CV (N=29)	JE-VAX® (N=26)	JE-CV (N=346)	JE-VAX® (N=365)	JE-CV (N=346)	JE-VAX® (N=365)
JE-CV Virus Seroconversion (%)	62.1	100.0	100.0	100.0	93.6	-	99.1	95.1
Nakayama Strain Seroconversion (%)	17.2	92.3	62.1	80.8	-	-	80.9	74.8
P3 Strain Seroconversion (%)	86.2	100.0	100.0	100.0	-	-	-	-

Seroconversion

Homologous JE Virus Challenge

Seroconversion rates over time for the PP and efficacy populations in a homologous JE virus challenge for studies H-040-008 and H-040-009 are presented in Tables 11 and 12 (NB, in Table 12, Days 14 and 28 on the table are pre-vaccination with JE-CV). There was a rapid immune response in subjects after vaccination with JE-CV; 14 days after a single dose of JE-CV (Day 42/44) the overall seroconversion rate was 62.1% in study H-040-008 and 93.6% in study H-040-009.

The seroconversion rate 14 days after the last dose in a full regimen of three doses of Je-Vax in study H-040-008 was 92.3%, which corresponded to the time point that Je-Vax subjects achieved the highest seroconversion rate against the homologous virus. At 28/30 days after the single dose of JE-CV, or the third dose of Je-Vax, the overall seroconversion rate was higher for the JE-CV group than for the Je-Vax group; after vaccination with JE-CV, 100% and 99.1% of subjects seroconverted in studies H-040-008 and H-040-009, respectively, compared with 80.8% and 74.8% after vaccination with Je-Vax. Seroconversion 30 days after the completion of JE vaccinations shows that statistical significance (p=0.0189) was established in study H-040-008 using Fisher's exact test. In study H-040-009, the difference in the proportions of subjects who seroconverted 30 days after vaccination (either the single dose of JE-CV or the third dose of Je-Vax) was 24.3% and the efficacy analysis established that JE-CV induced as high rates of seroconversion as did Je-Vax (that is, non-inferiority of JE-CV to Je-Vax was demonstrated).

Table 12: Seroconversion rates by vaccine group (JE-CV and JE-Vax) and PRNTJE-CV, PRNTNakayama and PRNTP3) in study H-040-008 (PP population).

$PRNT_{50}$ Challenge Virus	Group	Seroconversion (%)					
		Day 14	Day 28	Day 42*	Day 56†	Month 6	Month 12
JE-CV Virus	JE-CV	0.0	0.0	62.1	100.0	92.3	92.3
	JE-VAX®	53.8	88.5	100.0	100.0	70.8	59.1
Nakayama Strain	JE-CV	0.0	0.0	17.2	62.1	38.5	30.8
	JE-VAX®	26.9	61.5	91.3	80.8	29.2	18.2
Wild-type P3 Strain	JE-CV	0.0	3.4	86.2	100.0	92.3	88.5
	JE-VAX®	69.2	92.3	100.0	100.0	87.5	86.4

*14 days after the 3rd dose of Je-Vax or single JE-CV, †28 days after the 3rd dose of Je-Vax or single JE-CV

Comparison of the Two Vaccines Using the Same PRNT Challenge Virus

In both studies H-040-008 and H-040-009 the immune responses in the JE-CV and Je-Vax groups were compared using a single $PRNT_{50}$, that is, neutralizing antibody levels were measured with the JE-CV virus as the challenge virus (PRNTJE-CV) or with the Nakayama strain as the challenge strain (PRNTNakayama). On Day 28/30 after completion of vaccination the seroconversion rate using PRNTJE-CV was high for both JE-CV and Je-Vax groups in both studies. The seroconversion was 100.0% in PRNTJE-CV for subjects in both JE-CV and Je-Vax groups in study H-040-008, and 99.1% and 95.1% (for JE-CV and Je-Vax recipients, respectively) in study H-040-009. The seroconversion rates measured for the same Day 28/30 samples with PRNTNakayama were generally lower than with PRNTJE-CV. The seroconversion rates were 62.1% and 80.8 % for subjects vaccinated with JE-CV and Je-Vax, respectively, in study H-040-008 and 80.9% and 74.8% (JE-CV and Je-Vax recipients, respectively) in study H-040-009. Study H-040-008 also compared the two investigational vaccines in a challenge using the fully heterologous virus strain P3 as challenge strain in the $PRNT_{50}$. Twenty-eight days after completion of vaccination, 100.0% of subjects who received JE-CV or Je-Vax seroconverted to the P3 strain.

Conclusions

It could be concluded from studies H-040-008 and H-040-009 that whatever the strain used in the $PRNT_{50}$, one dose of JE-CV is as immunogenic as three doses of Je-Vax in the efficacy population. Moreover, results from the Phase III study H-040-009 confirmed the trend observed in the pilot Phase II study H-040-008; a high seroconversion rate is observed 14 days after the administration of a single dose of JE-CV.

Neutralizing Antibody Titers Post-vaccination

Homologous JE Virus Challenge

Similar to seroconversion rate results, there was a difference in the GMTs 14 days after vaccination (either a single dose of JE-CV or a third dose of Je-Vax) in the JE-CV group between study H-040-008 (64.5) and study H-040-009 (312.3). There were comparable GMTs observed in the JE-CV and the Je-Vax group (64.5 versus 70.0, respectively; study H-040-008 only) 14 days after vaccination (either the single dose of JE-CV or the third dose of Je-Vax). In subjects who received JE-CV, GMTs 30 days after vaccination were comparable across the studies (1082.8 and 1391.7). GMTs 30 days after a single dose of JE-CV were higher than those observed 30 days after the third dose of Je-Vax (1082.8 and 1391.7 for the JE-CV group compared with 24.1 and 37.4 for the Je-Vax group in studies H-040-008 and H-040-009, respectively). A statistically significant difference in the GMTs 30 days after vaccination (either the single dose of JE-CV or the third dose of Je-Vax) was established ($p<0.0001$) in study H-040-008. In study H-040-009, the ratio of neutralizing antibody GMTs between treatment groups at 30 days after completion of the vaccination schedule was 37.4 (95% CI: 29.7; 47.0), which demonstrated statistically that JE-CV is as immunogenic as Je-Vax.

Persistence of Efficacy

Long-term immunity data up to Month 12 are available from study H-040-008; and up to 5 years after a JE-CV vaccination (up to 48 months at the time of this application) from study H-040-005. Long-term immune response assessments have not been repeated in the late Phase III studies.

Seroconversion to JE Virus Strains

Seroconversion rates up to 6 and 12 months after JE-CV or Je-Vax administration from Phase II study H-040-008 using different JE viruses for challenge remained high, above or close to 90% (the the lowest point (nadir) being 88.5% with P3 strain) up to 12 months after a single-dose administration of JE-CV. In the Je-Vax group the persistence of seroconversion to the P3 strain decreased slowly until Month 12 at which point there were more than 85% still seroconverted.

Efficacy Results in Subpopulations

Subpopulation analysis was performed for the individual countries in which studies H-040-008 (USA only) and H-040-009 (USA and Australia) were performed (Table 13). Subpopulation analysis was performed for different age ranges (18 to 45 years, 45 to 60 years, and > 60 years) in study H-040-009. Subject characteristics were comparable across both countries for subjects enrolled in study H-040-009. There was no relevant difference in the immune responses between countries; a significant difference between the JE-CV and Je-Vax vaccine groups in both seroconversion rates and post-vaccination GMTs was observed in both Australia and the USA. Seroconversion rates and GMTs by age group in study H-040-009 were not markedly different from overall results. At 14 days after a single vaccination with JE-CV, the seroconversion rate in subjects 18 to 45 years was 94.1% (n=236), the seroconversion rate for subjects over 45 to 60 years was 89.9% (n=79), and the seroconversion rate for subjects over 60 years was 100% (n=31). Seroconversion rates 14 days after vaccination were not determined for Je-Vax. At 30

days after vaccination, the seroconversion rate in subjects 18 to 45 years was 98.7% for JE-CV (n=236) compared with 77.3% for Je-Vax (n=247); the seroconversion rate for subjects over 45 to 60 years was 100% for JE-CV (n=79) compared with 71.7% for Je-Vax (n=92); and the seroconversion rate for subjects over 60 years was 100% for JE-CV (n=31) compared with 61.5% for Je-Vax (n=26), highlighting greater seroconversion rates after vaccination with JE-CV compared with Je-Vax, whatever the age.

Table 13: Seroconversion rates against the homologous virus by age group for study H-040-009 (Efficacy population).

	H-040-009					
	Age Group ≥18 to ≤45 Years		Age Group >45 Years to ≤60 Years		Age Group >60 Years	
	JE-CV (N = 236)	JE-VAX® (N = 247)	JE-CV (N = 79)	JE-VAX® (N = 92)	JE-CV (N = 31)	JE-VAX® (N = 26)
14 days post-vaccination*						
n	236	—	79	—	31	—
Seroconversion n (%)	222 (94.1)	—	71 (89.9)	—	31 (100.0)	—
(95% CI)†	(90.2; 96.7)	—	(81.0; 95.5)	—	(88.8; 100.0)	—
30 days post-vaccination*						
n	236	247	79	91	31	26
Seroconversion n (%)	233 (98.7)	191 (77.3)	79 (100.0)	66 (71.7)	31 (100.0)	16 (61.5)
(95% CI)†	(96.3; 99.7)	(71.6; 82.4)	(95.4; 100.0)	(61.4; 80.6)	(88.8; 100.0)	(40.6; 79.8)

* Time points were relative to end of vaccination schedule (either single dose of JE-CV or third vaccination of JE-VAX®).
. Based on an exact binomial calculation. Only JE-CV virus was analyzed 14 days post-vaccination.

Paediatric efficacy data

In JEC01, JE antibody assessments were performed using the homologous JE-CV virus and four wild-type JE virus strains of genotypes I to IV relevant for Thailand and south-east Asia. Seroprotection was defined as in adults (seroconversion) or for subjects who were seropositive (≥10 1/dil[4]) at baseline, a more than four-fold rise in neutralizing antibody titer was required. Twenty-eight days after JE-CV vaccination, all 97 children previously immunised with MBDV (100.0%) in the PP set were seroprotected and 92.8% had seroconverted to the homologous JE-CV virus. The GMTs (95% CI) increased from the baseline level of 44.8 1/dil (33.8; 59.4) to a post-vaccination level of 2634 1/dil (1928; 3600). The GMTs to wild-type strains were generally lower than to the homologous JE-CV virus. The seroprotection rate in JE naïve toddlers (PP set, that is, seronegative to all tested wild-type strains) was 96.0% and 96.5% of subjects had seroconverted to the homologous virus. The GMTs (95% CI) increased from the baseline level of 5.41 1/dil (5.14; 5.69) to a post-vaccination level of 281 1/dil (219; 362). The immune response in terms of seroprotection and seroconversion to wild-type strains was similar to that observed with the homologous JE-CV virus (over 95% seroconversion and seroprotection), except for strain JKT 9092 TVP 6265 (genotype

[4] 1/dil unit refers to antibody titer.

IV) which elicited a lower immune response. The GMTs to wild-type strains were generally lower than to the homologous JE-CV virus. Six months after the last vaccination, 86.8% of toddlers (full analysis set (FAS)) remained seroprotected as assessed using the JE-CV virus. The level of seroprotection assessed using wild-type JE virus strains in FAS subjects decreased for all the tested strains compared to the level 28 days after JE-CV vaccination, with seroprotection rates ranging from 57.9% to 91.9%. The GMTs were lower than those at 28 days after JE-CV vaccination for both the JE-CV virus and the four wild-type strains.

In Study JEC02, 1200 toddlers aged 11.6 to 18.8 months were evaluated at screening. A consistent clinical immune response to three consecutive industrial scale lots was demonstrated following a single vaccination with JE-CV. Twenty-eight days after vaccination, seroconversion rates were superior to 92% in all JE-CV Thai lot groups and GMTs ranged between 168 1/dil and 206 1/dil, which demonstrated that the three lots of JE-CV (from Thailand) are bioequivalent in term of post-vaccination seroconversion rate and GMTs. BY pooling data of the three lots of JE-CV from Thailand, the study demonstrated that JE-CV from Thailand is bioequivalent to JE-CV from the USA in term of post-vaccination seroconversion rate and GMTs, with 92.2% to 97.9% of seroconverted subjects.

Safety

The safety of JE-CV was investigated in all clinical studies in the overall clinical development program in adults. Safety was assessed based on reported AEs (elicited by structured interview or spontaneously observed), vital signs and body temperature, physical examination, and routine laboratory testing (haematology, biochemistry, and urinalysis). Subjects in all studies were required to complete a diary card after vaccination to record daily signs and symptoms, oral temperature and any new medications or herbal treatments used. An independent Data and Safety Monitoring Board (DSMB) monitored the safety on an ongoing basis for studies H-040-005, H-040-006, H-040-007, H-040-009, and H-040-010. Study H-040-010 was a large, single dose, placebo controlled trial to collect safety data. The details of study structure for the collection of these data were summarized in the sponsor's Australian submission. The duration of serious adverse events (SAEs) follow-up varied. Safety data were combined for all studies in which at least one dose of JE-CV was administered (H-040-001, H-040-003, H-040-005, H-040-006, H-040-007, H-040-008, H-040-009, and H-040-010). The safety parameters collected for all the different studies used for safety data were also summarised in the Australian submission (these were minor differences). Eight clinical studies (H-040-001, H-040-003, H-040-005, H-040-006, H-040-007, H-040-008, H-040-009, and H-040-010) provided safety data in adults. A total of 3 457 subjects were included in the clinical development program, with 3 439 adult subjects integrated overall for the safety analyses. Specifically for JE-CV, 2 486 subjects were randomly assigned to receive JE-CV (any dose and formulation) and 2 459 subjects received a JE-CV vaccination and were included in the safety analyses. The safety population is defined as all randomized subjects who received at least one dose of study or control vaccine. Most subjects continued to be followed up to Day 30 (>94%), with lost to follow-up as the overall most common reason for withdrawal (<2%).

Results

AEs were evenly distributed between subjects vaccinated with the lyophilized formulation (66.3%) and subjects vaccinated with the liquid formulation (63.3%). The numbers of AEs reported in all groups, within 30 days after vaccination in the key studies were noted; a total of 65.8% of subjects in the JE-CV (4.0 $\log_{10}$ PFU/0.5-mL dose) group experienced at least one AE within 30 days compared with 68.5% of subjects in the Je-Vax (Dose 3) group. Almost half of the subjects (47.5%) experienced at least one AE considered related to JE-CV. The majority of subjects (63.2%) experienced at least one systemic AE. A total of 16.7% of subjects experienced at least one injection site AE. The most common systemic AEs were headache, fatigue, malaise, myalgia, injection site pain, feeling hot, and diarrhoea (>10% - Table 14 and >1% - Table 15). The percentages of subjects who experienced at least one related AE (Table 15) were higher for those vaccinated with Je-Vax (55.7%; Dose 3) or placebo (60.7%; Doses 1 and 2) compared with those vaccinated with JE-CV (48.8%; 4.0 $\log_{10}$ PFU/0.5-mL dose) or placebo only (51.0%). All AEs were more common in women than men, not related to age, and were slightly higher in the underweight group. There were three pregnancies reported in JE-CV recipients. Two were electively terminated and one carried to term without documented adverse events.

Table 14: Most commonly reported AEs in adults (>10% of subjects in any vaccine group) by system organ class, preferred term for key studies of JE-CV (lyophilized formulation versus comparators; Safety population).

System organ class / Preferred term	JE-CV 4.0 log_{10} PFU/0.5-mL Dose (N = 2046) n (%)	Events	JE-VAX® Doses 1 and 2* (N = 440) n (%)	Events	JE-VAX® Dose 3 (N = 422) n (%)	Events	Placebo Doses 1 and 2* (N = 440) n (%)	Events	Placebo (N = 435) n (%)	Events
All adverse events	1261 (61.6)	7271	363 (82.5)	2604	268 (63.5)	1367	312 (70.9)	1690	273 (62.8)	1388
General disorders and administration site condition	893 (43.6)	3114	324 (73.6)	1574	214 (50.7)	794	228 (51.8)	740	188 (43.2)	575
Fatigue	565 (27.6)	1155	120 (27.3)	277	66 (15.6)	135	134 (30.5)	250	124 (28.5)	205
Malaise	446 (21.8)	765	103 (23.4)	178	48 (11.4)	81	91 (20.7)	146	99 (22.8)	160
Injection site pain	242 (11.8)	356	257 (58.4)	598	147 (34.8)	276	89 (20.2)	149	40 (9.2)	55
Feeling hot	221 (10.8)	319	35 (8.0)	50	24 (5.7)	35	41 (9.3)	60	39 (9.0)	61
Injection site erythema	91 (4.4)	99	109 (24.8)	181	76 (18.0)	94	15 (3.4)	19	15 (3.4)	15
Injection site pruritus	76 (3.7)	91	86 (19.5)	125	54 (12.8)	65	23 (5.2)	32	12 (2.8)	16
Injection site swelling	27 (1.3)	27	61 (13.9)	94	54 (12.8)	62	7 (1.6)	7	4 (0.9)	5
Nervous system disorders	721 (35.2)	1498	180 (40.9)	380	99 (23.5)	207	178 (40.5)	337	143 (32.9)	291
Headache	709 (34.7)	1458	177 (40.2)	366	96 (22.7)	201	177 (40.2)	322	141 (32.4)	285
Musculoskeletal and connective tissue disorders	482 (23.6)	957	113 (25.7)	248	55 (13.0)	110	102 (23.2)	236	83 (19.1)	155
Myalgia	401 (19.6)	631	96 (21.8)	162	42 (10.0)	74	88 (20.0)	139	69 (15.9)	106
Arthralgia	198 (9.7)	290	43 (9.8)	71	24 (5.7)	30	45 (10.2)	84	27 (6.2)	43

System organ class / Preferred term	JE-CV 4.0 log_{10} PFU/0.5-mL Dose (N = 2046) n (%)	Events	JE-VAX® Doses 1 and 2* (N = 440) n (%)	Events	JE-VAX® Dose 3 (N = 422) n (%)	Events	Placebo Doses 1 and 2* (N = 440) n (%)	Events	Placebo (N = 435) n (%)	Events
Gastrointestinal disorders	402 (19.6)	886	96 (21.8)	196	51 (12.1)	101	97 (22.0)	102	74 (17.0)	149
Diarrhea	211 (10.3)	294	46 (10.5)	62	19 (4.5)	27	45 (10.2)	64	39 (9.0)	45
Abdominal pain	167 (8.2)	267	34 (7.7)	47	22 (5.2)	30	46 (10.5)	71	27 (6.2)	34

- JE-CV 4.0 log10 PFU/0.5-mL Dose: studies H-040-007 (4.0 log10 PFU/0.5-mL dose), H-040-008, H-040-009, and H-040-010
- JE-VAX® Doses 1 and 2 : studies H-040-008 and H-040-009
- JE-VAX® Dose 3: studies H-040-008 and H-040-009
- Placebo Doses 1 and 2: studies H-040-008 and H-040-009
- Placebo: studies H-040-007 and H-040-010

* A second injection was administered 7 days after the first.

Table 15: Occurrence of related adverse events in adults (>1% in the JE-CV group) within 30 days after vaccination by System Organ Class, preferred term key studies (lyophilized formulation versus comparators; Safety population).

	JE-CV 4.0 log10 PFU (N=2046)	JE-VAX® Dose 1 and 2* (N=440)	JE-VAX® Dose 3 (N=422)	Placebo Dose 1 and 2 (N=440)	Placebo (N=435)
System organ class Preferred term					
General disorders and administration site conditions					
Fatigue	21.0%	23.6%	10.9%	26.6%	22.1%
Malaise	17.0%	20.5%	9.0%	17.5%	16.3%
Injection site pain	11.8%	58.4%	34.8%	20.2%	9.2%
Feeling hot	8.4%	7.3%	4.7%	8.2%	6.9%
Chills	6.0%	5.5%	1.9%	7.3%	4.1%
Injection site erythema	4.4%	24.8%	17.5%	3.4%	3.2%
Injection site pruritus	3.6%	19.5%	12.6%	5.0%	2.5%
Injection site swelling	1.3%	13.9%	12.6%	1.6%	0.9%
Injection site bruising	1.1%	3.2%	1.4%	2.5%	1.1%
Pyrexia	0.9%	1.1%	1.2%	1.1%	1.4%
Nervous system disorders					
Headache	23.9%	32.5%	15.6%	30.7%	24.6%
Dizziness	1.1%	0.9%	0.2%	0.5%	0.7%
Musculoskeletal and connective tissue disorders					
Myalgia	14.7%	17.5%	6.9%	15.7%	11.5%
Arthralgia	6.6%	8.6%	3.8%	8.6%	4.6%
Gastrointestinal disorders					
Diarrhoea	7.6%	7.3%	2.4%	7.0%	5.7%
Nausea	6.5%	8.4%	4.3%	5.9%	6.4%
Abdominal pain	5.1%	5.7%	3.3%	8.0%	4.8%
Vomiting	1.0%	1.1%	0.9%	1.4%	1.6%
Respiratory, thoracic and mediastinal disorders					
Pharyngolaryngeal pain	2.9%	2.3%	1.2%	2.3%	2.3%
Dyspnea	2.7%	3.2%	1.4%	3.0%	2.3%
Rhinorrhoea	1.5%	0.5%	0.0%	0.5%	2.1%
Cough	1.4%	0.9%	0.9%	0.9%	1.8%
Wheezing	1.3%	1.4%	0.2%	2.3%	1.8%
Nasal congestion	1.0%	0.7%	0.7%	0.2%	2.1%
Skin and subcutaneous tissue disorders					
Rash	1.2%	3.9%	2.1%	2.3%	1.8%

Note: Percentages are based on the number of subjects in the safety population for each vaccine group.
Integrated results based on studies H-040-007 (4.0 log10 PFU and placebo group), H-040-008, H-040-009 and H-040-010. At each level of summarization, a subject is counted once for each preferred term even if the subject reported one or more events.
If the relationship of the AE is missing then the AE is reported as 'related'.
* A 2nd injection was administered 7 days after the first.
† Pyrexia was reported by less than 1% of subjects but is presented in the table as it is considered relevant

A small percentage of adult subjects experienced at least one severe AE (2.5%) and only two serious events were thought to be related to vaccination with the lyophilized formulation of JE-CV (viral infection). Eight subjects (0.3%) in the JE-CV group reported SAEs of viral infection (two reports), rectal haemorrhage, non-cardiac chest pain, inguinal hernia, viral gastroenteritis, fallopian tube cyst, and anxiety within 30 days after vaccination. All subjects completely recovered with no residual side effects. The two related SAEs of viral infection occurred 1 and 8 days after vaccination and were considered related to JE-CV vaccine. Viremia tests

were performed in one subject and were found negative. Overall no correlation was found between viraemia and either symptoms or fever. One subject in the Je-Vax (Doses 1 and 2) group and one subject in the Je-Vax (Dose 3) group reported two severe SAEs, both not related to vaccination and both subjects completely recovered. Two subjects in the placebo group reported two severe SAEs (streptococcal pneumonia and asthma) unrelated to vaccination. No related SAEs were reported at any time in any of the comparator groups. In the clinical development program of JE-CV in adults, 20 subjects reported 20 SAEs more than 30 days after a vaccination, none thought to be related to JE-CV. No deaths were reported within 30 days of a vaccination in any of the studies of the clinical development program for JE-CV in adults. During the 6 months after vaccination in study H-040-010, one death (sudden death, thought to be unrelated) was reported. A slightly larger percentage of subjects vaccinated with JE-CV (4.0 $\log_{10}$ PFU/0.5-mL dose) experienced at least one injection site AE compared with those receiving placebo only (17.2% versus 14.5%, respectively), but less than those vaccinated with Je-Vax (65.5% in the Dose 1 and Dose 2 groups and 41.9% in the Dose 3 group).

Other miscellaneous safety information contained in submission

In the clinical development program of JE-CV in adults, five subjects reported AEs that led to withdrawal: four subjects were vaccinated with placebo and one subject was vaccinated with JE-CV (3.8 $\log_{10}$ PFU/0.5-mL dose). In the liquid formulation study H-040-005, the subject experienced two AEs (anaemia and glomerulonephritis; anaemia was already reported in the medical history associated with hematuria and proteinuria) that led to withdrawal. Both events had a mild intensity, were not considered as SAEs, and were not considered to be related to JE-CV vaccination.

Paediatric safety data

In study JEC01, no immediate AEs were reported. No subject was withdrawn from the study for an AE. The most frequently reported solicited injection site reaction in children (2 to 5 years) after both JE-CV and hepatitis A vaccination was injection site pain, followed by injection site erythema and injection site swelling. In toddlers (12 to 24 months), the most frequently reported injection site reaction after both JE-CV and hepatitis A vaccination was injection site tenderness (Table 16), followed by injection site erythema and injection site swelling.

Table 16: Details of injection site and systemic reactions from study JEC01.

Solicited Injection Site Within 7 Days and Systemic Reactions Within 14 Days After Vaccination in the Safety Set

	Children				Toddlers			
	JE-CV		Hepatitis A		JE-CV		Hepatitis A	
Subjects experiencing at least one:	n/M	%	n/M	%	n/M	%	n/M	%
Solicited reaction	53/100	53.0	55/98	56.1	136/199	68.3	130/199	65.3
Injection site reaction	32/100	32.0	35/98	35.7	81/199	40.7	72/199	36.2
Injection site pain/tenderness	24/100	24.0	28/98	28.6	63/199	31.7	54/199	27.1
Injection site erythema	14/100	14.0	17/98	17.3	45/199	22.6	39/199	19.6
Injection site swelling	8/100	8.0	13/98	13.3	17/199	8.5	14/199	7.0
Systemic reaction*	44/100	44.0	35/98	35.7	97/199	48.7	101/199	50.8
Fever	22/100	22.0	13/98	13.3	42/199	21.1	41/199	20.6
Headache	21/100	21.0	14/98	14.3				
Malaise	33/100	33.0	26/98	26.5				
Myalgia	24/100	24.0	15/98	15.3				
Vomiting					40/199	20.1	44/199	22.1
Crying abnormal					45/199	22.6	39/199	19.6
Drowsiness					36/199	18.1	30/199	15.1
Appetite lost					52/199	26.1	58/199	29.1
Irritability					56/199	28.1	46/199	23.1

The majority of the solicited injection site reactions were of Grade 1 intensity, occurred within 3 days after vaccination, and lasted for 1-3 days. In children, the most frequently reported solicited systemic reaction after both JE-CV and hepatitis A vaccination was malaise. Fever was slightly more frequent after JE-CV (22.0%) than hepatitis A (13.3%) vaccination. In toddlers, the most frequently reported solicited systemic reactions after both JE-CV and hepatitis A vaccination were irritability and appetite lost. Fever was reported as frequently after JE-CV (21.1%) as after hepatitis A (20.6%) vaccination. The majority of the solicited systemic reactions were of Grade 1 or Grade 2 intensity, occurred within 7 days after vaccination, and lasted for 1-3 days. A Grade 3 solicited injection site reaction was reported in one toddler (injection site tenderness) after hepatitis A vaccination. Grade 3 solicited systemic reactions were reported in two children after JE-CV vaccination (fever) and after hepatitis A vaccination (fever), and in five toddlers after JE-CV vaccination and six toddlers after hepatitis A vaccination (appetite lost, fever, vomiting, crying abnormal and/or irritability). The incidences of unsolicited AEs 28 days after vaccination were comparable after JE-CV and hepatitis A vaccination overall and in each age group.

The most frequent events were upper respiratory tract infection, rhinorrhea, and nasopharyngitis. Unsolicited reactions were reported by few subjects (seven subjects after JE-CV and one subject after hepatitis A vaccination) and were mainly injection site reactions; no reaction was of Grade 3 intensity. A total of 27 subjects reported 32 SAEs up to 6 months after the last vaccination: 6 children experienced 7 SAEs and 21 toddlers experienced 25 SAEs. None of the SAEs were considered related to vaccination by the study investigator. All subjects recovered. No death was reported. In the period up to 28 days after vaccination, 9 subjects reported 9 SAEs; 2 were reported by children aged 2 to 5 years and 7 were reported by toddlers aged 12 to 24 months. Eight of these nine SAEs were reported after hepatitis A vaccination. During the follow-up period (from 28 days to 6 months after the last vaccination) 20 subjects reported 23 SAEs: 4 children experienced 5 SAEs and 16 toddlers experienced 18 AEs. One case of febrile convulsion was reported after hepatitis A vaccination, while no hypersensitivity reaction, vaccine failure or other neurological event was observed up to 28 days after any vaccination (Table 17). During the entire study, 5 subjects reported 6 episodes of febrile convulsion: one toddler within 28 days after hepatitis A vaccination, and one child and three toddlers during the 6-month follow-up period (53 to 117 days after the last of two vaccinations with JE-CV and hepatitis A, respectively). After the second vaccination in children, solicited injection site reactions

were reported more frequently after hepatitis A vaccination (Group 1, 37.5%) than after JE-CV vaccination (Group 2, 23.5%). Inversely, solicited systemic reactions were more frequent after JE-CV vaccination (Group 2, 43.1%) than after hepatitis A vaccination (Group 1, 33.3%).

Table 17: AEs of specific interest within 28 days after the 1st injection by System Organ Class and Preferred term-Toddlers aged 12-24 months. Safety Analysis set.

	JE-CV/Hepatitis A Group 3 (N= 101)				Hepatitis A/JE-CV Group 4 (N= 99)			
Subjects experiencing at least one:	n	%	(95% CI)	nAEs	n	%	(95% CI)	nAEs
Significant AE	27	26.7	(18.4; 36.5)	32	19	19.2	(12.0; 28.3)	20
Nervous system disorders	22	21.8	(14.2; 31.1)	22	14	14.1	(8.0; 22.6)	14
Febrile convulsion	0	0.0	(0.0; 3.6)	0	1	1.0	(0.0; 5.5)	1
Somnolence	22	21.8	(14.2; 31.1)	22	13	13.1	(7.2; 21.4)	13
Respiratory, thoracic and mediastinal disorders	4	4.0	(1.1; 9.8)	4	5	5.1	(1.7; 11.4)	5
Asthma	1	1.0	(0.0; 5.4)	1	0	0.0	(0.0; 3.7)	0
Cough	3	3.0	(0.6; 8.4)	3	3	3.0	(0.6; 8.6)	3
Wheezing	0	0.0	(0.0; 3.6)	0	2	2.0	(0.2; 7.1)	2
Skin and subcutaneous tissue disorders	5	5.0	(1.6; 11.2)	6	1	1.0	(0.0; 5.5)	1
Rash	4	4.0	(1.1; 9.8)	5	0	0.0	(0.0; 3.7)	0
Rash maculo-papular	0	0.0	(0.0; 3.6)	0	1	1.0	(0.0; 5.5)	1
Urticaria	1	1.0	(0.0; 5.4)	1	0	0.0	(0.0; 3.7)	0

n: number of subjects experiencing the endpoint listed in the first column

n AEs: number of AEs

JE-CV/ Hepatitis A: JE-CV as first injection and hepatitis A vaccine as second injection

Hepatitis A/ JE-CV: hepatitis A vaccine as first injection and JE-CV as second injection

The incidences of unsolicited AEs were comparable in the two groups after the second vaccination. Comparison of the first and the second vaccination indicates that solicited injection site reactions tended to be more frequently reported in Group 1 after both the first and the second vaccination, irrespective of the vaccine received (JE-CV or hepatitis A vaccine). Solicited systemic reactions tended to be more frequent after JE-CV than hepatitis A vaccination irrespective of the time-point of vaccination (that is, first or second vaccination). Unsolicited AEs were reported in comparable frequencies after the first and second vaccinations. After the first vaccination in toddlers, solicited injection site reactions were reported more frequently after JE-CV vaccination in Group 3 (49.5%) than after hepatitis A vaccination in Group 4 (30.3%). Solicited systemic reactions were as frequent after both vaccinations (Group 3 and Group 4). Only one subject reported an unsolicited AR after hepatitis A vaccination: maculo-papular rash in a toddler. Seven subjects (four children and three toddlers) experienced unsolicited AR after JE-CV vaccination. Among the children, vomiting was reported by two subjects, the other events (injection site pruritus, rash, maculo-papular rash) were reported by one subject each. Three toddlers reported injection site bruising. None of these reactions were of Grade 3 intensity. The incidences of unsolicited AEs 28 days after vaccination were comparable after JE-CV and hepatitis A vaccination overall and in each age group. Unsolicited AEs were more frequent in toddlers than in children whatever the vaccine received. The majority of the unsolicited AEs was of Grade 1 and Grade 2 intensity, occurred within 14 days, and had a duration of 7 days or less. Two toddlers in Group 4 reported grade 3 unsolicited AEs after hepatitis A vaccination, acute bronchitis and joint dislocation. In Group 1, three subjects (6.3%) experienced three AEs of specific interest (cough, epistaxis, and rash) after hepatitis A vaccination. In Group 2, one subject (2.0%) experienced cough after JE-CV vaccination. Among all these AEs of specific interest (Table 17 and 18), only rash might be suspected to be a symptom of hypersensitivity reactions. Only one subject (2.1%) in Group 1 reported non-serious rash of Grade 1 after hepatitis A vaccination, which was considered as not related to the vaccination by the study investigator, but occurred 2

days after vaccination. The most frequent event was somnolence (nervous system disorders), which was reported in 22 subjects (21.8%). Among all these AEs of specific interest, rash, urticaria, and rash maculo-papular might be suspected to be symptoms of hypersensitivity reactions. Four subjects (4.0%) in Group 3 presented rash (grade 1) after JE-CV vaccination, one subject (1.0%) in Group 3 presented urticaria (grade 1) after JE-CV vaccination, and one subject (1.0%) in Group 4 presented rash.

Table 18: AEs of specific interest within 28 days after the 2nd injection by System Organ Class and Preferred term-Children aged 2-5 years. Safety Analysis set.

	JE-CV/Hepatitis A Group 1 (N= 48)				Hepatitis A/JE-CV Group 2 (N= 51)			
Subjects experiencing at least one:	n	%	(95% CI)	nAEs	n	%	(95% CI)	nAEs
Significant AE	3	6.3	(1.3; 17.2)	3	1	2.0	(0.0; 10.4)	1
Respiratory, thoracic and mediastinal disorders	2	4.2	(0.5; 14.3)	2	1	2.0	(0.0; 10.4)	1
Cough	1	2.1	(0.1; 11.1)	1	1	2.0	(0.0; 10.4)	1
Epistaxis	1	2.1	(0.1; 11.1)	1	0	0.0	(0.0; 7.0)	0
Skin and subcutaneous tissue disorders	1	2.1	(0.1; 11.1)	1	0	0.0	(0.0; 7.0)	0
Rash	1	2.1	(0.1; 11.1)	1	0	0.0	(0.0; 7.0)	0

n: number of subjects experiencing the endpoint listed in the first column

n AEs: number of AEs

JE-CV/ Hepatitis A: JE-CV as first injection and hepatitis A vaccine as second injection

Hepatitis A/ JE-CV: hepatitis A vaccine as first injection and JE-CV as second injection

In study JEC02 no subjects experienced an immediate unsolicited AE or an AE that led to study discontinuation after vaccination. Overall, 64.2%, 64.9% and 67.0% of subjects reported at least one solicited reaction in the JE-CV Thai Lot 1, Lot 2 and Lot 3 groups, respectively. The proportion of subjects with at least one solicited injection site reaction during the 7 days following vaccination was the same in the JE-CV Thai Lot 1 and Lot 2 groups (34.8%) and was slightly higher in the JE-CV Thai Lot 3 group (43.8%). Similar proportions of subjects reported at least one solicited systemic reaction during the 14 days following vaccination (48.3%, 50.8% and 50.2% of subjects in the JE-CV Thai Lot 1, Lot 2 and Lot 3 groups, respectively). Almost 50% of subjects in each JE-CV Thai group reported at least one unsolicited AE (49.3%, 47.5% and 46.5% of subjects in the JE-CV Thai Lot 1, Lot 2 and Lot 3 groups, respectively). Most of these AEs were not related to vaccination and were systemic AEs. Thirty subjects (8 [2.6%] in the JE-CV Thai Lot 1 group, 12 [4.0%] in the JE-CV Thai Lot 2 group and 10 [3.4%] in the JE-CV Thai Lot 3 group) reported at least one SAE over the trial period. Among them, ten subjects (2 [0.7%] in the JE-CV Thai Lot 1 group, 5 [1.7%] in the JE-CV Thai Lot 2 group and 3 [1.0%] in the JE-CV Thai Lot 3 group) reported at least one SAE between Day 0 and Day 28. Over the entire trial period, no SAEs were related to vaccination and all subjects recovered. No deaths were reported. The overall safety profile was considered similar between the three JE-CV Thai lots, based on the observed means and corresponding 95% CI.

Post marketing experience

There are a number of ongoing or planned trials: Phase II H-040-004: Randomised, Double-blind, Controlled Safety, Tolerability and Immunogenicity Phase II Trial of ChimeriVax-JE and Japanese Encephalitis Inactivated Mouse Brain Vaccine in Children of Descending Age. Planned studies: JEC04 is a Phase III study designed to assess the interaction between JE-CV and the MMR (Measles Mumps Rubella) vaccine. JEC05 is a Phase III long-term follow-up study of immunogenicity (up to 5 years post vaccination) that will enrol a subset of subjects from study JEC02. JEC06 is a Phase III immunogenicity and safety study in India. JEC07 is a Phase III immunogenicity and safety study comparing JE-CV and SA14-14-2. JEC11 is a Phase III study designed to assess the interaction between JE-CV and a paediatric combination vaccine (including diphtheria, tetanus and pertussis).

Clinical Summary and Conclusions

This evaluation report is long because of the nature of the vaccine submission and the different formulations and information contained in all the different trials. They follow the development of the vaccine formulation, development of immunogenicity assessment criteria, the dose finding trials and immunogenicity, safety and lot to lot consistency data, followed by the review of the paediatric data.

This submission has sufficient data about the immunogenicity and safety of this new vaccine JE-CV to recommend its licensing for adults over the age of 18. JE-CV induced a high immune response 28 days after a single vaccination both in terms of post-vaccination seroconversion, seroprotection and GMT. In all, at least 95% of JE-CV recipients (irrespective of a production in Thailand or the USA) seroconverted; moreover, more than 94% of toddlers were seroprotected after a single dose administration of JE-CV. The latter would also support the licensing for children over 12 months if a caveat can be put in place for the submission of the data from the final report on JEC01 and assuming no new safety or immunogenicity issues arise. Overall, these studies showed that a single dose of JE-CV will produce long-term immunity, although the numbers in both the pharmacology and the immunogenicity trials are very small. These data need to be re-inforced by the collection of epidemiological data showing clinical protection from disease. This vaccine should be able to fill a void in relation to immunisation of travellers to JE endemic areas who are deemed to be at risk, as it will be easier to use, and safer than the killed vaccine currently available. It will be important for both prescribers and consumers to understand the not insignificant risks associated with this vaccine (not dissimilar to other vaccines) of both local (about 10%) and systemic (about 20%) adverse reactions (although generally not serious ones). Like other live virus vaccines, it will be contra-indicated in immuno-compromised people. Patients should be encouraged to read the Consumer Medicine Information. The incidence of these side effects is very similar to other live virus vaccines. It will also be important for ongoing data to be collected in relation to the possibility of adverse events related to viraemia.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM). A summary is provided in the table below (Table 19).

Table 19:

Safety concerns	Action(s) proposed	Objective of proposed action(s)	Rationale for proposed action(s)	Further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	Milestones for evaluation and reporting including justification for choices of milestones	Titles of protocols
Hypersensitivity reactions (allergic, anaphylactic/ anaphylactoid)	- Contraindications in case of hypersensitivity to any component of JE-CV or after previous administration of the vaccine (proposed PI) - Subject's surveillance in a medical care environment for 30 minutes after vaccination Routine Pharmacovigilance activities: - Close monitoring in further pediatric trials: AE considered event of interest, investigator training, safety management team analysis - Spontaneous reports post-licensure: all case reports will have enhanced follow-up - PSUR: comprehensive evaluation of these events will be presented periodically during the first two years of post-licensure experience according to HA requirements. - Batch investigation and medical investigation are systematically performed.	To characterize allergic reaction after JE-CV immunization To assess reporting rate trend in the general population and incidence in pediatric population (further trials)	Data from clinical trials are limited, this safety concern is considered from what is known from previous JE vaccines	Further measures: A more detailed analysis with identification of risk factors, severity, evolution. Decision criteria: cluster of serious cases in the first PSURs	Evaluation will continue in further pediatric trials and will begin post-licensure with the date of launch. PSUR with a 6 month periodicity. The PSURs will provide a cumulative overview on this issue and will be delivered during the first two years of post-marketing experience.	Not applicable

Table 19 continued.

Safety concerns	Action(s) proposed	Objective of proposed action(s)	Rationale for proposed action(s)	Further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	Milestones for evaluation and reporting including justification for choices of milestones	Titles of protocols
Convulsions (including febrile convulsions)	Routine Pharmacovigilance activities: - close monitoring in further pediatric trials: AE considered event of interest and always considered as serious, investigator training, close safety review by safety management team, standardization of definition according to the Brighton definition (26) attached to the protocols. A specific statistical analysis including the frequency and time to onset of these events in pediatric population is provided in 2.7.4 Section 2.2.2.3.3.1. - spontaneous reports post-licensure: all case reports will have enhanced follow-up - PSUR: comprehensive evaluation of these events will be presented periodically during the first two years of post-licensure experience according to HA requirements.	To characterize convulsions after JE-CV immunization To assess incidence in pediatric population (further trials) To calculate frequency of reporting	Data from clinical trials are limited, this safety concern is considered from what is known from live-attenuated and previous JE vaccines	Further measures: A more detailed analysis with identification of risk factors, severity, evolution. Decision criteria: cluster of cases in the first PSURs	Evaluation will continue in further pediatric trials and will begin post-licensure with the date of launch. PSUR with a 6 month periodicity. The PSURs will provide a cumulative overview on this issue and will be delivered during the first two years of post-marketing experience.	Not applicable

Table 19 continued.

Safety concerns	Action(s) proposed	Objective of proposed action(s)	Rationale for proposed action(s)	Further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	Milestones for evaluation and reporting including justification for choices of milestones	Titles of protocols
Other neurological disorders : encephalopathy, encephalitis, ADEM, myelitis, GBS, peripheral neuropathy, facial (Bell's) palsy	Routine Pharmacovigilance activities: - close monitoring in further pediatric trials: AE considered event of interest, guidelines for assessment of suspected YEL-AVD/AND attached to the protocols, investigator training, safety management team analysis. - spontaneous reports post-licensure: all case reports will have enhanced follow-up - PSUR: comprehensive evaluation of these events will be presented periodically during the first two years of post-licensure experience according to HA requirements. In addition: In case of convulsions, encephalopathy, encephalitis, ADEM, myelitis or GBS diagnosed, the differential diagnosis with YEL-AND will be made according to the internal process for Management of YEL-AND/AVD following Chimeric Vaccines.	To characterize these events To obtain reporting rate trend in the general population and incidence in pediatric population in further trials	This safety concern is considered from what is known from live-attenuated and previous JE vaccines	Further measures: A more detailed analysis with identification of risk factors, severity, evolution. Decision criteria: will depend on comparison of observed (reported) and expected rates of each AE in the first PSURs	Evaluation will continue in further pediatric trials and will begin post-licensure with the date of launch. PSUR with a 6 month periodicity. The PSURs will provide a cumulative overview on this issue and will be delivered during the first two years of post-marketing experience.	Not applicable

Yel-AVD and Yel-AND=yellow fever associated viscerotropic and yellow fever associated neurotropic diseases.ADEM=Acute Disseminated Encephalomyelitis; GBS= Guillain-Barré Syndrome.

Table 19 continued.

Safety concerns	Action(s) proposed	Objective of proposed action(s)	Rationale for proposed action(s)	Further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures	Milestones for evaluation and reporting including justification for choices of milestones	Titles of protocols
YEL-AVD/AND	Routine Pharmacovigilance activities: - close monitoring in further pediatric trials: guidelines for assessment of suspected YEL-AVD/AND attached to the protocols, investigator training, safety management team analysis. - spontaneous reports post-licensure: any suspected serious or confirmed case should be reported to HA; all case reports will have enhanced follow-up. In addition, the company has established an internal process to handle the situation where potentially one case of suspected AVD/AND is reported (Management of YEL-AVD/AND following Chimeric Vaccines). This process would be implemented in accordance with IDMC and EC's recommendations and taking into account any request of the HA. The proposed strategy is in two main steps: - to search for abnormal flavivirus chimeric virus replication. - to assess the case based on the criteria of the CDC YFWG guidelines and epidemiological data.	To confirm or reject any suspicion of AVD/AND based on the criteria of the CDC YFWG guidelines and update the benefit-risk ratio for the chimeric vaccines under investigation	This safety concern is considered as a theoretical risk related to the YF virus engine. This safety concern has been observed with YF vaccine only and the incidence of this risk is very low	Further measures: A specific evaluation and classification of this safety concern with detailed analysis Decision criteria: one case considered confirmed according to CDC YFWG	Evaluation will continue in further pediatric trials and will begin post-licensure with the date of launch. In case of confirmed first case: immediate evaluation and reporting in accordance with IDMC's recommendations, EC advice and the request of the HA	Not applicable

The immunising antigens of Imojev are the pre-membrane and envelope (E) proteins of another live, attenuated Japanese encephalitis virus vaccine (SA14-14-2 vaccine) which has been given to hundreds of millions of children in China without safety signals coherent with these events.

Imojev is indicated for prophylaxis of JE in individuals from 12 months of age.

The first dose of Imojev was administered in September 2000. Imojev was studied in a total of 2,459 healthy participants (adults aged 18 to 84 years). In children it was studied in 1,444 healthy participants including 1,312 toddlers (aged from 9 to 24 months) and 132 children (aged 2 to 10 years).

No important risk was identified for Imojev during clinical development.

Important potential risks for adult and paediatric populations after Imojev administration have been defined on the basis of previous experience with a mouse brain derived Japanese Encephalitis Vaccine (Je-Vax) and those expected for a live-attenuated vaccine; these include:

- hypersensitivity reactions (allergic, anaphylactic/anaphylactoid)
- neurological disorders including convulsions, encephalopathy, encephalitis, Acute Disseminated Encephalomyelitis (ADEM), myelitis, Guillain-Barré Syndrome (GBS), peripheral neuropathy and facial palsy
- The production of Imojev is based on technology which is driven by proteins from the yellow fever 17D virus, a potential risk that yellow fever associated viscerotropic and yellow fever associated neurotropic diseases (Yel-Avd and Yel-And) might also be observed with Imojev cannot be completely excluded.

The sponsor considers that no specific pharmacovigilance action plan or risk minimisation is needed for these events, only close monitoring in clinical trials and routine activities are planned.

The potential risks associated with Imojev will continue to be specifically monitored during the on-going and further paediatric studies and will be addressed in Periodic Safety Update Reports (PSURs).

The proposed application of routine pharmacovigilance, monitoring in ongoing trials and routine risk minimisation activities through the Product Information sheet as specified by the sponsor is accepted by the OMSM.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Japanese Encephalitis Chimeric Vaccine (JE-CV) virus was obtained via recombinant DNA technology, constructed by inserting RNA encoding the premembrane (prM) and envelope (E) structural proteins of JE SA14-14-2 virus into the genome of yellow fever (YF)17D virus. Source, history and generation and development of the JE-CV viral vaccine strain have been described. JE-CV virus is propagated in Vero cells grown in serum-free conditions using a seed lot system. Cell banking processes are satisfactory. All viral safety issues have been addressed. Specifications and stability of the JE-CV drug substance are considered satisfactory.

Manufacture of the Drug Product consists of the steps of blending of DS / excipients; sterile filtration; aseptic filling; lyophilisation; stoppering and crimping; inspection, labelling and secondary packaging. Manufacture of drug product in marketed vaccine will be undertaken in Thailand whereas adult clinical study batches were manufactured in the USA.

There were a number of issues requiring resolution before the product could be recommended for approval. The sponsor has provided commitments to provide validation of sterility and *Mycoplasma* testing of viral harvest and control cells before the marketing of the final product, that is, sale of the product in Australia. Submission of results of ongoing stability studies of validation and clinical trial batches of the drug product is required as a condition of registration.

Nonclinical

JE-CV is a live, attenuated, recombinant virus. The epitopes eliciting neutralising antibody production are largely on the E protein and the immune response induced by vaccination is directed largely at JE virus. JE-

CV was immunogenic in rhesus and cynomolgus monkeys, as evidenced by the production of high titre, JE-CV specific antibodies. All immunised monkeys showed protection against intracerebral challenge by wild type JE virus.

Attenuation of JE-CV was tested by intracerebral inoculation of mice and rhesus and cynomolgus monkeys. In all three species, it was found that the neurovirulence of JE-CV was comparable to or lower than that of the parental YF 17D virus, which is not neurovirulent in man.

No significant toxicological findings were identified in male or female cynomolgus monkeys during a 21-day test period after a single SC injection of the full human dose.

The attenuation sites in the E gene of the JE-CV virus were shown to be stably maintained as assessed by sequencing of samples from *in vitro* (in static and suspension cell culture) and *in vivo* cultures. *In vivo* studies demonstrated that JE-CV virus was genetically stable in both mice and monkeys. Sequences encoding the structural proteins prM, M, and E isolated from inoculated monkeys were identical to the sequences present in the virus vaccine lot used for their immunisation.

Repeat-dose toxicity studies were not performed as the vaccine is intended for delivery as a single dose. No genotoxicity or carcinogenicity studies were performed. This is consistent with the nonclinical vaccine guidelines.

The reproductive and developmental toxicity data on the parent wild-type viruses, parent vaccines, and relevant nonclinical data for JE-CV were evalauted. No reproductive and developmental toxicity study was submitted, however a study is planned by the sponsor. The high attenuation and low viraemia of JE-CV were considered to mitigate against a potential developmental risk, but the risk cannot be fully assessed from the available data.

Nonclinical data raised no objections to registration in adult males, and women without childbearing potential. The secondary nonclinical evaluation did not support registration in women of childbearing age in the absence of a reproductive and developmental toxicity study. However, prevention of inadvertent pregnancy and its management are clinical concerns, and clinical advice was also sought on this issue. Registration for use in children depended largely on adequate clinical data, as supporting nonclinical data in young animals were limited.

Clinical

An initial data package to support registration in adults 18 years of age and older was supplemented during the course of the evaluation with additional data consisting of one final report and one interim report of clinical studies in children.

Nine JE-CV clinical studies were conducted in adults involving a total of 3476 healthy adult subjects. 2486 subjects were randomly assigned to receive one dose of JE-CV. A total of 2136 subjects were randomized to the lyophilized formulation and 350 subjects were randomly assigned to the liquid formulation of JE-CV. Early studies of liquid formulation (Studies H-040-001, H-040-003, H-040-005) and the lyophilized (or freeze dried) formulation (H-040-006, H-040-007) provided data for dose finding, proof of concept, immunogenicity and safety data. Two Phase II/III studies provide efficacy data, H-040-008 (pilot) and H-040-009 (pivotal) provide efficacy data. Study H-040-010 was a pivotal Phase III safety study.

In children, submitted reports which involved 1800 children included an interim report on Study JEC01 in children and toddler 12 months to 5 years of age in Thailand (which includes 6 month follow up data but is planned to extend to 5 years follow-up) and a final report on Study JEC02 which is a Phase III study examining lot-to-lot consistency, bridging of manufacture, and safety in toddlers 12-18 months in Thailand and the Philippines.

Je-Vax was an appropriate comparator in clinical studies assessing efficacy in adults.

In the clinical development program immunogenicity has been used as a surrogate for clinical protection of JE vaccines measured by serum neutralizing antibodies. This is in line with WHO Guidance on licensure of new JE vaccines. The clinical evaluation report (CER) describes a LNI assay used in 2 initial studies, and a $PRNT_{50}$ assay with a threshold >1:10 used in the majority of clinical studies. Neutralization of homologous

(JE-CV) virus was assessed in all studies, with neutralization of a panel of wild type JE strains in JE genotypes I to IV assessed in Study H-040-007, H-040-001 and JEC01, and with neutralization of wild type JE strains also assessed in H-040-005, H-040-006, H-040-008 and H-040-009.

Pharmacology. The CER summarised Phase I/II studies supporting dose finding and number of doses with more detailed description in CER. Doses between 1.8 $\log_{10}$ PFU/0.5 mL dose and 5.8 $\log_{10}$ PFU/0.5mL dose (liquid formulation) were tested in studies H-040-001 and H-040-003, and based on immunogenicity and safety results a dose of 3.8 $\log_{10}$ PFU/0.5-mL was studied in H-040-005 and H-040-006. A repeat dose was assessed in H-040-003 at 28 days and in H-040-005 at 6 months. Effect of pre-existing YF immunity was assessed as was administration of JE-CV together with YF vaccine (concomitant, or sequential administration). A dose-ranging study, H-040-007, assessed lyophilized formulation doses between 3.0 $\log_{10}$ PFU/0.5-mL dose and 5.0 $\log_{10}$ PFU/0.5-mL dose. Across doses and studies the seroconversion rates one month after vaccination were high and no dose relationship was apparent.

Studies H-040-001, H-040-003, and H-040-007 showed viraemia, at low levels, up to 11 days after JE-CV administration, with 50% to 100% of subjects (liquid formulation) and 28% to 53% of subjects (lyophilized formulation) experiencing viraemia on at least one day. The data showed a trend for peak viraemia to occur around Day 4 to Day 6 after a single dose of JE-CV.

Study H-040-005 measured viraemia at Days 14 and 42 after vaccination with JE-CV. No viraemia was detected at either of these time points, indicating that any viraemia after vaccination had ceased within 2 weeks of JE-CV administration. In the paediatric study JEC01, viraemia was assessed on Day 4 in subjects who received JE-CV at the first vaccination (Group 1 and Group 3). No child 2-5 years old presented with quantifiable JE-CV viraemia, while 5 toddlers (5.1%) presented with low level viraemia.

A dose with a lower potency limit of 4.0 $\log_{10}$ PFU/0.5-mL was selected for adult efficacy studies of lyophilised formulation (H-040-008 & H-040-009) based on high seroconversion rates, rapid onset of immunity and good safety profile in single dose administration.

Antibody persistence data were well maintained to 48 months after vaccination in Study H-040-005 and are planned to be followed for up to 5 years. Immune memory was evaluated in H-040-002 by administering a dose of Je-Vax 6 months after a dose of JE-CV with 90% showing seroconversion measured by LNI. Cell mediated immunity was investigated by ELISPOT[5] with a higher proportion showing response after JE-CV compared to Je-Vax.

Efficacy in adults Studies H-040-008 and H-040-009 are the principal efficacy studies in adults. H-040-008 was a pilot Phase II study and H-40-009 was the pivotal Phase III study conducted in USA and Australia. The CER describes these studies. Both studies were randomised, double blind comparisons of Je-Vax administered in 3 dose schedule and JE-CV single dose (Day 28) and two placebo doses. Subject characteristics were similar in both treatment groups. Seroconversion rates reported in Study H-040-008 and Study H-040-009 at 14 days or 28/30 days after the vaccination course (with vaccine homologous virus) were 100% (95% CI : 88.1, 100) for JE-CV and 80.8% (95% CI: 60.6, 93.4) for Je-Vax. GMT results to homologous virus showed markedly lower GMTs at 28/30 days after vaccination reported in the JE-CV group compared to Je-Vax.

In both studies JE-CV and Je-Vax groups were compared using $PRNT_{50}$ assay measured with same challenge strains (JE-CV and Nakayama strains). This shows that with JE-CV used as challenge strain, 100% in both treatment groups seroconverted in Study H-040-008 at 28 days, and in Study H-040-009, 99.1% of the JE-CV treatment group and 95.1% of the Je-Vax group seroconverted. With Nakayama used as the challenge strain, in Study H-040-008 at 28 days 62.1% in the JE-CV and 80.8% in the Je-Vax group seroconverted, whereas in

[5] ELISPOT is an immunological assay based on ELISA (*Enzyme-Linked Immunosorbent Assay*). Basically, the difference between the two is that in ELISA, the substance containing the "unknown" is stuck at the bottom of the well, whereas in ELISPOT the substance with the "unknown" is placed in the well after the bottom of the well has been coated with cytokine-specific antibody. In both cases, the wells are typically contained within a generic microtiter plate. The ELISPOT method is most often used to determine the amount (that is, the concentration) of activated antigen-specific cytotoxic T-cells in a given sample of splenocytes harvested from immunized animals, usually mice.

Study H-040-009 seroconversion rates were 80.9% in the JE-CV and 74.8% in the Je-Vax group. The $PRNT_{50}$ using Nakayama strain was lower for both treatment groups but not consistently lower for JE-CV than Je-Vax. In Study H-040-008, $PRNT_{50}$ with a wild type P3 showed 100% seroconversion 28 days after completion of vaccination schedule in both JE-CV and Je-Vax groups. The CER concludes that no matter which strain was used in the PRNT, one dose of JE-CV could be accepted as being as immunogenic as 3 doses of Je-Vax.

Subpopulation analysis in Study H-040-008 and H-040-009 showed no differences in seroconversion rates across countries and across age groups but lower seroconversion rates in older age groups (45 to 60 years, over 60 years) for Je-Vax.

Paediatric efficacy Study JEC01 is a randomised, cross-over, open, active comparator (Hepatitis A vaccine) study conducted in Thailand. 100 children 2 to 5 years and 200 toddlers 12 -24 months were enrolled to receive a single dose of JE-CV and one dose of hepatitis A vaccine one month apart, and a second dose of hepatitis A vaccine 6 months later. Groups 1 and 3 received JE-CV as first injection. Seroprotection and seroconversion results for homologous virus and wild type JE strains of genotypes I to IV for the two age groups were evaluated in the CER. Four weeks after JE-CV, 100% were seroprotected and 92.8% seroconverted to homologous virus in the PP analysis. GMTs increased from 44.8 1/dil at baseline to 2634 1/dil. Seroprotection and seroconversion rates against wild type strains were similar to homologous virus but GMTs to wild type strains were generally lower. In the PP toddler analysis seroprotection rates were 96% and seroconversion rates were 96.5% to homologous virus and GMTs increased from 5.4 1/dil at baseline to 281 1/dil post vaccination. Seroprotection and seroconversion rates were similar for wild type strains of genotypes I, II and III, and lower for the JKT 9092 TVP 6265 (genotype IV). At 6/7 months follow-up seroprotection rates were 86.8% for homologous virus and ranged from 57.9% to 91.9% for w.t. strains.

Study JEC02 is a Phase III randomised controlled observer–blind study examining lot–to-lot consistency of JE-CV manufactured in Thailand and compared to JE-CV manufactured in the USA and hepatitis A vaccine. A total of 1200 toddlers from 12 months to 18 months were vaccinated with a single dose of JE-CV or hepatitis A vaccine and assessed for immune response at 28 days. At 28 days after vaccination seroconversion rates were above 92% in all JE-CV (Thailand) groups with GMTs in the range 168 1/dil to 206 1/dil. The criteria for equivalence were satisfied with 95% CI for ratio of GMTs between ½ and 2. The study also reported equivalence of the pooled JE-CV Thai lots and JE-CV from the USA in seroconversion rates and GMTs.

Safety

The methods and time windows for assessment of safety in clinical studies are described in the CER. Safety data were combined for all adult studies in which at least one dose of JE-CV was administered. The numbers of AE reported in JE-CV (n=2459) and comparator groups (Je-Vax n=422; placebo single dose n=565) were noted. A total of 65.8% of subjects in the JE-CV (4.0 $\log_{10}$ PFU/0.5-mL dose) group experienced at least one AE within 30 days compared with 68.5% of subjects in the Je-Vax (Dose 3) group. Almost half of the subjects (47.5%) experienced at least one AE considered related to JE-CV. The majority of subjects (63.2%) experienced at least one systemic AE. A total of 16.7% of subjects experienced at least one injection site AE. The most common systemic AEs reported were headache, fatigue, malaise, myalgia, injection site pain, feeling hot, and diarrhoea. The percentages of subjects who experienced at least one related AE were higher for those vaccinated with Je-Vax (55.7%; Dose 3) or two placebo doses (60.7%) compared with those vaccinated with JE-CV (48.8%; 4.0 $\log_{10}$ PFU/0.5-mL dose) or placebo only (51.0%). All AEs were more common in women than men, not related to age, and were slightly higher in the underweight group. There were three pregnancies reported in JE-CV recipients. Two were electively terminated and one carried to term without documented adverse events.

Eight subjects (0.3%) in the JE-CV group reported SAEs two of which were considered vaccine related SAEs of viral infection (which occurred 1 and 8 days after vaccination). No vaccine related SAEs were reported in comparator groups. No deaths occurred in the clinical developmental program within 30 days of vaccination. One death occurred during the 6 month follow-up; it was sudden and considered unrelated to vaccine.

Adverse event experience in paediatric studies were discussed in the CER. In JEC01 the incidences of solicited reactions were 63.2% in JE-CV and 62.3% in hepatitis A vaccine groups. In children 2-5 years

systemic events were more frequent in the JE-CV group (44% versus 35.7%) (including fever, headache & malaise) and in toddlers injection site reactions were modestly more frequent in the JE-CV group (40.7% versus 36.2%). Unsolicited reactions were reported in 7 subjects after JE-CV and 1 subject after hepatitis A vaccine, and were mainly injection site reactions.

In the 28 days after vaccination, 9 subjects reported 9 SAE. Eight of the 9 were reported after hepatitis A vaccine. During the 1-6 month follow-up, 20 subjects reported 23 SAE. None were considered vaccine related by investigator. All subjects recovered . No deaths were reported. AE of special interest were discussed in the CER. Only rash, urticaria and rash maculopapular might be suspected to be symptoms of hypersensitivity reactions.

In study JEC02 an overview of safety was presented. The incidences of solicited reactions were 66.5% in combined JE-CV and 63.7% in hepatitis A vaccine groups. The incidence of solicited injection site reactions and solicited systemic reactions was similar in combined CE-CV and hepatitis A groups. The incidence of solicited injection site reactions and solicited systemic reactions tended to be lower in the JE-CV (Thai lot) groups than the JE-CV (USA lot) group, although incidence of solicited injection site reactions to lot 3 (Thai) was similar to the USA lot group . Unsolicited adverse reactions were reported at a similar frequency in JE-CV and hepatitis A vaccine groups. SAEs during the period Day 0-28 were reported in 10 subjects (1.1%) in the combined JE-CV group and in 2 (2%) hepatitis A vaccine subjects. SAEs in the follow-up to 6 months were reported in 3.4% of the JE-CV group and 4.9% of hepatitis A group. No SAEs were considered vaccine related by the investigators. No deaths were reported.

CER Recommendation

The CER considers there are sufficient immunogenicity and safety data to support licensing in adults over the age of 18 years. After a single dose high immune response was shown in terms of post-vaccination seroconversion, seroprotection and GMTs, irrespective of production in Thailand or the USA. Antibody persistence has been well maintained to 48 months after vaccination and is planned to be followed to 5 years after vaccination. Safety has been acceptable in adult and paediatric studies to date although numbers of subjects are limited. The CER notes that numbers of paediatric clinical studies are ongoing including comparison with JE MBDV and SA-14-14-2 vaccine, as well as studies with concomitant vaccines. The CER supports licensing for children over 12 months of age, in the context of limited Australian vaccination of travellers and a non endemic population, on condition that reports from ongoing clinical studies are provided.

Risk Management Plan

OMSM have conducted an evaluation of a Risk Management Plan submitted for Imojev. The proposed application of routine pharmacovigilance, monitoring in ongoing studies and routine risk minimisation activities through product information is acceptable, although some amendment is required to the proposed Australian PI document.

Risk-Benefit Analysis

There are a number of quality issues requiring resolution before the product can be recommended for approval. The sponsor has undertaken to submit relevant information in timeframe that would allow PSC and ACPM consideration of outstanding sterility issues, and a commitment to submit results from ongoing stability studies.

A secondary nonclinical evaluation did not support registration in women of childbearing age in the absence of a reproductive and developmental toxicity study. The initial nonclinical evaluation accepted the lack of reproductive and developmental toxicity studies in view of the contraindication of this vaccine in pregnancy, which similar to the contraindication of currently registered live attenuated viral vaccines in pregnancy and the EMA Vaccine Guideline (CPMP/SWP/465/95, 1997). Phase III clinical studies were conducted in Australia (under Clinical Trial Exemption Scheme (CTX)) and in USA without a requirement for reproductive and developmental toxicity studies. A current draft EMA Guideline on live, recombinant, viral vectored vaccines (EMEA/CHMP/VWP/141697/2009) is clearer in the recommendation for a reproductive and developmental toxicity study if there is potential for the use of the vaccine in pregnancy. A reproductive and developmental toxicity study is now planned by the Sponsor with results expected in third quarter of 2011. Although the clinical study program included pregnancy as a contraindication there were inadvertent vaccine exposures in 3

women who became pregnant. The nonclinical report notes the high attenuation and low viraemia of JE-CV were considered to mitigate against a potential developmental risk. JE-CV was not detected in the monkey testes or ovary, nor was it shed in injection site swabs, urine, faeces or saliva. Human data regarding transplacental infection with flaviviruses are limited but published reports of transplacental JEV infection and spontaneous abortion in pregnancy, but no reports of foetal malformations. After YF epidemics, spontaneous abortions, stillbirths and foetal abnormalities have not been observed in humans. Published studies of YF (17D strain) vaccination during inadvertent pregnancy have reported rates of abortion, stillbirths and major foetal malformations within normal population ranges and only 1 unconfirmed report of virus specific IgM in a cord sample. The Delegate considered there is sufficient reassurance that JE-CV is not distributed reproductive organs and potential for tropism towards reproductive organs or foetus is remote. Subject to the condition that results of the reproductive and developmental toxicity study now planned by the sponsor are submitted to the TGA, the Delegate considered this product could be registered without exclusion of use in women of childbearing age, with the proposed contraindication under the 'Use in Pregnancy' statement (recommending exclusion of pregnancy by testing in women of child bearing age, and a recommendation that women should avoid becoming pregnant for two weeks after vaccination).

There is similarly a contraindication to administration of JE-CV to individuals with congenital or acquired immune deficiency impairing cellular immunity with potential for inadvertent exposure post-licensure.

Je-Vax was an appropriate comparator in clinical studies assessing efficacy in adults. This inactivated mouse brain derived vaccine, based on the Nakayama-NIH strain, was registered and supplied in Australia, USA and Europe for travellers to JE endemic areas and was registered for use from 12 months of age. Je-Vax has established efficacy in a field study of protective efficacy, although manufacture of Je-Vax was discontinued in 2005.

An inactivated JE (whole virus), aluminium adjuvanted vaccine, Jespect, based on the attenuated JE SA14-14-2 strain and grown in Vero cells, was registered in Australia in 2008 and in the EU and USA for use in adults 18 years and older.

A live attenuated SA14-14-2 vaccine grown in primary hamster kidney cells is manufactured in China and registered in several countries in Asia.

A live, attenuated yellow fever (YF) vaccine (Stamaril) based on the YF 17D strain, is registered in Australia and other countries, including the EU and USA. It is recommended for use as a single dose in adults and children over the age of 6 months.

In the clinical development program immunogenicity has been used as a surrogate for clinical protection of JE vaccines measured by serum neutralizing antibodies. This is in line with WHO Guidance on licensure of new JE vaccines. The primary assay reported is a $PRNT_{50}$ using a threshold >1:10 used. Neutralization of homologous (JE-CV) virus was assessed in all studies, with neutralization of a panel of wild type JE strains in JE genotypes I to IV assessed study H-040-007, H-040-001 and JEC01, and with neutralization of wild type JE strains also assessed in H-040-005, H-040-006, H-040-008 and H-040-009. The Delegate considered that JE-CV has demonstrated seroprotection measured by $PRNT_{50}$ against a range of wild type JE strains in a high proportion of subjects in the clinical developmental program, and is non inferior to 3 doses of Je-Vax across the wild type strains tested. JE vaccines in current use demonstrate activity across the range of JE genotypes. In a nonclinical study all immunised monkeys showed protection against intracerebral challenge by wild type (IC-37) JE virus which also provides a stringent test of effective immunity.

Two reports of paediatric clinical studies have been submitted which demonstrated high rates of seroprotection after a single dose is administered to toddlers in an endemic country. In Australia there is no JEV currently registered for use in children. There is a limited regional immunisation program in far north Queensland following several human JE cases in Torres Strait Island since 1995. The use of this product could be considered for the Far North Queensland JE program, including children from 12 months of age, provided the vaccine was not concurrently administered with other vaccines. There are no current data on co-administration of JE-CV with current paediatric vaccines, particularly National Immunisation Program (NIP) vaccines. The Delegate considered that the lack of interaction studies with paediatric NIP vaccines would currently preclude any generalised paediatric vaccination program in endemic areas.

The Office of Gene Technology Regulator (OGTR) on 27 April 2010 published a consultation Risk Assessment and Risk Management Plan for commercial release of Imojev, the comment time for which extended beyond the date of the ACPM meeting. The TGA was to take advice from OGTR into account when finalising a decision on registration of Imojev.

TGA is current participating in a WHO sponsored parallel review of Japanese encephalitis vaccine (Imojev) submitted for marketing authorization in Thailand and Australia.

Delegate's Proposed Action

The Delegate proposed to register Japanese Encephalitis Vaccine (live, attenuated), Imojev, which contains 4.0 – 5.8 $\log_{10}$ plaque forming units (PFU) of recombinant JE virus per dose (0.5 mL). The Delegate proposed registration for the indications "Prophylaxis of Japanese encephalitis caused by the Japanese encephalitis virus, in individuals from 12 months of age and older".

The recommended dose in individuals 12 months and older is a single 0.5 mL dose administered by subcutaneous injection.

Registration is proposed subject to the conditions that reports of a nonclinical reproductive and developmental toxicity study and currently ongoing clinical studies be submitted to TGA, and that product information be amended to the satisfaction of TGA.

The advice of ACPM was requested.

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

The ACPM recommended approval of the submission from Sanofi Pasteur Pty Ltd to register the new chemical entity of Japanese encephalitis vaccine (live, attenuated) (Imojev) 4.0 – 5.8 $\log_{10}$ plaque forming units (PFU) of recombinant JE virus per 0.5 mL dose, for the indication:

The prophylaxis of Japanese encephalitis caused by Japanese encephalitis virus in individuals from 12 months of age and older.

The recommended dose in individuals 12 months and older is a single 0.5 mL dose administered by subcutaneous injection.

In making this recommendation, the ACPM noted that based on the high seroconversion rates in the children older than 12 months, there were sufficient safety and efficacy data to approve this product for this population. The ACPM supported the Delegate's proposed indication.

The ACPM supported the Delegate in recommending that approval should be subject to the following conditions:

-further submission of safety data from paediatric studies;

-reports of a nonclinical reproductive and developmental toxicity study and currently ongoing clinical studies be submitted to TGA as soon as possible;

-the satisfactory resolution of the product sterility and shelf life testing as recommended by the PSC; and product information be amended to the satisfaction of TGA.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Imojev Japanese encephalitis vaccine (live, attenuated) powder for injection containing live, attenuated, recombinant Japanese encephalitis virus (strain SA 14-14-2) 4.0 - 5.8 log PFU (Plaque Forming Units) plus diluents vial 0.5 mL per dose, indicated for:

> The prophylaxis of Japanese encephalitis caused by the Japanese encephalitis virus, in individuals from 12 months of age and over.

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Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

AUSTRALIAN PRODUCT INFORMATION

NAME OF THE MEDICINE

IMOJEV®

Japanese encephalitis vaccine (live, attenuated)

DESCRIPTION

IMOJEV® is a monovalent, live attenuated viral vaccine. The virus was obtained via recombinant DNA technology. It is based on the 17D-204 yellow fever vaccine virus in which two genes have been replaced by the corresponding genes from Japanese encephalitis virus. These are the premembrane (prM) and envelope (E) coding sequences of the SA14-14-2 live attenuated Japanese encephalitis vaccine virus. The immunising antigens are the prM and E proteins from the SA14-14-2 vaccine virus.

After reconstitution:

Active ingredients:

Live, attenuated, recombinant Japanese encephalitis virus*: 4.0 - 5.8 log PFU**

* Propagated in Vero cells

** Plaque Forming Unit

Excipients:

- Mannitol
- Lactose
- Glutamic acid
- Potassium hydroxide
- Histidine
- Human Serum Albumin
- Sodium chloride
- Water for injections

No adjuvant or antimicrobial preservative is added.

The powder is a white to creamy white homogeneous cake which might be retracted from the sides of the vial. The diluent is a clear solution. After reconstitution, IMOJEV® is a colourless to amber suspension.

PHARMACOLOGY

Mechanism of action

The vaccine is a live attenuated virus. Following administration, the virus replicates locally and elicits neutralising antibodies and cell-mediated immune responses that are specific to the Japanese encephalitis virus. Available results indicate that protection is mainly mediated by neutralising antibodies.

In nonclinical studies, all animals that received a single dose of the vaccine developed specific neutralising antibodies against Japanese encephalitis (JE) virus and were protected against infection by a virulent JE virus experimental challenge.

CLINICAL TRIALS

Immunogenicity

Passive antibody transfer results in a small animal model indicate that protection is mediated by neutralising antibodies and that the threshold for protection is a plaque reduction neutralisation titre of 1:10.

Immunogenicity data in adult populations

A single dose administration of IMOJEV® is as immunogenic as a three-dose regimen of an inactivated Japanese encephalitis (JE) comparator vaccine administered in adults 18 years of age and over.

A seroprotective level of antibodies is generally reached 14 days after vaccination.

In a randomised comparative Phase III trial, 410 individuals over 18 years of age received a single dose of not less than 4.0 log PFU/dose of 0.5 mL of IMOJEV® and 410 individuals over 18 years of age received a three-dose regimen of 1 mL of an inactivated JE comparator vaccine.

Thirty days after vaccination, the seroprotection rates for the individuals who received IMOJEV® were more than 99% when measured against the homologous virus strain. These results are non-inferior to those observed after the three-dose regimen of the inactivated JE comparator vaccine.

Fourteen days after a single dose of IMOJEV®, more than 93% of the vaccinees showed seroprotective levels of neutralising antibodies.

Table 1 shows the seroprotection rates measured against the homologous virus strain, 14 and 30 days after vaccination with a single dose of IMOJEV® or a three-dose regimen of the inactivated JE comparator vaccine.

Table 1: Seroprotection Rates to Homologous Virus Strain, 14 and 30 Days after the Administration of IMOJEV® or of the Inactivated Japanese Encephalitis Comparator Vaccine

Days post last-immunisation	14 days		30 days	
	IMOJEV®	Inactivated Japanese encephalitis comparator vaccine	IMOJEV®	Inactivated Japanese encephalitis comparator vaccine
Seroprotection* † (%) (95% confidence interval)	93.6% (90.5; 96.0)	-‡	99.1% (97.5; 99.8)	74.8% (70.0; 79.2)

* Based on homologous virus strain

† "Seroprotection" refers to neutralising antibody titre above the threshold of protection

‡ Not applicable

Neutralising antibody levels were also assessed against a panel of wild-type strains belonging to the four main genotypes and originating from different countries. In a Phase II trial, more

than 89% of vaccinees showed neutralising antibody levels above the 1:10 threshold against the tested wild-type strains, 28 days after a single dose administration of IMOJEV®.

In a long-term follow-up assessment in a randomised control phase II trial, 97.6% (95% CI, 93.3; 98.8) of individuals showed seroprotective levels six months after a single administration of IMOJEV®. The probability of being still seroprotected 48 months after vaccination for those who were seroprotected at six months is 91.5%.

Long-term immunogenicity data up to Month 48 are presented as Kaplan-Meier estimates in Table 2.

Table 2: Long-Term Immunogenicity after a Single Dose of IMOJEV®

Visit time point	N Seropositive	N Seronegative	N Censored*	Kaplan-Meier estimate	95% confidence interval
Month 6	90	0	11	100.0%	100.0; 100.0
Month 12	77	2	8	97.5%	94.0; 100.0
Month 24	66	3	11	93.2%	87.5; 99.0
Month 36	54	1	16	91.5%	85.0; 98.1
Month 48	37	0	38	91.5%	85.0; 98.1

* Individuals who were lost to follow-up were censored

Immunogenicity data in paediatric populations

- Immune response 28 days after a single dose administration of IMOJEV®

A seroprotective level of antibodies is generally reached 28 days after vaccination.

Subjects previously immunised with an inactivated JE vaccine

A single dose administration of IMOJEV® in children 2 to 5 years previously vaccinated with a two-dose regimen of an inactivated JE vaccine showed a good booster response in a Phase II trial (n=97 subjects): more than 92% of individuals seroconverted and they were all seroprotected (neutralising antibody level above the threshold of protection).

Table 3: Immune Response 28 Days after a Single-Dose of IMOJEV® in Children (2 to 5 Years) Previously Immunised with a JE Vaccine

	28 days post IMOJEV® vaccination	
	%	95% confidence interval
Seroprotection* †	100.0	96.3; 100.0
Seroconversion*‡	92.8	85.7; 97.0

* Based on homologous virus strain

† "Seroprotection" refers to neutralising antibody titre above the threshold of protection

‡ Seroconversion refers to:

- In individuals previously immunised and who are seronegative at baseline: neutralising antibody titre above the threshold of protection after vaccination with IMOJEV®
- In individuals who are seropositive at baseline: at least a fourfold rise in neutralising antibody titre after vaccination with IMOJEV®

In addition, more than 99% of children previously vaccinated with a JE vaccine showed seroprotective antibody levels against JE wild-type strains belonging to the four main genotypes, 28 days after a single dose administration of IMOJEV® in a Phase II trial.

Subjects not previously immunised with an inactivated JE vaccine

A single dose administration of IMOJEV® in 2 randomised trials in 1,231 toddlers 12 to 24 months previously not immunised with a JE vaccine showed that more than 95% of individuals seroconverted and were seroprotected (neutralising antibody level above the threshold of protection).

Table 4: Immune Response 28 Days after a Single-Dose of IMOJEV® in Toddlers (12 to 24 Months) not Previously Immunised with a JE Vaccine

	28 days post IMOJEV® vaccination	
	%	95% confidence interval
Seroprotection*†	95.2	93.9; 96.4
Seroconversion*‡	95.4	94.0; 96.5

* Based on homologous virus strain

† "Seroprotection" refers to neutralising antibody titre above the threshold of protection

‡ Seroconversion refers to:

- In individuals who are seronegative at baseline: neutralising antibody titre above the threshold of protection after vaccination with IMOJEV®
- In individuals who are seropositive at baseline: at least a fourfold rise in neutralising antibody titre after vaccination with IMOJEV®

In addition, more than 96% of a subset of toddlers previously not immunised with a JE vaccine in a Phase II trial seroconverted to three of the four tested JE wild-type strains 28 days after a single dose administration of IMOJEV®, and approximately 70% seroconverted to the fourth strain.

- Immune response 6 months after a single dose administration of IMOJEV®

The assessment on the persistence of seroprotection was assessed in a Phase II trial in both children (aged 2 to 5 years; n=100) and toddlers (aged 12 to 24 months; n=200) population.

All the children previously vaccinated with a two-dose regimen of an inactivated JE vaccine and who received a single dose administration of IMOJEV® as a booster dose were shown to still have seroprotective antibody levels 6 months after the vaccination.

More than 86% of toddlers who did not receive any JE vaccine before the single dose administration of IMOJEV® were shown to still have seroprotective antibody levels 6 months after the vaccination.

Table 5: Immune Response 6 Months after a Single-Dose of IMOJEV® in Children (2 to 5 Years) Previously Immunised with a JE Vaccine and in Toddlers (12 to 24 Months) not Previously Immunised with a JE Vaccine

	6 months post IMOJEV® vaccination	
	Children Aged 2 to 5 Years	Toddlers Aged 12 to 24 Months
Seroprotection*† (%) (95% confidence interval)	100.0 (96.3; 100.0)	86.8 (81.3; 91.2)

* Based on homologous virus strain

† "Seroprotection" refers to neutralising antibody titre above the threshold of protection

INDICATIONS

IMOJEV® is indicated for prophylaxis of Japanese encephalitis caused by the Japanese encephalitis virus, in individuals from 12 months of age and over.

CONTRAINDICATIONS

IMOJEV® should not be administered to anyone with a history of severe allergic reaction to any component of the vaccine or after previous administration of the vaccine or a vaccine containing the same components or constituents.

Vaccination must be postponed in case of febrile or acute disease.

Congenital or acquired immune deficiency impairing cellular immunity, including immunosuppressive therapies such as chemotherapy, high doses of systemic corticosteroids given generally for 14 days or more.

IMOJEV® must not be administered to individuals with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function.

IMOJEV® must not be administered to pregnant women (see Section "Use in Pregnancy").

IMOJEV® must not be administered to breastfeeding women (see Section "Use in Lactation").

PRECAUTIONS

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following administration of the vaccine.

For patients following a treatment with high doses of systemic corticosteroids given for 14 days or more, it is advisable to wait for at least one month or more following the interruption of therapy before carrying out the vaccination until immune function has recovered.

IMOJEV® should under no circumstances be administered intravascularly.

The need for and timing of booster doses of IMOJEV® is currently being assessed. Immunogenicity has currently been shown to be well maintained for at least 48 months after vaccination in adults and for at least 6 months after vaccination of toddlers (aged 12-24 months) and children (aged 2-5 years) (see Section "Clinical Trials").

Effects on Fertility

IMOJEV® has not been tested for the possible effects on fertility. A nonclinical biodistribution study in animals did not detect vaccine virus in the ovaries or testes following IMOJEV® injection.

Use in Pregnancy (Category B2)

No animal reproduction studies have been conducted with IMOJEV®.

As with all live attenuated vaccines, pregnancy constitutes a contraindication (see Section "Contraindications").

There is a theoretical risk that a live vaccine virus can cross the placenta and infect the foetus. It is not known whether IMOJEV® can cause foetal harm when administered to a pregnant woman.

Women of childbearing age should be advised not to become pregnant for 4 weeks after vaccination.

Use in Lactation

It is not known whether this vaccine is excreted in human milk.

IMOJEV® vaccination is contraindicated in breastfeeding women (see Section "Contraindications").

Studies with some other live, attenuated virus vaccines have shown that a lactating postpartum woman may secrete the virus in breast milk and infect a breast-fed infant.

Genotoxicity

IMOJEV® has not been tested for genotoxic potential.

Carcinogenicity

IMOJEV® has not been tested for carcinogenic potential.

Interactions with other Medicines

No studies have been conducted of concomitant administration of IMOJEV® and other vaccines with the exception of yellow fever vaccine in adults. In adults, IMOJEV® may be administered at the same time as yellow fever vaccine using separate syringes, and into separate limbs.

In children, IMOJEV® should not be administered concomitantly with other vaccines, particularly paediatric vaccines that are included in the national immunisation program.

In the case of immunosuppressive therapy or corticosteroid therapy, refer to Section "Contraindications" and "Precautions".

In order to avoid any neutralisation of the attenuated viruses contained in the vaccine, vaccination must not be performed within 6 weeks, and preferably not within 3 months of injection of immunoglobulins or blood products containing immunoglobulins, such as blood or plasma.

Effect on Ability to Drive

No studies on the effects on the ability to drive or use machines have been performed.

ADVERSE EFFECTS

Clinical Trials Experience

Data in adult populations

The safety of IMOJEV® has been assessed in 8 randomised clinical trials in individuals over 18 years of age. During the development in the adult population, approximately 2,500 individuals received an injection of IMOJEV®.

Safety evaluation was performed for all individuals during the first 4 weeks following vaccination and serious adverse reactions were collected during at least six months of follow-up after a single dose of IMOJEV®.

The most frequently reported systemic reactions after the administration of IMOJEV® vaccine were headache, fatigue, malaise and myalgia. All these reactions were as frequently reported as after the administration of the inactivated Japanese encephalitis comparator vaccine or a placebo.

The most frequently reported reaction at the injection site after the administration of IMOJEV® vaccine was injection site pain. All the injection site reactions were less frequently reported than after the administration of the inactivated Japanese encephalitis comparator vaccine and as frequently reported as after the administration of a placebo.

Table 6 below summarises the possibly related Adverse Events (frequency ≥1.0%) that were reported during clinical trials within 30 days after the administration of a single dose of IMOJEV®, of the two first doses and the third dose of the inactivated Japanese encephalitis comparator vaccine and of the placebo doses.

Table 6: **Possibly Related Adverse Events (≥1.0%) Reported Within 30 Days After the Administration of IMOJEV®, of the Inactivated Japanese Encephalitis Comparator Vaccine and of the Placebo**

Adverse events	IMOJEV® (N=2046)	Inactivated Japanese encephalitis comparator vaccine Dose 1 and 2 (N=440)	Inactivated Japanese encephalitis comparator vaccine Dose 3 (N=422)	Placebo Dose 1 and 2 (N=440)	Placebo (N=435)
General disorders and administration site conditions					
Fatigue	21.0%	23.6%	10.9%	26.6%	22.1%
Malaise	17.0%	20.5%	9.0%	17.5%	16.3%
Injection site pain	11.8%	58.4%	34.8%	20.2%	9.2%
Feeling hot	8.4%	7.3%	4.7%	8.2%	6.9%
Chills	6.0%	5.5%	1.9%	7.3%	4.1%
Injection site erythema	4.4%	24.8%	17.5%	3.4%	3.2%
Injection site pruritus	3.6%	19.5%	12.6%	5.0%	2.5%
Injection site swelling	1.3%	13.9%	12.6%	1.6%	0.9%
Injection site bruising	1.1%	3.2%	1.4%	2.5%	1.1%
Pyrexia	0.9%	1.1%	1.2%	1.1%	1.4%
Nervous system disorders					
Headache	23.9%	32.5%	15.6%	30.7%	24.6%
Dizziness	1.1%	0.9%	0.2%	0.5%	0.7%
Musculoskeletal and connective tissue disorders					
Myalgia	14.7%	17.5%	6.9%	15.7%	11.5%
Arthralgia	6.6%	8.6%	3.8%	8.6%	4.6%
Gastrointestinal disorders					
Diarrhoea	7.6%	7.3%	2.4%	7.0%	5.7%
Nausea	6.5%	8.4%	4.3%	5.9%	6.4%
Abdominal pain	5.1%	5.7%	3.3%	8.0%	4.8%
Vomiting	1.0%	1.1%	0.9%	1.4%	1.6%
Respiratory, thoracic and mediastinal disorders					
Pharyngolaryngeal pain	2.9%	2.3%	1.2%	2.3%	2.3%
Dyspnea	2.7%	3.2%	1.4%	3.0%	2.3%
Rhinorrhoea	1.5%	0.5%	0.0%	0.5%	2.1%
Cough	1.4%	0.9%	0.9%	0.9%	1.8%
Wheezing	1.3%	1.4%	0.2%	2.3%	1.8%
Nasal congestion	1.0%	0.7%	0.7%	0.2%	2.1%
Skin and subcutaneous tissue disorders					
Rash	1.2%	3.9%	2.1%	2.3%	1.8%

The following possibly related Adverse Events (frequency <1.0%) were reported during clinical trials within 30 days after the administration of a single dose of IMOJEV®. These events were as frequently reported as after the administration of the inactivated Japanese encephalitis comparator vaccine or the placebo:

- **General disorders and administration site conditions:** Influenza like illness, injection site rash, chest discomfort, injection site reaction, injection site induration, oedema peripheral, irritability, injection site haemorrhage, injection site warmth, injection site paraesthesia, asthenia, injection site joint pain, injection site discomfort, tenderness

- **Nervous system disorders:** Sinus headache, lethargy, paraesthesia, migraine, somnolence, syncope vasovagal, dizziness postural
- **Musculoskeletal and connective tissue disorders:** Back pain, neck pain, pain in extremity, musculoskeletal pain, pain in jaw, musculoskeletal stiffness, muscle spasms, muscle tightness, intervertebral disc compression
- **Gastrointestinal disorders:** Abdominal pain upper, dry mouth, lip swelling, dyspepsia, palatal oedema, tongue oedema
- **Infections and infestations:** Viral infection, urinary tract infection, gastroenteritis, subcutaneous abscess
- **Respiratory, thoracic and mediastinal disorders:** Sneezing, asthma, pharyngeal erythema, throat irritation
- **Skin and subcutaneous tissue disorders:** Pruritus, pruritus generalized, rash maculo-papular, rash generalised, swelling face, eczema, urticaria, rash popular, rash macular, rash erythematous
- **Investigations:** Alanine aminotransferase increased, lymph node palpable
- **Injury, poisoning and procedural complications:** Sunburn
- **Blood and lymphatic system disorders:** Lymphadenopathy, leukopenia, lymph node pain, lymphopenia
- **Psychiatric disorders:** Insomnia
- **Ear and labyrinth disorders**: Ear pain, tinnitus, vertigo
- **Eye disorders:** Eye pain, vision blurred, eye pruritus, eye swelling
- **Vascular disorders:** Flushing, hot flush, hypertension
- **Cardiac disorders:** Sinus tachycardia
- **Immune system disorders:** Hypersensitivity
- **Metabolism and nutrition disorders:** Decreased appetite, increased appetite

Data in paediatric populations

The safety of IMOJEV® has been assessed in 2 randomised clinical trials in individuals between 12 months and 5 years of age. During the development in paediatric populations, approximately 1,400 individuals (100 children and 1,300 toddlers) received an injection of IMOJEV®.

Safety evaluation was performed for all individuals during the first 4 weeks following vaccination and serious adverse reactions were collected during at least six months of follow-up after a single dose of IMOJEV®.

The most frequently reported systemic reactions were malaise, fever, headache and myalgia in children 2 to 5 years; and fever, appetite lost and irritability in toddlers 12 to 24 months.

The most frequently reported reactions at the injection site after the administration of IMOJEV® vaccine was injection site pain/tenderness and injection site erythema.

These adverse events observed during paediatric clinical trials were generally of mild intensity and of short duration. The onset of systemic reactions was generally seen within 3 days after immunisation.

Table 7 below summarises the solicited reactions that were reported during clinical trials after the administration of a single dose of IMOJEV® or of a control vaccine.

Table 7: Solicited Reactions after the Administration of IMOJEV® or of a Control Vaccine (Reported Within 7 Days for Injection Site Reactions and 14 Days for Systemic Reactions)

Solicited reactions	IMOJEV® (N=1396)	Hepatitis A (N=400)
Injection site reaction		
Injection site pain/tenderness	23.6%	25.1%
Injection site erythema	23.4%	20.6%
Injection site swelling	7.2%	7.8%
Systemic reactions		
Fever	20.7%	18.8%
Headache	21.0%	14.3%
Malaise	33.0%	26.5%
Myalgia	24.0%	15.3%
Vomiting	19.2%	19.9%
Crying abnormal	19.1%	19.9%
Drowsiness	18.4%	16.6%
Appetite lost	25.9%	28.2%
Irritability	28.5%	24.6%

Table 8 below summarises the non-serious adverse reactions that were reported during clinical trials within 28 days after the administration of a single dose of IMOJEV® or of a control vaccine.

Table 8: Unsolicited Non-serious Adverse Reactions within 28 days after the Administration of IMOJEV® or of a Control Vaccine

Unsolicited Non-serious Adverse Reactions	IMOJEV® (N=1396)	Hepatitis A (N=400)
General disorders and administration site conditions		
Injection site bruising	0.2%	0.3%
Injection site haematoma	0.3%	0.0%
Injection site haemorrhage	0.2%	0.0%
Injection site induration	0.1%	0.0%
Injection site pruritus	0.1%	0.0%
Gastrointestinal disorders		
Vomiting	0.1%	0.0%
Infections and infestations		
Upper respiratory tract infection	0.1%	0.0%
Viral infection	0.1%	0.0%
Skin and subcutaneous tissue disorders		
Post inflammatory pigmentation change	0.1%	0.0%
Rash	0.1%	0.0%
Rash maculo-papular	0.1%	0.3%
Urticaria	0.1%	0.0%

No serious adverse events within 28 days of administration of IMOJEV® were related to vaccination.

Febrile convulsions within 14 days of administration of IMOJEV® were reported in three children. In all cases, febrile convulsions were not related to vaccination and were associated with concomitant infectious diseases.

Adverse Reactions from Post-Marketing Surveillance

There is no safety data from post-marketing experience with IMOJEV®.

DOSAGE AND ADMINISTRATION

Individuals 12 months of age and over: a 0.5 mL single injection of the reconstituted vaccine.

Once the freeze-dried vaccine has been completely reconstituted using the diluent provided (see Section "Instructions for use"), it is administered via the subcutaneous route.

In individuals 2 years of age and over, the recommended injection site is the deltoid region of the upper arm.

In individuals between 12 and 24 months of age, the recommended injection site is the anterolateral aspect of the thigh or the deltoid region.

Do not administer by intravascular injection.

IMOJEV® must not be mixed with any other injectable vaccine(s) or medicinal product(s).

Contact with disinfectants is to be avoided since they may inactivate the vaccine virus.

Product is for single use in one patient only. Discard any residue.

Instructions for use

Using aseptic technique, IMOJEV® vaccine is reconstituted by injecting all the 0.4% sodium chloride solution into the vial of freeze-dried vaccine, using the syringe and one of the needles provided in the carton. The vial is gently swirled. After complete dissolution, a 0.5 mL dose of the reconstituted suspension is withdrawn into this same syringe. For injection, the syringe is fitted with the second needle provided in the package.

The product should be used once reconstituted and must be discarded if it is not used within one hour of reconstitution.

After use, any remaining vaccine and container must be disposed of safely, preferably by heat inactivation or incineration, according to locally agreed procedures.

OVERDOSE

No case of overdose has been reported.

PRESENTATION AND STORAGE CONDITIONS

One dose of freeze-dried vaccine and one dose of diluent in separate vials (type I glass), each equipped with a stopper (halo-butyl) and a flip off cap (aluminium), with one syringe (polypropylene) and two needles (stainless steel). Pack size of 1 powder vial and 1 diluent vial, 1 syringe and 2 needles.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the vials in the outer carton in order to protect from light.

NAME AND ADDRESS OF THE SPONSOR

Sanofi Pasteur Pty Ltd

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POISON SCHEDULE OF THE MEDICINE

S4 Prescription Only Medicine

DATE OF APPROVAL

16 August 2010

Therapeutic Goods Administration

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