PUBLIC ASSESSMENT REPORT
FOR
IMOJEV

Common Name: Japanese Encephalitis Vaccine (recombinant)

Application No. 1 A 90001/52(NBC)

Assessment Report as adopted by the TFDA with
all information of a commercially confidential nature deleted

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant **GPO-MBP** submitted on 30 Nov 2009 an application for Marketing Authorization to the Thailand Food and Drug Administration (TFDA). At the time of submission and validation, IMOJEV was designated as medicinal product in the following indication: For prophylaxis of Japanese encephalitis caused by the Japanese encephalitis virus, in adults 18 years of age and over.

The legal basis for this application refers to: Drug Act 2510 B.E.

The application submitted was a complete dossier: composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

Scientific Advice / Protocol Assistance:

The applicant received Scientific Advice in May and October 2010 (External Experts) and Protocol Assistance in October 2010 (Clinical External Experts) from the TFDA. The Scientific Advice in 2010 pertained to Quality, Non-clinical and Clinical Aspects of the dossier and the Protocol Assistance in 2010 pertained to clinical aspects of the Phase IV Clinical Study.

Licensing status:

The product was not licensed in any country at the time of submission of the application.

TFDA Product Team Leader: (PTL)

Quality:	Mrs. Tasanee	Lorchaivej
Non-clinical:	Mr. Pramote	Akarapanon
Clinical:	Ms. Prapassorn	Thanaphollert

The Co Product Team Leader (Co- PTL)

Quality:	Mr. Morakot	Prapatsiripan
Non-clinical:	Mr. Kritsada	Limpananon
Clinical:	Ms. Jaruwan	Toron

TFDA External Experts

- Quality:
- Non Clinical
- **Clinical**

1.2 Steps taken for the assessment of the product

- The application was received by the TFDA on 26 June 2009.
- The procedure started on 30 Nov 2009.
- A List of questions, the overall conclusion and review of the scientific data were prepared by the TFDA and sent to the applicant on 24 Feb 2010
- The applicant submitted of the responses, including revised SPC, labeling and package leaflet texts in English and/ or Thai (where required by Drug Act) on 26 Feb 2010
- TFDA revised the Assessment Report based on responses from the applicant and dispatched the assessment report to external experts for their consideration and comments on 31 Mar 2010
- During the Preliminary assessment the external experts agreed on the consolidated List of Questions to be sent to the applicant.
    - **Quality**: 7 May 2010
    - **Non Clinic** 12 Apr 2010
    - **Clinic**: 7 Apr 2010
- During the In dept assessment the external experts agreed on the consolidated List of Questions to be sent to the applicant.
    - **Quality**: 8 Oct 2010
    - **Non Clinic**: 21 Jun 2010
    - **Clinic**: 6 Oct 2010
- TFDA considered the consolidated list of questions, identifying "major objections" and/or "other concerns" may be adopted. These were sent to the applicant together with the TFDA recommendation and scientific discussion on 21 Oct 2010.
- Final draft of English SPC, labeling and package leaflet was sent by applicant to the TFDA PTL on 26 Oct 2010
- TFDA adopted the decision on marketing authorization on 29 Oct 2010

2. SCIENTIFIC DISCUSSION

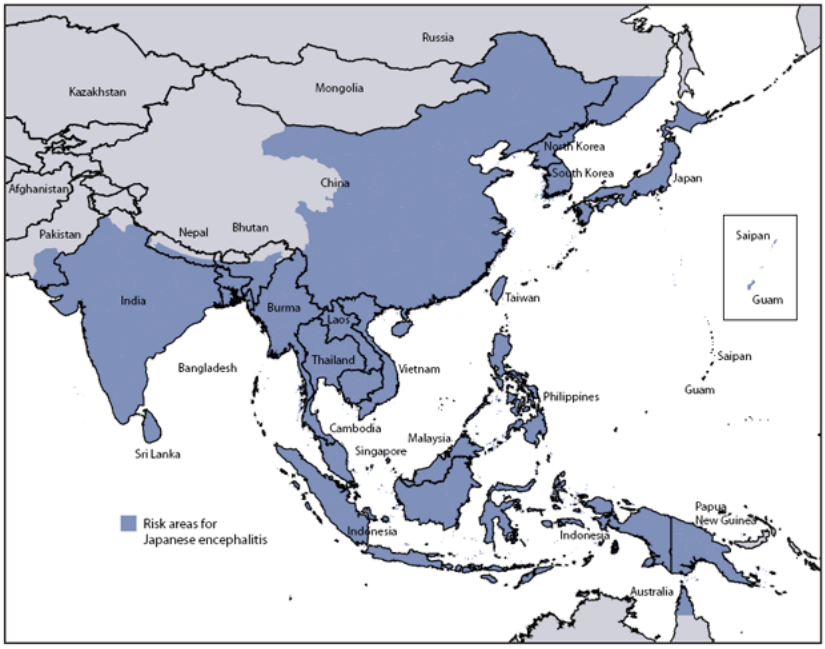
2.1 Introduction

Japanese encephalitis (JE) is a mosquito-borne arboviral infection and the leading cause of viral encephalitis worldwide with an estimate of at least 50,000 cases of clinical disease per year. Children less than 10 years of age are primarily affected. Japanese encephalitis (JE) is the most common cause of viral encephalitis in the Asia Pacific region. The virus exists in a transmission cycle between mosquitoes and pigs and/or water birds such as herons and egrets, which are the main host reservoir. JE is therefore a mosquito-borne zoonotic viral infection, the reservoirs of which are water birds and in which pigs play the role of amplifying host in rural areas. JEV is transmitted to humans through the bite of infected mosquitoes. Humans usually do not develop a level or duration of viremia sufficient to infect mosquitoes. Therefore,

humans are dead-end hosts, and human JE cases imported into nonendemic areas represent a minimal risk for subsequent transmission of the virus. Direct person-to-person spread of JEV does not occur except rarely through intrauterine transmission. On the basis of experience with similar flaviviruses, blood transfusion and organ transplantation also are considered potential modes of JEV transmission.

JE used to be mostly prevalent in countries with a temperate climate, including Japan, but data from tropical countries (Thailand, Cambodia, Indonesia) (See Picture 1) show that these zones also are favorable for JE transmission. Indeed, JE can now be found from the extreme south-eastern part of Russia to the North of Australia and Papua New Guinea, and from Japan to the west of India.

Picture 1 Approximate geographic range of Japanese encephalitis



Clinical Signs and Symptoms

The majority of human infections with JEV are asymptomatic; <1% of people infected with JEV develop clinical disease. Acute encephalitis is the most commonly identified clinical syndrome with JEV infection. Milder forms of disease (e.g., aseptic meningitis or undifferentiated febrile illness) also can occur but have been reported more commonly among adults.

Among patients who develop clinical symptoms, the incubation period is 5-15 days. Illness usually begins with acute onset of fever, headache, and vomiting. Mental status changes, focal neurologic deficits, generalized weakness, and movement disorders might occur over the next few days. Seizures are common, especially among children. The classical description of JE includes a parkinsonian syndrome with mask-like faces, tremor, cogwheel rigidity, and choreoathetoid movements. Out of the approximately annual 50,000 cases of JE more than 10,000 end fatally, and about 15,000 survivors are left with neurological and/or psychiatric sequelae requiring rehabilitation and continued care. Acute flaccid paralysis, with clinical and

pathological features similar to poliomyelitis, also has been associated with JEV infection. Status epilepticus, brain hypoxia, increased intracranial pressure, brainstem herniation, and aspiration pneumonia are the most common complications associated with poor outcome and death.

The overall risk of JE for travellers to endemic areas is considered rather low and was calculated to be about 1:5,000 to 1:20,000 per week. However, the risk may significantly increase when travelling in rural destinations and during the season of enhanced transmission (mostly May to September). The CDC reviewed cases of JE among expatriates and travellers that occurred during 1978–1992. From a total of 24 cases outcome information was available for 15 patients, of whom 6 died, 5 were listed as disabled, and 4 recovered. Only 2 of these 24 patients were tourists; the other patients were doing research or medical relief work or were soldiers. Further cases of JE were reported from tourists visiting Bali, Indonesia or Thailand.

The immune response to JEV infection has not been fully characterized, and both humoral and cellular responses may play a role. However, it is widely accepted that virus neutralizing antibodies provide the best evidence that protective immunity against JEV has been established. A linear titre-protection relationship has been demonstrated and data from efficacy studies in humans and animals corroborate the role of neutralizing antibodies in protection. Monoclonal antibodies to epitopes on the envelopeglycoprotein both neutralize JEV in vitro and protect mice from lethal challenge. Murine studies have also demonstrated that protection can be mediated through either adoptive transfer of T-lymphocytes or passive administration of antisera from mice infected with JEV. Historically, passive transfer of human post-infection sera to at-risk subjects was protective and correlated with detectable neutralizing antibodies in recipients.

JE Vaccines

The control of JE is based essentially on three interventions: mosquito control, avoiding human exposure to mosquitoes and immunization. Mosquito control has been very difficult to achieve in rural settings and avoidance of exposure is difficult as Culex mosquitoes bite during daytime. Immunization is the only effective method for sustainable control. Routine immunization of school-age children is currently in use in Korea, Japan, China, Thailand and Taiwan. There is currently no medication treatment available for JE and thus pre-exposure protection against the disease is essential. The introduction of the JE vaccine into the Expanded Program of Immunization has helped curb the disease in countries like Thailand, Vietnam, Sri Lanka and China

The vaccines for JE are divided to 3 types of vaccines.

1. Inactivated Vaccine, among the currently available vaccines is a formalin-inactivated vaccine derived from mouse brain-grown JEV strain Nakayama, which still is produced by manufacturers in Korea, Thailand and Vietnam. The vaccine is relatively expensive, requires three doses on days 0, 7 and 30, followed by a booster at 1 year and thereafter at intervals of 3 years. The vaccine can often generate neurological adverse reactions. In addition to local and

systemic side effects, individual cases of generalized urticaria and angioedema were reported in about 1 case per 1000 vaccinees after vaccination of travelers from western countries.

2. The live attenuated JE vaccine strain, SA14-14-2, which was obtained after 11 passages in weaning mice followed by 100 passages in primary hamster kidney cells, has been developed and used in China since 1988. The vaccine, which is produced by the Chengdu Institute of Biological Products in China, was licensed in recent years in several Asian countries and was extensively used from 2006 to 2008 in mass immunization campaigns in India. Although the product is not WHO prequalified at this time, much investment and efforts have been made to bring the production and quality control to international standards. The vaccine is produced on primary hamster kidney cells, lyophilized, and administered to children at one year of age and again at two years, in annual spring campaigns. Initial observational studies in southern China involving more than 200 000 children had demonstrated the vaccine safety, immunogenicity (99-100% seroconversion rate in nonimmune subjects) and protective efficacy over 5 years. The short-term effectiveness of a single dose of SA14-2-14 was demonstrated in 2001 in a case control study on Nepalese children where an efficacy of 99.3% was reported. A five year follow-up study found the single-dose efficacy was maintained at 96.2%. Another five-year follow up study showed that neutralizing antibody persistence was close to 90% at 4 years and 64% at 5 years after a single-dose of the vaccine in adult volunteers. Recent studies in the Philippines have demonstrated the safety and efficacy of the vaccine even when co-administered with measles vaccine at 9 months of age. Similar studies in Sri Lanka and Indonesia will help confirm these findings in other Asian settings.

3. Chimeric vaccines, A promising approach for a future JE vaccine has been the construction of a YF-JE chimera based on the attenuated 17D YF virus genome, in which the YFV sequences encoding viral structural proteins prM and E were replaced by the corresponding prM and E sequences from JEV strain SA14-2-14.

IMOJEV is indicated for prophylaxis of Japanese encephalitis caused by the Japanese encephalitis virus, in subjects from 12 months of age and over. The vaccination schedule consists of a single 0.5 mL dose of the vaccine administered by the subcutaneous route.

2.2 Quality aspects

Introduction

IMOJEV™, the Japanese Encephalitis Chimeric Virus vaccine, (also referred to in this application as Chimeric Vax™ - JE or JE-CV) is a monovalent, live attenuated viral vaccine, which belongs to the pharmacotherapeutic group of encephalitis vaccines (J07BA). It contains between 4.0 and 5.8 log plaque forming units (PFU) of live, attenuated, recombinant JE virus per dose (0.5 mL). This PFU is used to assess the potency of JE-CV.

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 YF 17D virus provides the replication engine while the pre-membrane (prM) and envelope (E) proteins are from the SA14-14-2 JE virus. The E protein is the antigen responsible for induction of neutralising antibodies, while the M protein is needed to ensure to the correct conformation of E. 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.

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 stabilizer constituted of lactose, mannitol, histidine, glutamic acid, human serum albumin and salts. The JE-CV formulation is then freeze-dried.

The vaccine comprises a freeze-dried powder and a 0.4% NaCl diluent for reconstitution in single dose presentation. JE-CV is indicated for the prophylaxis of JE caused by the JE virus, in adults 12 years of age and over. The vaccination schedule consists of a single 0.5 mL dose of the vaccine administered by the subcutaneous route.

Active Substance

After reconstitution, one dose (0.5 mL) contains:

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

* Plaque Forming Unit

Manufacturers

The manufacturing steps and testing of the JE-CV vaccine are performed in the following site under Good Manufacturing Practice (GMP) as shown in table 1.

Table 1: Manufacturing sites and Operations

Manufacturing Facility	Operations
Sanofi Pasteur Biologics Co.*, 38 Sidney St, Cambridge, MA 01581 USA	Manufacture of Pre-Master Seed (PMS)
Sanofi Pasteur Biologics Co., 50-90Shawmut Rd, Canton, MA 02021 USA	Manufacture of Master Seed Lot (MSL), Working Seed Lot (WSL) and Drug Substance (DS)
BioReliance Corporation** 14920 Broschart Rd Rockville, MD 20850 USA	- Quality Control (QC) testing
Government Pharmaceutical Organization-Merieux Biological Product Company Limited (GPO-MBP)	- Manufacture of the Drug Product, - Manufacturing of 0.4 sodium chloride diluent solution

241 Moo 7, Gateway City Industrial Estate, Tambon Huasamrong, Amphoe Plaengyao, Chachoengsao 24190, Thailand.	- Quality Control (QC) testing - Batch release
Cogenic (formerly Lark, A Clinical Data Company) 9441West Houston Parkway South Suite 103 Houston, TX 77099 USA	Quality Control (QC) testing
Wuxi AppTec, Inc. 4751 League Island Blvd. Philadelphia, PA 19112 USA	Quality Control (QC) testing
Sierra Biomedical Charles River Laboratories, Inc. (CRL) Discovery and Development Services (DDC) Sierra Division (Sierra) 587 Dunn Circle, Sparks, NV 89431 USA	Quality Control (QC) testing

*Please note that Acambis Inc., is part of Sanofi Pasteur since September 2008, nevertheless this document may refer to Acambis as development of product and validation lots were manufactured before September 2008.

** Please note that some documentation may refer to Q-One Biotect, which is now part of BioReliance Corporation.

The TFDA recommended on The Quality Dossiers as the followings:

With regard to Manufacturing, Quality control and Viral safety issues the following should be raised with the company and satisfactory responses should be receive before approval is given for the registration of IMOJEV vaccine.

1. The company stated that Human Serum Albumin is voluntarily added as a stabilizer at the final concentration of 0.1%. The amount of HAS in the product is strictly the amount added during the process, their addition is controlled under GMP conditions and recorded in the batch record. For this reason, the company does not plan to perform quantification of HAS in the final product. *However, the residual human serum albumin/protein in final product should be performed.* (Add the test in FPS)

2. The filter integrity testing during in-process control is performed after filtration. *The company should performed both pre-post filtration.*

3. The company stated that the abnormal toxicity test was performed and found conform on six batches of single dose (3 for validation batches and 3 for clinical batches). This is also the case for the 3 multidose validation batches. As recommended by Ph.Eur. Monographs e.g. MMR vaccine (1057) or Hepatitis A vaccine (1107) and WHO TRS 932, and taking into account that following the data obtained on these 9 lots, the production method is validated to demonstrate that the product, if tested, would comply with the test for abnormal toxicity of vaccine for human use, abnormal toxicity test is not classically included in the routine release profile. *The abnormal toxicity test (required by TRS 932) should be performed in final products until consistency of the production has been satisfied, when the GMP is in place.* (Add the test in FPS)

4 The company has proposed shelf-life for the vaccine of 3 years storage at +5℃ ±3 ℃ *(Approve at 30 months based on real time stability data available). The company should submit more stability data performed on the validation and clinical batches stored at 2-8 ℃ at 30 - 36 months (submitted when available). The company commits to provide the stability data at 3 years as soon as available.*

5. Since the available data shows some increase in the moisture content as time goes by. *The company should submit data on residual moisture content on 18, 24 and 36 months. The company commits to provide the stability data at 3 years as soon as available.*

6. The thermal stability study test of DP should be performed in parallel with the potency at T0, T3, T6, T9, T12, T18, T24, T30, T36 rather than T0 and T36. *The company commits to provide thermostability data of validation batches at the next time points (T31 months in addition to T36 months which was already planned).*

7. *The company should provide the Certificates of subcontract laboratory.*

8. *The company should provide data on the shipment validation result of DP and validation result of the vaccine package for International transportation of DS and DP.*

9. *The company should submit the test result of vaccine samples to the TFDA PTL for consideration in finalizing the TFDA Assessment Report.*

The company responded to the above recommendations as the followings:

1. The company informed that human serum albumin is presented as a stabilizer at the final concentration of 0.1%. Different concentrations of albumin were tested during the development studies. Drug product showed that, in absence of albumin, the recovery of virus titer was only 25% and that the recovery of virus titer was above 79% in all formulations with albumin. In the light of these data, an insufficient concentration of albumin would be detected through low virus recovery and the applicant did not set up a control of the albumin content, Furthermore, the volume of albumin added in the JE stabilizer is easily mixed as it is added as a liquid form (400 ml of 20% solution) in an aqueous solution. All these manufacturing operations are checked and traceable and, as evidence, the site operates in GMP conditions.

Since the amount of stabilizer is added in the formulation is important point, if the amount of the human serum albumin was added lower or higher than the option range. The stability and immunogenicity of vaccine may be affected. Because of the measurement of human serum albumin/protein in final product dose not performed. Beside the manufacturer controlling, We would like to request the manufacturer to inform the amount of HAS added during the process of each lot in summary protocol for lot release.

The company should inform the amount of HAS added during the formulation of each lot in summary protocol for lot release.

2. The manufacturer committed to implement sterilizing filter integrity testing both before and after use for all future commercial batches. This is satisfactory.

3. The company informed the consistency of production was demonstrated through the validation and 9 lots tested for abnormal toxicity. And will continue to perform the abnormal toxicity on the next lots and up to a significant number of lots. This is satisfactory.

4. The company should submit the stability data as soon as possible.

5. The company committed to provide the data on residual moisture content at T30 month for clinical batches and T36 month for all batches as soon as available. This is satisfactory.

6. The company committed to provide the thermostability data as soon as available. This is satisfactory.

7. The manufacturer provides the certificate as follow;

1. GMP Clearance of Bio Reliance Corporation, USA (Manufacturing step: Testing laboratory)

2. GLP Declaration Statement of Sierra Biomedical Charles River laboratories, Inc. (CRL) as the site for Quality Control testing:

- QC testing of the Working Seed Lots (WSL) and the time of testing.
- Compared with part 58 (Good Loboratory Practice for Nonclinical laboratory studies) of title 21 of the Code of federal regulations.

3. GMP Clearance Congenics QC testing laboratory;

- Existing manufacturer: Lark Technologies Inc.
- Existing manufacturer site: Texas, USA.
- Supporting document: attached documents
- Cogenics_Diviation and Incident Reporting Procedure 11 Feb 2008
- Cogenics_Laboratory Out of Specification Investication 11 Feb 2008
- Cogenics_EIR Dec 2005 Evidence request: Overseas Regulator: USA-Food &Drug Administration_API only with outside USA.

4. GMP Clearance Wuxi Apptc Inc. QC testing laboratory

- Existing manufacturer: Wuxi Apptec Inc.
- Existing manufacturing site: Philadelphia, PA, USA
- Supporting documents: attached documents
- Wuxi Apptec_Diviation process 13 May 2008
- Wuxi Apptec_EIR July 2008
- Evidence report: Overseas Regulator: USA Food & Drug Administration_API only with outside USA.
- Last inspection: 06/07/2008

This is satisfactory.

8. The manufacturer provides the data on the shipment validation as follow;

1. Shipment validation of Drug product

1.1 For multidose presentation

The shipment is performed in high density polyurethane boxes and

transported in refrigerated trucks at 2-8 °C temperature along the shipment. The shipping validation was performed with the GPO-MBP commercial Hepatitis B vaccine, which has the same packaging and shipping conditions as multidose JE-CV. Both Hepatitis B and JE-CV have the same vial and pack size. The company considers the results obtained with Hepatitis B vaccine are fully representative to support their validation and apply to multidose JE-CV. Data from shipping validation showed that the temperature is maintained at 2-8 °C for more than 16 hrs. The primary containers were qualified with 3 validation studies. 16x 20 boxes x 10 vials were placed in two layers. Four thermocouples were put in the boxes close to the products, two thermocouples per layer. The fifth one was put in the box, which was located at the center among the boxes. The sixth one served at measuring the room temperature. Eight cold packs were put at the side of product boxes, two for each side with a cardboard sheet in between the cold packs and the products as insulator. The five thermocouples inside the box confirmed the temperature is maintained within 2-8 °C for more than 16 hrs while the room temperature varied from 19-25 °C during the *study. This is satisfactory*

1.2 For single dose presentation

The primary containers were qualified with 3 validation studies. 8 X 20 boxes x 1vial were place in two layers. One thermocouple was put in the boxes close to the products at each different corner, four thermocouples per layer in opposite position of each layer. The nineth one was put in between the box which was located at the center among the two layers boxes. The tenth one served at measuring the room temperature. Eight cold packs were put at the side of product boxes, two for each side with plastic sheet in between the cold packs and the products as insulator. On the top part of the products, one ice blanket was put in between two sheets of aluminum foil before closing the container.

The nineth thermocouples inside the boxes confirmed that the temperature is maintained within 2-8 °C for more than 40 hrs while the room temperature varied from 20-25 °C during the study. This is satisfactory.

2. Validation results for International transportation of Drug product

2.1 For multidose presentation

Shipping validation was performed in double insulated boxes: one internal carton containing the boxes of vaccine and ice packs, included in one external carton container ice packs and insulator card board paper. 18 shipping boxes of vaccine X 20 boxes X 10 vials were placed in the internal carton in three layers, 6 boxes each. Four thermocouples probes were placed at 4 different corners at the lower layer, another 4 probes placed at 4 different corners at the upper layer and one probe at the middle among 18 boxes in the second layer. 4 pieces of ice packs were put on the top part of this internal carton with one insular cardboard paper in between before closing the carton. The carton was then packed in the external carton with required ice pack and insulator.

Three times validation results and conformed to WHO requirements. Temperature can be maintained lower than 30 packaging and shipping procedures of products using these double insulated boxes method revealed good lower than 30 °C in the chamber of 43± 1 °C for at least 58 hrs. This is satisfactory.

2.2 Single dose presentation

Not aimed for WHO prequalification and shipping validation for international transportation was not performed. This will be performed according to each country specific requirements and transportation condition. This is satisfactory.

3. Validation results for International transportation of Drug product

The drug substance is stored at ≤-60 °C in PETG 125 ml bottle which are placed in a secondary container. Before transportation between Sanofi Pasteur (USA) to GPO-MBP (Thailand), the container is placed in a tertiary insulated container, with 30-35 kg of dry ice and two data loggers which are secured next to the product. The container is shipped from the USA to Thailand by plane with a total duration of less than 5 days. Upon arrival on site at GPO-MBP, containers are inspected for general appearance, integrity, presence of dry ice. Data loggers are downloaded for confirmation of acceptable temperature during shipment.

The primary containers were qualified for the storage temperature at ≤-60 °C and for integrity after shipment as documented in the CTD in section 3.2.S.6 container closure system. Shipping qualification (Acambis bulk), Acambis carton facility validation protocol: Summary report for shipping qualification: ChimeneriVax JE purified bulk at ≤-60 °C to Thailand. The successful of the shipping qualification that packing configuration utilizing the TC-100 over pack, the Bio tube container and 30-35 kg dry ice is effective in maintaining the temperature of ChimeriVax JE purified bulk at ≤-60 °C. The maximum duration for this qualification effort was 4 days, 23 hrs and 22 min. (119.3 hrs). This is satisfactory.

9. The company attached NCL the test result of vaccine samples to the TFDA. *This is satisfactory.*

The company responded to the amount of HAS added during the formulation of each lot and real time stability result of IMOJEV and diluent as follows;

1. The company commits to provide and inform the amount of HAS added during the formulation of each lot in summary protocol for lot release. This is satisfactory.

2. The company commits to provide the real time stability data of

- IMOJEV™ ;
  - Process validation batches: 0871001, 0871002, 0871003
  - Clinical batches: 0880101, 0880202,0880203
  - 0.4% NaCl
  - Batch number: 1290401, 1290402, 1290403

This is satisfactory.

TFDA PTL AND EXTERNAL EXPERT'S OVERALL CONCLUSIONS ON QUALITY ASPECTS

The vaccine is manufactured in accordance with standard GMP, WHO Guidelines, Ph. Eur. Monograph for live attenuated viral vaccine and experience gained during pharmaceutical and clinical development. The reference standards for release specification of the drug product are WHO TRS no. 932, 2006: Guidelines for the production and quality control of candidate tetravelent dengue virus vaccines (live), WHO TRS no. 910, 2002: Guidelines for the production and control of Japanese encephalitis vaccine (live) for human use and Ph. Eur. monograph 0520 and Ph. Eur. monograph 0153.

The company should perform the test, submit more data and fulfill their commitments according to the recommendation above and monitoring documents regarding pharmacovigilance plan before approval is given for the registration of IMOJEV vaccine.

Proposals for Pre-authorization Testing

Samples for testing the proposed vaccine are not required at time of submission of the application. However the TFDA requests the applicants to submit samples of vaccine and/or its constituents of their vaccines for testing at the Division of Biological, Department of Medical Sciences as early as possible in order to obtain test results in due course.

The NCL (Division of Biological, Department of Medical Sciences) in close collaboration with the TFDA will specify a test protocol (type of samples, number of samples, number of batches, testing to be performed and methods and specifications to be used). The results of the tests are reported to the TFDA PTL for consideration in finalizing the TFDA Assessment Report.

2.3 Non Clinical aspects

CHIMERIC VACCINES JE CV

In the course of vaccine development of JE CV, The Preclinical Pharmacology studies for JE-CV are limited to Primary Pharmacology studies and included one formal GLP and two Non GLP studies, which conducted in monkeys (rhesus and/or cynomolgus monkeys). Toxicology studies submitted in support of JE-CV licensure are Pharmacokinetics, General Toxicological and Other Toxicity Studies, which comprised two neurovirulence studies and a single dose toxicity and biodistribution study.

The multiple JE-CV virus preparations (Precursor virus A to E, Pilot virus, and Large-scale virus) were produced by independent transfections of messenger RNA obtained from the same plasmids (see Table 1).

- **Precursor JE-CV** virus, which was not tested in clinical trials, was produced in diploid Fetal Rhesus Lung cells (FRhL).
- **Pilot JE-CV**, used in Phase I and II clinical trials, was produced in LS5 African Green Monkey Kidney cells (Vero/LS5) from sanofi pasteur in the presence of fetal bovine serum (FBS)
- **Large-scale JE-CV**, used in Phase II and III clinical trials, was produced in Vero cells from Baxter Biosciences adapted to grow in serum free medium (SF Vero) as will be the licensed product.

Table 1: JE-CV Preparations Used in Nonclinical and Clinical Studies

Material used	Nonclinical studies		Clinical studies (2.5 Clinical Overview)
	Type of study (study number)	Transfection cells and passage levels used	Type of study (study number)
Precursor JE-CV virus*	Pharmacology in monkeys (US01-DTR-173)	FRhL P5 (RL†)	NA‡
Pilot JE-CV§	Pharmacology in monkeys (US01-DTR-180)	Vero/LS5 P5 (VB**)	NA
	Neurovirulence in monkeys (T-040-002)	Vero/LS5 P3 (MSL††) Vero/LS5 P5 (VB)	NA
	Pharmacology in monkeys (T-040-005)	Vero/LS5 P5 (VL‡‡)	Phases I and II (H-040-001, H-040-003, H-040-005, H-040-006)
Large-scale JE-CV§§	Pharmacology in monkeys (T-040-005)	SF Vero P13 (VB)	NA
	Neurovirulence in monkeys (T-040-004)	SF Vero P11 (MSL) SF Vero P12 (WSL***)	NA
	Toxicology and biodistribution in monkeys (JEV.BDmk08/07)	SF Vero P13 (VL)	Phases II and III (H-040-004, H-040-007, H-040-008, H-040-009, H-040-010, JEC01, JEC02)

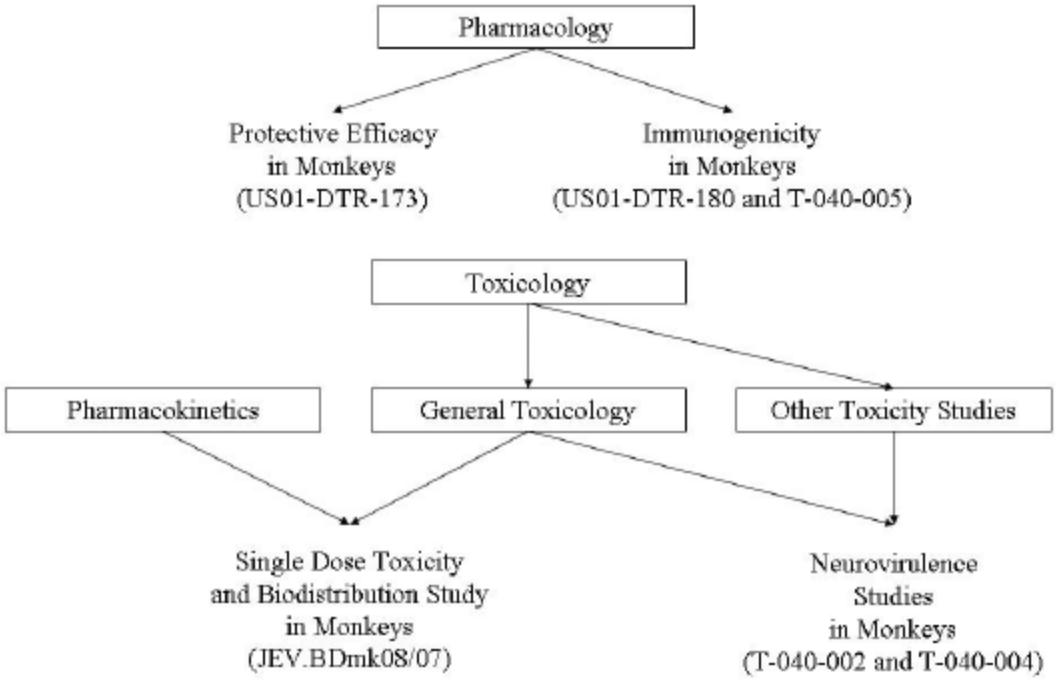
* Material produced in FRhL cells
† Research Lot
‡ Not applicable: not used in clinical trials
§ Material produced in Vero/LS5 cells
** Vaccine Bulk
†† Master Seed Lot
‡‡ Vaccine Lot
§§ Material produced in SF Vero cells
*** Working Seed Lot

Pharmacology

• **Primary pharmacodynamics**

The objectives of the nonclinical studies were to characterize the primary pharmacodynamics profile of the vaccine and to evaluate its safety, as detailed in Figure 1.

Figure 1: Strategy for Pharmacology and Toxicology Studies



For primary pharmacodynamics, studies to demonstrate immunogenicity and protective efficacy of JE-CV were conducted in monkeys, which are widely used as models for many flavivirus Infections including JE virus, the following three studies were conducted in monkeys inoculated by the subcutaneous (s.c.) route; one immunogenicity and protective study using the Precursor JE-CV virus, one immunogenicity study using the Pilot JE-CV and one immunogenicity study of the Large-scale JE-CV in comparison to the Pilot JE-CV.

- **Protective efficacy:** Precursor JE-CV virus produced in FRhL cells in rhesus monkeys after one subcutaneous (s.c.) administration (US01-DTR-173). (Table 2)

In US01-DTR-173, A research study (non-GLP) entitled "Chimeric Yellow Fever 17D-Japanese Encephalitis Vaccine: Dose-Response Effectiveness and Extended Safety Testing in Rhesus Monkeys" was conducted to determine the viremia profile, immunogenicity, and protective efficacy of a wide range of graded doses of the Precursor JE-CV virus.

TFDA Finding

1. The vaccine induced a low, self-limited viremia (mean peak titer <2.1 log PFU/mL, nearly identical across all inoculation doses, and no viremia detectable after 6 days post-inoculation).
2. The onset of viremia was however dose-dependent; it appeared sooner in monkeys in the higher dose group (i.e. Day 2 in the 5.0 log PFU/dose group) than in those of the lower dose group (i.e. Day 4 in the 2 log PFU/dose group).
3. Single immunizations with doses as low as 2 log PFU and up to 5 log PFU elicited

high titers of JE-specific neutralizing antibodies with no obvious dose response on Day 30 sera (Geometric Mean Titer (GMT)) of 761, 320, 453 and 761 for 2, 3, 4 and 5 log PFU/dose, respectively, were not significantly different across the dose groups).

4. However, similar to the onset of viremia, neutralizing antibodies appeared earlier in the higher dose group (i.e. Day 6-7 for the 5.0 log PFU/dose group) than in the lower dose group (i.e. Day 10 for 2.0 log PFU/dose group).

5. All animals that received the vaccine were protected from a severe i.c. challenge with a highly virulent WT JE virus. None of the immunized monkeys developed viremia or any sign of illness post-challenge, whereas all control monkeys developed viremia, severe encephalitis and were euthanized.

6. The results of these studies demonstrated that a single s.c. inoculation in the range of 2.0 to 5.0 log PFU/dose of JE-CV in non-human primates elicits specific neutralizing antibodies against JE virus and provides protection against the disease.

Table 2: Chimeric Yellow Fever 17D-Japanese Encephalitis Vaccine: Dose Response Effectiveness and Extended Safety Testing in Rhesus Monkeys (a non-GLP Study) (US01-DTR-173)

Species (total number of animals)	Products administered and number of animals (N)	Administration schedule and follow-up	Doses (Volume)	Main results
Rhesus monkeys (N = 18)	**Unimmunized Control** (Group 1): N = 2 **Test article** (Group 2): Precursor JE-CV virus (5.0 log PFU) N = 4 **Test article** (Group 3): Precursor JE-CV virus (4.0 log PFU) N = 4 **Test article** (Group 4): Precursor JE-CV virus (3.0 log) PFU N = 4 **Test article** (Group 5): Precursor JE-CV virus (2.0 log PFU) N = 4 **Challenge article:** IC37 (5.2 log PFU) N = 18	**Vaccination:** One administration at D0 by s.c. route. Viremia samples collected before immunization and daily for 10 days. Antibody samples collected D15, D30 and D52 **Challenge:** D54 with IC37 virus by the intracerebral (i.c.) route. Post-challenge, viremia samples collected for 9 days. For neutralizing antibody testing, serum samples collected D18 and D33 post-challenge, and cerebrospinal fluids (CSF) samples collected two days before and D33 after challenge	1.0 mL/animal of Precursor JE-CV virus 0.25 mL/animal of IC37	**Immunization:** - Viremia: Low level viremia across all dose groups (mean peak viremias 1.7 – 2.1 log PFU/mL, mean duration 1.8-2.3 days). - Neutralizing antibody response: All monkeys in the two higher dose groups (4.0 and 5.0 log PFU) seroconverted earlier (D6-D7) than those in the lower dose (3.0 log PFU) groups (D8-D10). Geometric Mean Titers (GMTs) for neutralizing antibodies were similar among all treatment groups on D30 (320-761) and D52 (640-1280) (pre-challenge). Antibody titers to the homologous strain ≥4-fold higher than to the heterologous wild type (WT) JE strains. **I.c. Challenge:** None of the immunized monkeys developed viremia or signs of illness post-challenge, whereas both sham-immunized controls became viremic (1.3-1.7 log PFU/mL), developed severe encephalitis and were euthanized on D11 after inoculation. Immunized monkeys developed significant (≥4 fold) rise in serum and CSF neutralizing antibodies post-challenge.

- **Immunogenicity:** Both Pilot and Large-scale JE-CV were evaluated in

Immunogenicity studies in rhesus and/or cynomolgus monkeys after one s.c. administration (US01-DTR-180 and T-040-005, respectively). The objectives were to demonstrate that the immune responses elicited by these vaccines were equivalent to that induced by the Precursor JE-CV virus. Based on the experiences with other live viral vaccines, the s.c. route was selected for the pharmacology studies as it is considered the most efficient route for delivery of the vaccine to the biological targets, as seen with similar vaccines, such as YF 17D vaccine, and is also the intended route of administration in humans. (Table 3)

In US01-DTR-180, A research study (non-GLP) entitled "Viremia and Immunogenicity of ChimeriVax™-JE (VeroPMC) Vaccine in Non-human Primates" was conducted to evaluate the immunogenicity of graded doses of the Pilot JE-CV human vaccine

candidate in rhesus monkeys. Groups of young adult rhesus monkeys were inoculated with Pilot JE-CV at doses of 5.0, 4.0 and 3.0 log PFU. Over the following 12 days, daily samples of blood were collected from each monkey for viremia assessments. Sixteen and 30 days post-inoculation, monkeys were bled for determination of homologous neutralizing antibody titers (measured by PRNT50 against JE-CV virus).

Table 3: Viremia and Immunogenicity of ChimeriVax™-JE (VeroPMa) Vaccine in Non-human Primates (a non-GLP Study) (US01-DTR-180)

Species (total number of animals)	Products administered and number of animals (N)	Administration schedule and follow-up	Doses (Volume)	Main results
Rhesus monkeys (N = 12)	**Test article** (Group 1): Pilot JE-CV (5.0 log PFU) N = 4 **Test article** (Group 2): Pilot JE-CV (4.0 log PFU) N = 4 **Test article** (Group 3): Pilot JE-CV (3.0 log PFU) N = 4	One administration at D0 by s.c. route. Viremia sampling from D1-D12. Neutralizing antibody sampling on D16 and D30 post-inoculation	0.5 mL/animal	Viremia: Low level viremia across all dose groups (mean peak viremias 1.6 - 2.3 log PFU/mL, mean duration 3-5 days). Neutralizing antibody response: Neutralizing antibodies developed by D16 in all monkeys (GMT 905-1810). GMTs not significantly different across dose groups. GMTs at D30 were 960-1981. The results obtained with this virus were comparable to historical data with Precursor JE-CV virus (Table 1) conducted to establish efficacy of JE-CV.

TFDA Finding

1. Viremia

No monkey exhibited any signs of illness or adverse reactions to vaccination. All monkeys became viremic and viremia titers were again low and self-limiting. The mean peak titers for monkeys that received 5.0, 4.0, or 3.0 log PFU of the vaccine were 1.6, 2.1, and 2.3 log PFU/mL, respectively. The mean duration of viremia for these monkeys was 3, 3.5, and 5 days,

2. Neutralizing Antibody Response

All monkeys developed neutralizing antibodies against the homologous virus by Day 16 post-immunization. In this study, earlier time points were not tested to determine the exact onset of neutralizing antibodies, but considering their high titers on Day 16 (GMT values were 1810, 905, and 905 for monkeys that received 5.0, 4.0 or 3.0 log PFU of the vaccine, respectively) and the data from the previous experiment described above, it is highly likely that neutralizing antibodies appeared much earlier than Day 16. By Day 30 after immunization, all monkeys remained seroconverted and the GMT values (1810, 1810 and 1522 for monkeys that received 5.0, 4.0 or 3.0 log PFU of the vaccine, respectively) did not differ significantly across groups.

3. All monkeys that received Pilot JE-CV developed low, self-limited viremia, and high titers of neutralizing antibodies following immunization. The results obtained with Pilot JE-CV were comparable to historical data with Precursor JE-CV virus conducted to establish protective efficacy of JE-CV. The presence of a mutation at E491 Leu to Phe (at the transmembare domain of the E protein) did not appear to adversely affect the attenuation or immunogenicity of the Pilot JE-CV and the vaccine was considered acceptable for transition to human trials.

In T-040-005, A GLP study entitled "A 31-Day Comparative Safety and Immunogenicity Study of Two ChimeriVax™-Japanese Encephalitis (JE) Vaccines Following Single Subcutaneous Administration to Cynomolgus Monkeys" was conducted to compare the viremia, immune response, and safety of Pilot and Large-scale JE-CV over a 30-day period following a single. s.c. administration in cynomolgus monkeys.(Table 4)

All monkeys were dosed once (0.5 mL dose volume) on Day 1 via s.c. injection at a single site in one arm. The monkeys were evaluated for clinical signs of toxicity (twice daily), changes in body weight (weekly), and serum chemistry, hematology, and coagulation parameters. Blood samples were collected on Day 1 (pre-inoculation) and Days 4, 7, 15, and 31 for serum chemistry, hematology, and coagulation analysis. Additional blood samples were collected on Day 1 (pre-inoculation) and Days 2 through 11 for quantitative viremia analysis, and on Day 1(pre-inoculation) and Day 31 for JE virus-specific serum neutralizing antibody titer analysis.

Table 4: A 31-Day Comparative Safety and Immunogenicity Study of Two ChimeriVax™-Japanese Encephalitis (JE) Vaccines Following Single Subcutaneous Administration to Cynomolgus Monkeys (a GLP Study) (T-040-005)

Species (total number of animals)	Products administered and number of animals (N)	Administration schedule and follow-up	Doses (Volume)	Main results
Cynomolgus monkeys (N = 18)	**Comparator** (Group 1): Diluent N = 6 (4 seronegative) **Test article** (Group 2): Pilot JE-CV (3.8 log PFU) N = 6 (5 seronegative) **Test article** (Group 2): Large-scale JE-CV (4.0 log PFU) N = 6 (4 seronegative)	One administration at D1 by s.c. route. Blood sampling on D1 (pre-inoculation) and D4, D7, D15, and D31 for serum chemistry, hematology, and coagulation analysis. Viremia sampling on D1 (pre-inoculation) and D2-D11. Neutralizing antibody sampling on D1 (pre-inoculation) and D31.	0.5 mL/animal	Viremia: Pilot JE-CV: 5/5 monkeys had detectable viremia (mean peak titer 2.4 log PFU/mL, mean duration 3.4 days). Large-scale JE-CV: 4/4 monkeys had detectable viremia (mean peak viremia of 2.2 log PFU/mL; mean duration 3.75 days). No significant difference in viremia between the Pilot and Large Scale vaccine groups. Neutralizing antibody response: All seronegative monkeys seroconverted following JE-CV inoculation on D31 (neutralizing antibody titers for Pilot JE-CV group, 640-5120 (GMT 1689), and for Large-scale JE-CV, 320–2560 (GMT 761). No significant difference in neutralizing antibody responses between the Pilot and Large-scale JE-CV groups.

TFDA Finding

Non Clinical Summary

There were no vaccine-related clinical signs or changes in food consumption, body weight, or serum chemistry, hematology or coagulation parameters.

1. Viremia

Similar to Precursor JE-CV virus, all monkeys developed a low level viremia (2 to 5 days duration) with a mean peak of 2.4 and 2.2 log PFU/ml for Pilot and Large-scale vaccines, respectively.

2. Neutralizing Antibody Response

All monkeys seroconverted as assessed by PRNT50, 30 days following dosing. Titers which ranged from 640 to 5120 (GMT 1689) for the Pilot and from 320 to 2560 (GMT 761) for the Large-scale vaccine did not differ significantly between the two vaccine groups.

3. Large-scale JE-CV was compared to Pilot JE-CV with respect to viremia and

immunogenicity in cynomolgus monkeys. Both vaccine preparations at a dose level of approximately 4.0 log PFU (intended human dose) were safe and well tolerated (there were no vaccine-related clinical signs or changes in food consumption, body weight, or serum chemistry, hematology or coagulation parameters). No significant differences were noted in terms of viremia or immunogenicity between the two test articles. The presence of a mutation at M60 from Arg to Cys (at the transmembrane domain of the M protein) did not appear to adversely affect the attenuation or immunogenicity of the Large-scale JE-CV and the vaccine was considered acceptable for transition to human trials.

CONCLUSION FOR PHARMACOLOGY

1. The viruses used for Pre clinical characterization of the product (in vitro and in vivo) and in clinical studies were different in terms of product preparation, that is in Pre Clinical Studies the viruses were not produced under current GMP or they had an unacceptable mutation. However, later additional immunogenicity studies in monkeys were performed with JE virus challenge.

2. Study phases during determination of immunogenicity and viremia were conducted in Non-GLP laboratories.

3. No crucial objections, these "Pharmacodynamic Studies (Immunogenicity of the Vaccine)" could be accepted.

4. Biodistribution studies in monkeys by the s.c. route in both target and non-target tissues/organs of the vaccine using large-scale JE-CV lot were conducted in accordance with GLP regulations. The data showed that the distribution of JE-CV virus was transient and limited to the injection site 3 days.

5. No other pharmacokinetic studies were done.

6. No adjuvant added to the vaccine, no new routes of administration. The vaccine is intended to be given subcutaneously, and the pharmaceutical form of this vaccine is in freeze-dried powder for reconstitution using 0.4% sterile sodium chloride as the diluent.

7. Based on the studies design and results these "Pharmacology Studies" could be **accepted.**

Toxicology

The nonclinical safety evaluation of JE-CV comprised two neurovirulence studies and a single dose toxicity and biodistribution study monkeys. (Table 5)

- A general toxicity and biodistribution study by the s.c. route, was conducted (JEV.BDmk08/07). The distribution and persistence of Large-scale JE-CV were evaluated in both target and non-target tissues/organs to examine the potential risk of long-term expression of the recombinant virus.
- Neurovirulence was also an endpoint considered in the toxicological Evaluation

of JE-CV and was evaluated in monkeys (T-040-002 and T-040-004), for which a study design based on the safety release test for the YF vaccines, established by the WHO was used. The studies assessed the presence of encephalitis and included a specific histopathological examination of the brain and central nervous system. Both these neurovirulence studies included the commercial YF 17D vaccine (YF-VAX) as a comparator reference, to enable comparison and acceptance of any potentially induced encephalitis by JE-CV. The degree of neurovirulence induced by the commercially available YF 17D vaccines when inoculated by the intracerebral route (i.c.) has been well established.

Table 5: Toxicology Overview

Test Item: JE-CV

Type of study	Species	Method of administration	Duration of dosing	Products administered and doses	GLP compliance	Testing facility	Study number	Location of study report
Single Dose Toxicity	Cynomolgus monkey	Subcutaneous (s.c.)	One injection	Large-scale JE CV P13* (VL)† 5.2 log PFU/dose‡	Yes	Charles River Laboratories Sparks NV 89431 - USA	JEV.BDmk08/07	4.2.3.1 Single-Dose Toxicity
Other Toxicity Neurovirulence	Rhesus monkey	Intracerebral (i.c.)	One injection	- Pilot JE-CV P3 (MSL)§ 5.5 log PFU/dose - Pilot JE-CV P5 (VB)** 6.0 log PFU/dose	Yes	Sierra Biomedical Sparks NV89431 - USA	T-040-002	4.2.3.7.7 Other
Neurovirulence	Cynomolgus monkey	Intracerebral (i.c.)	One injection	- Large-scale JE-CV P11 (MSL) 5.0 log PFU/dose - Large-scale JE-CV P12 (WSL)†† 5.0 log PFU/dose	Yes	Sierra Biomedical Sparks NV89431 - USA	T-040-004	4.2.3.7.7 Other

* Px = x^{th} passages in Vero cells
† Vaccine Lot
‡ PFU = Plaque Forming Unit
§ Master Seed Lot
** Vaccine Bulk
†† Working Seed Lot

Single dose toxicity

A single dose toxicity study in cynomolgus monkeys was conducted to assess the systemic safety of JE-CV and included the evaluation of local reaction, biodistribution and viral shedding.

JE-CV Vaccine: A Single Dose Toxicity and Biodistribution Study Following One Subcutaneous Administration to Cynomolgus Monkeys (JEV.BDmk08/07)

This study evaluated the systemic toxicity, local reactions, biodistribution and shedding of the Large-scale JE-CV VL (P13) in the cynomolgus monkeys. The cynomolgus monkey was selected as it is an established model for systemic toxicity assessment and elicits an immune response to JE-CV virus.

TFDA Finding

There were no premature deaths, no adverse clinical signs, no injection site reactions, no treatment-related changes in body weight food consumption or body temperature. There were no ophthalmic findings, no changes in serum chemistry, hematology and urinalysis parameters. There were no vaccine-related macroscopic findings and no changes in organ weights. Vaccine-related microscopic findings were limited to localized, minimal to moderate mononuclear and/or mixed cell infiltrates at the injection site in five out of ten JE-CV vaccinated animals on Day 4. There were no vaccine-related macroscopic and microscopic findings on Day 22. All monkey given JE-CV and sampled on Day 22 seroconverted.

All urine, feces, injection site swabs and saliva samples were negative for JE-CV on both Days 4 and 22.

There were no differences in viral sequences between the inoculated virus and the virus recovered from sera of viremic animals.

The results showed that there were no vaccine-related adverse clinical signs or changes in food consumption, body weight, or serum chemistry and hematology parameters or histopathological changes in extra-neural organs/tissues compared to YF 17D vaccine group.

Repeat-Dose Toxicity

A repeat-dose toxicity study was not considered necessary as the vaccine is the live viral vaccine is intended for use as a single dose.

Genotoxicity

A genotoxicity evaluation was not performed as the vaccine was not considered to have any genotoxicity potential. In addition, there were no new components in the final formulation for which genotoxicity tests were considered necessary, as in accordance with EMEA Note for guidance on preclinical pharmacological toxicological testing of vaccines and WHO Guidelines on nonclinical evaluation of vaccines.

Carcinogenicity (Including Supportive Toxicokinetics Evaluations)

Carcinogenicity studies were not considered as appropriate as the vaccine has no genotoxicity risks and as in accordance with EMEA Note for guidance on preclinical pharmacological and toxicological testing of vaccines and WHO Guidelines on nonclinical evaluation of vaccines.

Reproductive and Developmental Toxicity

No reproductive and developmental toxicity study was conducted with JE-CV at the time of licensure application. Vaccination with JE-CV is contraindicated in pregnant and lactating women.

CONCLUSION FOR GENERAL TOXICOLOGY

1. The tests were conduced in cynomolgus monkeys either separately or during immunogenicity studies. The studies include single dose toxicity and neurovirulence studies.
2. The neurovirulence and toxicology studies in monkeys were conducted in accordance with GLP regulations.
3. The results showed that there were non vaccine-related adverse clinical signs or changes in food consumption, body weight or serum chemistry and hematology parameters or neurohistological scores.
4. Local toxicity of JE-CV, by the s.c . route was also conducted in monkeys using large scale JE-CV lot. There were no injection site reactions.
5. Based on the studies design and results these “General Toxicology” studies could be **accepted.**

6. Toxicity Studies in Special Populations

Not applicable

7. Genotoxicity and Carcinogenicity Studies, when applicable

Not applicable

8. Reproductive Toxicity Studies for Vaccines to be administered to pregnant women or individuals of fertile age

i. Not applicable
ii. No reproductive and developmental toxicology studies since the company started that vaccination with JE-CV is contraindicated in pregnant and lactating women.

Local Tolerance

Local tolerance was assessed in the toxicology and biodistribution study. There were no injection site reactions and microscopic findings were limited to localized, minimal to moderate mononuclear and/or mixed cell infiltrates at the injection site in five out of ten JE-CV vaccinated animals on Day 4 only.

Other Toxicity Studies

Two monkey neurovirulence studies were conducted to assess the neurovirulence of JE-CV after a single i.c. administration. The studies were similar in design and included some systemic toxicological parameters: clinical signs, body weights, clinical pathology and limited histopathology

A 30-Day Single-Dose Neurovirulence Study of ChimeriVax™-JE Given by Intracerebral Administration to Rhesus Monkeys (T-040-002)

This study investigated the neurovirulence and systemic toxicity of Pilot JE-CV MSL (P3) and VB (P5) over a 30-day period after a single i.c. inoculation in monkeys and was compared to YF 17D vaccine (YF-VAX).

TFDA Finding

1. There were no premature deaths. One monkey given Pilot JE-CV VB developed on Days 16 and 19 transient tremors of the arms. The tremors resolved spontaneously within 24 hours.

2. One monkey in each group given JE-CV showed decreased activity on Day 1. They were however no differences in scores of clinical signs of encephalitis.

3. Slight decrease in body weight was noted in all treatment groups (up to 6.8% mean body weight reduction between pre-inoculation and Day 31), with reduced food consumption and/or watery liquid stool.

4. There were no vaccine-related changes in hematological and clinical chemistry parameters. All monkeys tested seroconverted.

There were no gross lesions at necropsy attributable to the JE-CV or YF 17D vaccines.

5. Histopathologic examination of the selected organs did not reveal any alterations related to administration of the vaccines.

A Single-Dose Neurovirulence Study of ChimeriVax™-Japanese Encephalitis (JE) Vaccine Master Seed Lot and Working Seed Lot Stocks Following Intracerebral Administration to Cynomolgus Monkeys (T-040-004)

This study investigated the neurovirulence and systemic toxicity of Large-scale JE-CV MSL (P11) and WSL (P12) over a 30-day period after a single i.c. inoculation in monkeys and was compared to the YF 17D vaccine.

TFDA Finding

1. The histopathological evaluation of the brain and spinal cord was performed according to the methods described in the monkey safety test.

2. There were no premature deaths or no vaccine-related adverse clinical signs. They were no differences in scores of clinical signs of encephalitis and no effects on food consumption, body weight, or serum chemistry and hematology parameters.

3. Lymphoid hyperplasia with increased size and number of lymphoid nodules in the spleen were observed in 9 out of 11, 4 out of 11, and 8 out of 11 monkeys from the YF 17D vaccine, Large-scale JE-CV MSL and WSL, respectively was considered secondary to the expected immune response induced by the vaccines.

CONCLUSION FOR PHARMACOKINETICS AND OTHER TOXICITY STUDIES

1. For the nonclinical safety evaluation of JE-CV, a single dose toxicity study in monkey inoculated via the s.c. route was conducted to assess the systemic and local toxicity, biodistribution and viral shedding (JEV.BDmk08/07) and two neurovirulence studies in monkey via the i.c. route were conducted for assessment of neurovirulence (T-040-002 and T-040-004).

2. No adverse systemic effects was seen in the single dose toxicity or the neurovirulence studies. A reduction in body weight was seen in all groups (including the YF 17D vaccine) in the neurovirulence study with JE-CV (T-040-002). The reason for the finding is unclear but it was minor and was not seen in any other studies, including the single toxicity (JEV.BDmk08/07), neurovirulence (T-040-004) and immunogenicity studies and was therefore not considered toxicologically significant. The neurovirulence studies showed that JE-CV is less neurovirulent than the YF 17D vaccine, the comparator reference. Therefore JE-CV was within the WHO acceptance criteria for a marketed product and is considered to have an acceptable neurotoxic profile when administered via the i.c. route. The evaluation in monkeys correlates with neurovirulence studies in mice, which also demonstrated that the vaccines were less neurovirulent for neonatal animals than YF 17D vaccine and that differences in Pilot and Large-scale JE-CV virus sequences (M60 mutation) does not change the highly attenuated phenotype

of the vaccine in this model. There was one minor adverse clinical sign noted in the neurovirulence study with the Pilot JE-CV (T-040-002), in which one monkey had a tremor of the arms. This finding could be indicative of neurovirulence. However it was not associated with any histopathology findings in the neuronal tissues, and was not seen in the subsequent neurovirulence (T-040-004) or single dose toxicity study (JEV.BDmk08/07). Therefore, although noted, it is not considered a major toxicological concern.

3. Local reactions evaluated in the single dose toxicity study showed minor and transient inflammatory reactions at the site of injection and were considered part of the immune response. Viscerotropism was assessed using the viremia and biodistribution data. The levels of viremia and/or viral load were low in all studies, including the immunogenicity studies. The highest value was 3.3 log PFU/mL which is below the WHO acceptable limits for viremia. The levels of circulating virus were less than 500 mouse lethal dose 50 (LD50) per 0.03 mL after i.c. administration (equivalent to about 5 to 6 log PFU/mL) and not exceed 100 mouse LD50/0.03 mL (equivalent to about 4 to 5 log PFU/mL) in more than one animal. The biodistribution data showed JE-CV was limited to the injection site, with no replication in the main target organs involved in viscerotropism diseases such as liver and kidneys. JE-CV was detected in the injection site (half of the animals) 3 days post-immunization, and was no longer present by 21 days post administration and the presence of JE-CV in the injection site did not correlate with an increased incidence and/or severity of histopathological findings. In addition, there was no correlation between the level of viral replication in blood, the distribution and/or histopathological findings in the injection site.

4. The viremia and distribution data showed limited risk of viscerotropism after JE-CV immunization. Analysis of JE-CV shedding showed that JE-CV was not detected in urine, feces, injection site swab and saliva samples 3 and 21 days after immunization.

5. The nonclinical data demonstrated no major safety concern following vaccination with a single dose of JE-CV. The nonclinical data concurred with the clinical data which showed that JE-CV was well tolerated during the clinical trials with no reported major safety concerns.

OVERALL CONCLUSIONS ON NON-CLINICAL ASPECTS

1. From pharmocodynamic studies on immunogenicity of the vaccine in mice and in cynomolgus monkeys have demonstrated the immunogenicity and protective efficacy of the JE-CV.

2. Single dose toxicity and neurovirulence studies showed that there were no vaccine related-adverse clinical signs or changes in food consumption, body weight, or serum chemistry and hematology parameters or histopathological changes. In addition, there were no injection site reactions.

3. All those results from Non clinical studies are **acceptable**. However, there were no reproductive and developmental toxicity studies. Since the risk of vaccine receivers to become

pregnant is possible, reproductive and developmental toxicity studies **are there for recommended.**

4. Since the company did not performed any toxicity studies of impurities and the reasons were that the raw materials and process residues are similar to that of other vaccine licensed by Sanofi Pasteur with respect to this, the quality control part should extremely concern with purity of raw materials.

5. To follow TFDA regulation relating biological product for vaccines including with the safety monitoring program and waiting for the result of analysis from DMS, which is on process.

2.3 Clinical aspects

Introduction

JE-CV was evaluated in adult populations in nine clinical studies in the USA and Australia starting with a Phase I/II study and concluding with two pivotal Phase III studies of safety and of efficacy based on a serological correlate of protection.

JE-CV was evaluated in pediatric populations in Thailand, the Philippines and India. To date, safety and immunogenicity data are available from one Phase III study and two Phase II studies; additional studies designed to complete the development of JE-CV in pediatric populations are currently ongoing.

Clinical Development Program as conducted at the time of submission of dossier

-Biopharmaceutic Studies and Associated Analytical Methods

H-040-001: Phase I/II Proof-of-Concept Study

H-040-003: Phase II Dose-Ranging Study

H-040-005: Phase II Duration of Immunity and 6-Month Booster Study

H-040-007: Phase II Dose-ranging Study with the Lyophilized Formulation

-Clinical Pharmacology Studies

H-040-001: Phase I/II Proof-of-Concept Study

H-040-003: Phase II Dose-ranging Study

H-040-005: Phase II Duration of Immunity and 6-Month Booster Study

H-040-006: Phase II Interaction Study

H-040-007: Phase II Dose-ranging Study with the Lyophilized Formulation

-Clinical Safety Studies

H-040-001: Phase I/II Proof of Concept Study

H-040-002: Phase II

H-040-003: Phase II Dose-Ranging Study

H-040-005: Phase II Duration of Immunity and 6-Month Booster Study

H-040-006: Phase II Interaction Study

H-040-007: Phase II Dose-Ranging Study With the Lyophilized Formulation

H-040-008: Phase II Comparative Immunogenicity Study

H-040-009: Phase III Pivotal Efficacy Study

H-040-010: Phase III Safety Study

-Clinical Efficacy Studies

H-040-008: Phase II Comparative Immunogenicity Study

H-040-009: Phase III Pivotal Immunogenicity Study

H-040-001: Randomized, Double-Blind, Phase I/II Trial of The Comparative Safety, Tolerability and Immunogenicity of ChimeriVax™-JE, Live, Attenuated Vaccine Against Japanese Encephalitis and Yellow Fever 17D Vaccine (YF-VAX®) in Subjects Immune or Non-immune to Yellow Fever.

Table 1: Tabular Listing of Individual Clinical Study H-040-001

Study Identifiers	Location of Study Report	Objective(s) of the Study	Study design and Type of Control	Test Product(s); Dosage regimen; Route of administration	Number of subjects	Countries; Trial period (FVFS – LVLS*)	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
H-040-001	5.3.4.1	Comparative safety, tolerability and immunogenicity between different JE-CV dosages (4.0 and 5.0 logs) and Yellow 17D vaccine in subjects immune or non immune to Yellow Fever	Phase I/II randomized, double-blind, single center, controlled study	**JE-CV** - 5.0 $\log_{10}$ PFU† in 0.5 mL or - 4.0 $\log_{10}$ PFU in 0.5 mL **Control vaccine: YF-VAX®** 5.04 PFU in 0.5 mL One dose at D1 Subcutaneous injection	36 included 36 randomized • 18 yellow fever immune subjects • 18 yellow fever non-immune subjects	USA 13 Sep 2000 to 15 Nov 2000	Healthy subjects	Completed; Full CSR‡

H-040-002: The Immune Response to Challenge with JE-VAX , Six Months (or more) after Vaccination with ChimeriVax -JE, Live, Attenuated Vaccine Against Japanese Encephalitis

Table 2: Tabular Listing of Individual Clinical Study H-040-002

Study Identifiers	**Location of Study Report**	**Objective(s) of the Study**	**Study design and Type of Control**	**Test Product(s); Dosage regimen; Route of administration**	**Number of subjects**	**Countries; Trial period (FVFS – LVLS*)**	**Healthy Subjects or Diagnosis of Patients**	**Study Status; Type of Report**
H-040-002	5.3.4.1	• Characterize the safety of the administration of JE-VAX® in subjects who were vaccinated at least 6 months Previously with JE-CV • Characterizethe magnitude and kinetics of the rapid recall(anamnestic) response to challenge with JE-VAX® vaccine for Japanese encephalitis in subjects who were vaccinated at least 6 months previously with JE-CV	Phase II, single center, open-label, age- and sex-matched parallel group study	**JE-VAX** · One dose at D0 1.0 mL Subcutaneous injection, in the deltoid region of the arm	20 included: • 10 naïve subjects • 10 previously exposed subjects (vaccinated at least 6 months previously with JE-CV in Study H-040-001) - 5.0 log10 PFU: 4 - 4.0 log10 PFU: 6	USA 12 Jun 2001 to 24 Aug 2001	Healthy subjects	Completed; Full CSR

H-040-003: The safety, tolerability and immunogenicity of two doses of ChimeriVax™-JE, live attenuated vaccine, or one dose of ChimeriVax™-JE vaccine administered 30 days before or after yellow fever 17D vaccine or placebo.

Table 3: Tabular Listing of Individual Clinical Study (H-040-003)

Study Identifiers	Location of Study Report	Objective(s) of the Study	Study design and Type of Control	Test Product(s); Dosage regimen; Route of administration
H-040-003	5.3.4.1	Evaluation of safety, tolerability and immunogenicity of two doses of JE-CV, or one dose of JE-CV administered 30 days before or after yellow fever 17D vaccine or placebo	Phase II randomized, double-blind, placebo-controlled, single-center study	**JE-CV** *5 dose levels for groups 1–5:* - 5.8 log10 PFU in 0.5 mL - 4.8 log10 PFU in 0.5 mL - 3.8 log10 PFU in 0.5 mL - 2.8 log10 PFU in 0.5 mL - 1.8 log10 PFU in 0.5 mL Two doses: at D0 and D30 *1 dose level for groups 6-9:* - 4.8 log10 PFU in 0.5 mL One dose: at D0 or D30 **Control vaccine: YF- VAX** 5.04 PFU in 0.5 mL *Group 6*: one dose at D30 *Group 7*: one dose at D0 **Placebo** 0.5 mL *Group 8*: one dose at D0 *Group 9*: one dose at D30 Subcutaneous injection

H-040-005: Randomised, Double-blind, Phase II Study of the Safety, Immunogenicity, and Duration of Immunity of ChimeriVax™-JE, Live Attenuated Vaccine in Healthy Adults

Table 4: Tabular Listing of Individual Clinical Study H-040-005

Study Identifiers	Location of Study Report	Objective(s) of the Study	Study design and Type of Control	Test Product(s); Dosage regimen; Route of administration	Number of subjects	Countries; Trial period (FVFS – LVLS*)	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
H-040-005	5.3.4.1	● Descriptive safety data for a single dose of JE-CV compared with a placebo ● Descriptive immunogenicity data after 1 or 2 doses of JE-CV ● Assessment of the durability of the immune response over 60 months following 1 or 2 Doses of JE-CV vaccine	Phase II randomized, double-blind, placebo-controlled, single center, cross-over design	Primary Vaccination Series **JE-CV** ● Group *A* 3.8 log10 PFU in 0.5 mL. One dose at Day 0 ● Group B 3.8 log10 PFU in 0.5 mL. One dose at Day 28 **JE-CV Diluent (placebo)** ● Group A 0.5 mL at Day 28 ● Group B 0.5 mL at Day 0 Booster injection **JE-CV**0.5 mL at M6 Subcutaneous injection in the deltoid region of the arm	202 included 202 randomized Primary Vaccination Series 101 in Group A 101 in Group B Booster Injection 55 in Group A 43 in Group B	Australia 14 Apr 2003 to 20 Aug 2008	Healthy subjects	Completed; Full CSR up to M24, CSR addendum up to M48, Final CSR addendum for long-term follow-up.

H-040-006: Randomised, double-blind, Phase II evaluation of the safety and immunogenicity following administration of live attenuated JE vaccine (ChimeriVax™-JE) and yellow fever vaccine (STAMARIL®).

Table 5: Tabular Listing of Individual Clinical Study H-040-006

Study Identifiers	Location of Study Report	Objective(s) of the Study	Study design and Type of Control	Test Product(s); Dosage regimen; Route of administration	Number of subjects	Countries; Trial period (FVFS – LVLS*)	Healthy Subjects Or Diagnosis Of Patients	Study Status; Type of Report
H-040-006	5.3.4.1	● Descriptive safety for a single dose of JE-CV when administered concurrently, one month before or one month after Stamaril® ● Descriptive immunogenicity for a single dose of JE-CV when administered concurrently, one month before or one month after Stamaril® ● Assessment of the durability of the immune response 6 months after administration	Phase II, randomized double-blind, single-centre,	**JE-CV** ● *Group 1* 3.8 log10 PFU in 0.5 mL One dose at D0 ● *Group 2* 3.8 log10 PFU in 0.5 mL One dose at D30 ● *Group 3* 3.8 log10 PFU in 0.5 mL One dose at D0 or 30 Co-administration with STAMARIL **STAMARIL** contained no less than 1000 mouse LD50 units of 17D attenuated strain yellow fever virus in 0.5 mL ● *Group 1* One dose at D30 ● *Group 2* One dose at D0 ● *Group 3* 3.8 log10 PFU in 0.5 mL One dose at D0 or 30 Co-administration with JE-CV **JE-CV Diluent (placebo)**	108 included 108 randomized in 3 groups: ● *Group 1*: 36 JE-CV then Stamaril® ● *Group 2*: 36 Stamaril® then JE-CV ● *Group* 3: 36 split into two groups - 18 Co-administration of Stamaril® - JE-CV then Diluent or - 18 Diluent then co-administration of Stamaril® - JE-CV	Australia 27 Jul 2004 to 13 Apr 2005	Healthy subjects	Completed; Full CSR
				● *Group 3* 0.5 mL One dose at D0 or D30 Subcutaneous injection in the deltoid region of the upper arm				

H-040-007: Randomised, double-blind, placebo-controlled Phase II dose-ranging study of the safety, tolerability and immunogenicity of live attenuated ChimeriVax™-JE vaccine (lyophilised)

Table 6: Tabular Listing of Individual Clinical Study H-040-007

Study Identifiers	Location of Study Report	Objective(s) of the Study	Study design and Type of Control	Test Product(s); Dosage regimen; Route of administration	Number of subjects	Countries; Trial period (FVFS –LVLS*)	Healthy Subjects Or D iagnosis Of Patients	Study Status; Type of Report
H-040-007	5.3.4.1	● Descriptive safety of a single administration of JE-CV at three dose levels ● Descriptive immunogenicity of a single administration of JE-CV at three dose levels ● Assessment of the durability of the immune response up to 12 months following a single administration of JE-CV at three dose levels	Phase II, randomized, double-blind, placebo-controlled, dose-ranging	**JE-CV** ● *Group 1* - 3.0 log10 PFU in 0.5 mL (effective administered dose 3.3 log10 PFU) One dose at Day 0 ● *Group 2* - 4.0 log10 PFU in 0.5 mL (effective administered dose 4.3 log10 PFU) One dose at Day 0 ● *Group 3* - 5.0 log10 PFU in 0.5 mL (effective administered dose 5.3 log10 PFU) One dose at Day 0 **JE-CV Diluent (placebo)** ● *Group 4* 0.5 mL One dose at D0 Subcutaneous injection in the deltoid region of the upper arm	128 included 128 randomized in 4 groups: JE-CV ● 3.0 log10 PFU: 32 ● 4.0 log10 PFU: 32 ● 5.0 log10 PFU: 32 Diluent : 32	Australia 19 Nov 2004 to 27 Feb 2006	Healthy subjects	Completed; Full CSR

H-040-008: Randomized, double-blind, phase II study of the safety, tolerability, and immunogenicity following administration of live attenuated JE vaccine (ChimeriVax™-JE) compared with mouse brain derived inactivated JE vaccine (JE-VAX)

Table 7: Tabular Listing of Individual Clinical Study H-040-008

Study Identifiers	Location of Study Report	Objective(s) of the Study	Study design and Type of Control	Test Product(s); Dosage regimen; Route of administration	Number of subjects	Countries; Trial period (FVFS – LVLS*)	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
H-040-008	5.3.5.1	● Comparative safety between a single vaccination of JE-CV and a three-dose schedule of JE-VAX® ● Comparative immunogenicity between a single vaccination of JE-CV and a three-dose schedule of JE-VAX® ● Comparative assessment of the durability of the immune response up to 12 months after, between a single vaccination of JE-CV and a three-dose schedule of JE-VAX	Phase II, randomized, double-blind, single center	**JE-CV Diluent** One dose at D0 and D7 followed by **JE-CV** One dose at D28, 4.0 log10 PFU in 0.5 mL (effective administered dose 4.3 log10 PFU) **JE-VAX®** One dose at D0, D7 and D28 1.0 mL Subcutaneous injection in the deltoid region of the upper arm	60 included 60 randomized: ● JE-CV: 30 ● JE-VAX®: 30	USA 26 Apr 2005 to 26 Sep 2006	Healthy subjects	Completed; Full CSR

H-040-009: A multicentre, randomised, double-blind, Phase III study of the comparative immunogenicity, safety and tolerability of two Japanese Encephalitis vaccines (ChimeriVax™-JE and JE-VAX®)

Table 8: Tabular Listing of Individual Clinical Study H-040-009

Study Identifiers	Location of Study Report	Objective(s) of the Study	Study design and Type of Control	Test Product(s); Dosage regimen; Route of administration	Number of subjects	Countries; Trial period (FVFS – LVLS*)	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
H-040-009	5.3.5.1	● Test of non-inferiority of JE-CV to JE-VAX® ● Comparative safety between JE-CV and JE-VAX® ● Comparative immunogenicity 30 days after immunization with a single dose of JE-CV or three doses of JE-VAX® ● Ability of JE-CV to elicit a rapid immune response at 14 days post-vaccination ● Comparison of three JE-CV conformance lots	Phase III, randomized, double-blind, multicentre	**JE-CV** - at D0 and D7: single injection of placebo 1.0 mL - at D30 : 4.0 log10 PFU in 0.5 mL (effective administered dose between 4.4 and 4.8 log10 PFU) concomitant injection with placebo 1.0 mL **JE-VAX®:** 1.0 mL - at D0 and D7: single vaccination - at D30: concomitant injection with placebo 0.5 mL Subcutaneous injection(s) in the deltoid region of the upper arm; at D30, simultaneous injections into different arms	820 included 820 randomized: ● JE-CV: 410 divided in 3 groups per conformance lots: 137 – 135 and 138 ● JE-VAX®: 410	Australia – USA 7 Nov 2005 to 08 Jun 2006 Last visit for the month 7 follow-up : 15 Nov 2006	Healthy subjects	Completed; Full CSR Addendum to CSR for additional analyses

H-040-010: Randomised, Double Blind, Multicentre, Placebo Controlled Phase III Study of the Safety and Tolerability Following Administration of Live Attenuated JE Vaccine (ChimeriVax™-JE)

Table 9: Tabular Listing of Individual Clinical Study H-040-010

Study Identifiers	Location of Study Report	Objective(s) of the Study	Study design and Type of Control	Test Product(s); Dosage regimen; Route of administration	Number of subjects	Countries; Trial period (FVFS – LVLS*)	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
H-040-010	5.3.5.1	● Comparative safety data 30 days after a single vaccination of JE-CV or placebo	Phase III, randomized, double-blind, placebo-controlled, multicentre	**JE-CV** 4.0 log10 PFU in 0.5 mL (effective administered dose between 4.4 and 4.8 log10 PFU) One dose at D0 **Placebo** 0.5 mL One dose at D0 Subcutaneous injection into the deltoid region of the upper arm	2004 included 2004 randomized: ● 1601§: JE-CV ● 403: Placebo	Australia – USA 10 Oct 2005 to 01 May 2006 Last visit for the month 6 follow-up: 15 Nov 2006	Healthy subjects	Completed; Full CSR

H-040-004: Phase II study investigating the safety and immunogenicity of JE-CV in infants, toddlers and children aged between 9 months and 10 years.

Table 10: Tabular Listing of Individual Clinical Study H-040-004

Study Identifiers	Location of Study Report	Objective(s) of the Study	Study design and Type of Control	Test Product(s); Dosage regimen; Route of administration	Number of subjects	Countries; Trial period (FVFS – LVLS*)	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
H-040-004	5.3.4.1	• Comparison of safety and immunogenicity after a single vaccination of JE-CV with a 2-dose schedule of inactivated mouse brain – derived vaccine (MBDV) in children aged ≥9 months to 10 years	Phase II, randomized, double-blind, controlled, multicenter	**JE-CV Group** **Placebo** 0.5 mL One dose at D0 **JE-CV** 4.0 $\log_{10}$ PFU (effective administered dose: 4.5 $\log_{10}$ PFU, 4.8 $\log_{10}$ PFU, 4.9 $\log_{10}$ PFU) One dose at D14 **MBDV Group** - 1.0 mL for subjects ≥3 years - 0.5 mL for subjects <3 years One dose at D0 and at D14 and at M12 for booster vaccination All vaccinations subcutaneous in 1.0 mL for subjects ≥3 years in 0.5 mL for subjects <3 years Subjects >12 months: the deltoid region of the upper arm For subjects ≤12 months: the anterolateral aspect of the thigh	96 included 96 randomized: 48 : JE-CV 48: MBDV JE-CV: 48 - :≥5 to <10 years: 16 - ≥2 to <5 years: 16 - ≥9 months to <2 years: 16 MBDV: 48 - :≥5 to <10 years: 16 - ≥2 to <5 years: 16 - ≥9 months to <2 years: 16	India 03 Jan 2007 (Screening) to 13 Jan 2009 (D42 visit)	Healthy infants and children aged ≥9 months up to <10 years	Ongoing; Interim CSR up to 28 days after vaccination.

JEC01: A Controlled Study of the Safety and Immunogenicity of ChimeriVax™-Japanese Encephalitis Vaccine in Thai Toddlers and Children

Table 11: Tabular Listing of Individual Clinical Study JEC-001

Study Identifiers	**Location of Study Report**	**Objective(s) of the Study**	**Study design and Type of Control**	**Test Product(s); Dosage regimen; Route of administration**	**Number of subjects**	**Countries; Trial period (FVFS – LVLS*)**	**Healthy Subjects Or Diagnosis Of Patients**	**Study Status; Type of Report**
JEC01	5.3.5.1	• Safety and immunogenicity after a single dose of JE-CV with hepatitis A control vaccine in children aged 2 to 5 years previously vaccinated with 2 doses of a mousebrain-derived inactivated JE MBDV and in toddlers aged 12 to 24 months previously not vaccinated with any JE vaccine To describe the yearly persistence of immune response to JE after a single dose of JE-CV (5-year follow-up)	Phase II trial, randomized, crossover, open, active controlled (hepatitis A vaccine), multicenter	**JE-CV** 4.0 log10 PFU in 0.5 mL (effective administered dose 4.5 log10 PFU) One dose at D0 for group 1 and group 3 and at D28 for group 2 and group 4 **Hepatitis A (Avaxim 80 U pediatric Vaccine)** One 0.5 mL dose at D28 for group 1 and group 3 and at D0 for group 2 and group 4 JE-CV: subcutaneous injection into the deltoid region of the arm (2 to 5 years of age) or into the anterolateral aspect of the thigh (12 to 24 months of age) Hepatitis A vaccine : intramuscular injection into the deltoid region of the arm (2 to 5 years of age) or into the anterolateral aspect of the thigh (12 to 24 months of age)	301 included 301 randomized Sequential enrolment in two age cohorts: • 101 children ed 2 to 5 years - 50 in group 1 (JE-CV/Hepatitis A) - 51 in group 2 (Hepatitis.A/JE-CV) • 200 toddlers ed 12 to 24 months - 101 in group 3 (JE-CV/Hepatitis A) - 99 in group 4 (Hepatitis.A/JE-CV)	Thailand 02 Mar 2008 (Screening) to 19 Jun 2009 (year 1)	Healthy toddlers and children aged 12 months to 5 years	Ongoing; Interim CSR up to Year 1.

JEC02: Lot-to-lot Consistency, Bridging, and Safety Trial of ChimeriVax™-Japanese Encephalitis Vaccine in Toddlers in Thailand and the Philippines

Table 12: Tabular Listing of Individual Clinical Study JEC002

Study Identifiers	Location of Study Report	Objective(s) of the Study	Study design and Type of Control	Test Product(s); Dosage regimen; Route of administration	Number of subjects	Countries; Trial period (FVFS – LVLS*)	Healthy Subjects Or Diagnosis Of Patients	Study Status; Type of Report
JEC02	5.3.5.1	● Bioequivalence of three lots of JE-CV manufactured at GPO-MBP ● Bioequivalence of a lot of JE-CV manufactured by Acambis and JE-CV lots manufactured at GP0-MBP. ● Descriptive safety of vaccination in all subjects	Phase III, randomized, controlled (hepatitis A vaccine), observer - blind multicenter	**JE-CV** **Groups 1, 2 and 3** ≥4.0 and ≤5.8log10 PFU in 0.5 mL [effective administered doses 4.8 log10 PFU and 4.9 log10 PFU (two lots)] One dose at D0 from one of the 3 GP0-MBP lots **Group 4** ≥4.0 log10 PFU in 0.5 mL (effective administered dose 4.7 log10 PFU) One dose at D0 from Acambis lot. Subcutaneous injection into the anterolateral aspect of the thigh **Hepatitis A (Avaxim 80 U pediatric Vaccine)** **Group 5** One 0.5 mL dose at D0 Intramuscular injection into the anterolateral aspect of the thigh	1200 included 1200 randomized 5 groups: - 899 in the JE-CV GPO-MBP group divided in group 1: 303, group 2: 300, group 3: 296 - 199 in the JE-CV Acambis lot group (group 4) - 102 in the Hepatitis A group (group 5)	Thailand and Philippines 02 Aug 2008 (Screening) to 27 Mar 2009	Healthy toddlers aged 12 to 18 months	Completed; full CSR.

2. Compliance with Good Clinical Practice Guidelines

All studies were designed and conducted according to the Declaration of Helsinki as far as adopted by the concerned regulatory authorities, the applicable national and local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

Study initiation, monitoring, data collection, and data analysis were carried out in concordance with current clinical research approaches. The use of standardized methodology for these activities guarantees robustness and consistency of the clinical study data provided in the present submission. All studies were conducted in compliance with GCP, US Title 21 Code of Federal

Regulations [CFR] Parts 50, 54, 56, and 312, and International Conference on Harmonization (ICH) guidelines, including the archiving of essential documents.

The design of the clinical studies of JE-CV took into account the recommendations from the European Medicines Agency (EMEA) “Guideline on Clinical Evaluation of New Vaccines” (1) as well as WHO "Guidelines on clinical evaluation of vaccines: regulatory expectations" (2).

3. Clinical Development Program

General considerations

JE-CV was developed as a monovalent, live attenuated virus vaccine for the prevention of JE. The vaccine is constituted of a chimeric flavivirus comprising sequences encoding the prM and E proteins of the live-attenuated JE SA14-14-2 virus and the C and non-structural (NS) proteins of the YF 17D virus. The JE-CV virion is made of the genomic RNA, the C protein of the YF 17D virus, and the coat proteins (prM and E) of the SA14-14-2 virus inserted into a lipid bilayer. In its final formulation, JE-CV is supplied as a lyophilized powder and sodium chloride solution for injection. It is administered subcutaneously after reconstitution. A liquid formulation was used in an earlier development stage, but for ease of storage a lyophilized formulation was developed during the later stage of the adult development. A lyophilized formulation for industrial scale production was prepared during the pediatric development and a bridging study demonstrated equivalence with the previously used lyophilized formulation.

The clinical development of JE-CV was performed in a step-wise fashion in accordance with Good Clinical Practice (GCP), the WHO Guidelines on clinical evaluation of vaccines (2), and WHO’s JE specific guidance for the development of new JE vaccines (3) (4).

The JE-CV clinical development program in adults was conducted under a Food and Drug Administration (FDA) Investigational New Drug application (IND) application (BB-IND 9167) in the USA and under a Clinical Trial Exemption (CTX 99/2/4014) issued by the Therapeutic Goods Administration (TGA) in Australia. The pediatric study H-040-004 was conducted under an USFDA IND (BB-IND 9167) in India, while the subsequent pediatric studies were not conducted under IND.

In the clinical development program of JE-CV, a serological correlate of protection was used for the demonstration of efficacy. Given the availability of JE vaccines, a placebo-controlled protection study was not ethically possible. Moreover, a comparative study between a licensed vaccine and JE-CV using the endpoint of prevention of clinical illness would require too large sample sizes due to the low incidence of JE (3). A serological correlate based on neutralizing antibodies is accepted and recommended by the WHO (3) (4).

The WHO organized a consultation in 2004 to identify immunological markers for evaluation and licensure of new JE vaccines (3). A threshold of >1:10 using 50% plaque reduction neutralization test (PRNT50) is accepted as evidence of protection. Passive antibody transfer experiments in animals have shown a linear titer-protection relationship (5).

This consultation further recommended that the analysis of neutralizing antibodies should be conducted as a head-to-head comparison with a licensed vaccine following a non-inferiority design, and that non-inferiority should be measured as percentage of seroconversion. Additional supportive data on long-term immunological memory including T-cell response were also recommended. It was noted that careful consideration should be given to the selection of the virus strain used for neutralization in PRNT50.

In the clinical development of JE-CV, protection levels were mainly assessed using the homologous virus to administered vaccine as a challenge virus in PRNT50.

4. Clinical Development in Adult Populations

4.1 Clinical Studies in Adult Populations

4.1.1 Studies Evaluating the Liquid Formulation of JE-CV (Studies 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 (6), the liquid formulation of JE-CV was compared to a live attenuated YF vaccine (YF-VAX®) in subjects with and without prior YF immunity. 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 virus strains. Vaccinal viremia was measured and was detected at low levels and was of short duration in the majority of subjects.

Safety results were satisfactory and similar in YF immune and non-immune subjects.

A Phase II dose-ranging study (H-040-003 (7) established that JE-CV doses from 1.8 to 5.8 log10 PFU/0.5 mL dose resulted in similar seroconversion rates and safety profiles. No clinically relevant dose-effect on the level of viremia was detected. A second dose of JE-CV administered 30 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 YF seroconversion rate in this study.

On the basis of the results from the previous studies, the dose of 3.8 log10 PFU/0.5 mL was chosen for the subsequent studies set up with the liquid formulation.

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 viremia showed that it was undetectable 14 days after vaccination. The long-term immunity provided by JE-CV was investigated by measuring the seroconversion up to 5 years after vaccination in subjects having received JE-CV either as single administration, or in a two-dose schedule with an interval of 6 months. 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.

The safety and immunogenicity of JE-CV in comparison to a live attenuated YF vaccine (STAMARIL®), with both vaccines administered concomitantly or sequentially in a single-dose schedule, were evaluated in a Phase II study (H-040-006). 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. This study also evaluated the immune response to different wild-type JE virus strains after a single dose of JE-CV.

4.2.2 Studies Evaluating the Lyophilized Formulation of JE-CV (Studies 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, viremia, 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 log10 PFU/0.5 mL dose) in comparison to placebo. Balancing safety and immunogenicity considerations, a dose of at least 4.0 log10 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, viremia, and immunogenicity. JE-CV in the lyophilized formulation was further assessed in a Phase II pilot H-040-008 on safety and immunogenicity up to 12 months to prepare 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 virus strains.

In addition, cell-mediated immunity was assessed by measuring the gamma-interferon (IFNγ) T-cell response.

Study H-040-009 was a pivotal study of efficacy based on a serological correlate of protection, in which JE-CV was compared to JE-VAX® in a non-inferiority design according to recommendation of WHO (3) (2).

This study demonstrated that JE-CV provides high seroconversion rates and is as immunogenic as JE-VAX®.

The JE-CV clinical development was completed with a pivotal Phase III study (H-040-010) to compare the safety and tolerability of JE-CV to placebo 30 days after a single subcutaneous vaccination of JE-CV or placebo in approximately 2000 healthy subjects (≥18 years). The study contained double-blind vaccination (up to 30 days) and follow-up periods (up to 6 months).

5. Clinical Development in Pediatric Populations

5.1 Clinical Studies in Pediatric Populations

In all studies in pediatric populations JE-CV was administered as a single dose of at least 4.0 log10 PFU (lyophilized formulation).

The first administration of JE-CV to pediatric subjects was in the Phase II study H-040-004, which was conducted to assess the safety and immunogenicity of JE-CV in India in subjects aged from 9 months to 10 years.

Preliminary safety data generated in this study allowed the start of the Phase II study JEC01, which is a study in children aged 2 to 5 years and toddlers aged 12 to 24 months in Thailand to assess clinical and biological safety, viremia and immune response to different JE viruses; a long-term follow-up of the immune response up to 5 years after vaccination is ongoing.

Study JEC01 showed that JE-CV is safe and elicits an immune response persisting up to one year after vaccination in both children and toddlers.

Study JEC02 was a Phase III study in toddlers aged 12 to 18 months, which demonstrated the equivalence of different lots manufactured at GPO-MBP in Thailand and between GPO-MBP lots and a lot manufactured by Acambis in USA. This study also provided immunogenicity and safety data in a large number of pediatric subjects in Thailand and the Philippines.

6. Clinical Database

6.1 Adult Populations

A total of 3476 healthy adult subjects were involved in nine JE-CV clinical studies. Of these 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 (PP population) and H-040-009 (efficacy population).

6.2 Pediatric Populations

A total of 1594 healthy infants, toddlers, and children were involved in three JE-CV clinical studies. Among these, 1444 subjects received JE-CV in a single-dose administration.

PP populations for efficacy assessments (using a serological correlate of protection) included 97 children who received JE-CV in study JEC01 and 1231 toddlers in studies JEC01 and JEC02.

7. Criteria for Analysis of the Immune Response to Vaccination in Individual Clinical Trials

The immunogenicity of JE-CV was investigated through the measurement of neutralizing antibodies in seven studies in adult populations (H-040-001, H-040-003, H-040-005, H-040-006, H-040-007, H-040-008, and H-040-009) and in three studies in pediatric populations (H-040-004, JEC01, and JEC02).

Protection against JE is mainly mediated by neutralizing antibodies, as demonstrated in passive transfer experiments. Neutralizing antibodies are therefore the most relevant indicator of protection. (3) (8) (5).

Neutralizing antibodies were measured with different assays as follows:

- JE-CV virus LNI assay was used in the early phase of development in studies H-040-001 and H-040-003. This assay uses a fixed dilution of serum and various concentrations of challenge virus. As this method is not widely used and the data are limited for comparison among JE studies, it was replaced by the PRNT50 assay in the subsequent studies.
- JE-CV and JE virus PRNT50 (constant virus, serum dilution 50% plaque-reduction neutralization test) were used in studies H-040-005, H-040-006, H-040-007, H-040-008, H-040-009, H-040-004, JEC01, and JEC02. It is based on a fixed amount of virus and different dilutions of serum. It is the most commonly accepted test methodology for measuring functional antibodies able to inactivate and neutralize JE virus (3) (9) and a titer of 1:10 is regarded as the minimum protective level (10). The titer represents the highest dilution of serum at which ≥50% of JE challenge virus is neutralized. Results generated by PRNT are expressed as the inverse of the dilution (1/dil).

7.1 Criteria Used in Studies in Adult Populations

Immunogenicity endpoints included both seroconversion and post-vaccination neutralizing antibody titers. The definition for seroconversion varied during the development of JE-CV because different tests were used. In the early clinical studies (H-040-001 and H-040-003), seroconversion was defined as an LNI of ≥0.7. LNI threshold ≥0.7 for seroconversion is the minimum cut-off for protective immunity against YF (11). During qualification of the LNI assay, it was determined that an LNI of 0.7 corresponded to a PRNT50 titer of 1:20 (data not shown) (6).

For the next three clinical studies (H-040-005, H-040-006, and H-040-007), seroconversion with a threshold of PRNT50 1:20 was initially chosen as the surrogate for protection. Subsequently, the threshold of PRNT50 1:10 was defined by the WHO Expert Committee on Biological Standardization as the accepted cut-off for seroprotection from JE infection (3) (10); this threshold was used in the late phase of the development in the Phase II study (H-040-008) and the Phase III study (H-040-009). Within this application, the PRNT50 1:10 threshold is presented when data were available from the Clinical Study Report (CSR), otherwise the PRNT50 1:20 threshold is quoted. The PRNT50 1:20 threshold was more conservative than the PRNT50

1:10 threshold. In addition to the absolute PRNT50 thresholds for subjects who were seronegative (titer <1:10) at baseline, seroconversion for seroprotected subjects (titer ≥1:10) was defined as a four-fold increase in PRNT50 titers for studies H-040-005, H-040-006, H-040-007, H-040-008, and H-040-009 (10). Antibody titer increases of less than four-fold can result from inter-test variations, therefore a four-fold increase was considered the minimum level for the determination of seroconversion.

The primary immunogenicity outcome in each study was the proportion of JE naïve subjects who seroconverted to homologous JE virus one month (28 or 30 days) after vaccination. The challenge virus used for the primary immunogenicity objectives was the homologous JE virus (i.e. the JE-CV virus for subjects receiving JE-CV and the Nakayama strain for subjects receiving JE-VAX®).

A second approach was also employed in studies H-040-008 and H-040-009; it consisted in the comparison of JE-CV and JE-VAX® groups using the same challenge virus (i.e. JE-CV or Nakayama) in the PRNT for both groups.

In addition, the immune response against wild-type JE viruses originating from different Asian countries and belonging to the four main genotypes was evaluated.

The durability of immune response was assessed based on the proportion of subjects who remained seroprotected (titer ≥1:10) over time in studies H-040-005, H-040-006, H-040-007 and H-040-008.

Long-term persistence of immune response was analyzed in study H-040-005 using the Kaplan-Meier estimate methodology. This represents a standard approach used to evaluate and predict binary clinical study outcomes over time.

In study H-040-005, the binary outcome was that of presence or absence of seroprotection after administration of JE-CV in the intent to treat (ITT) population. Thus, the Kaplan-Meier estimates provided the probability for subjects to maintain a PRNT50 ≥1:10 over time.

Because of its potential beneficial role in protection against JE, cell-mediated immunity was assessed in study H-040-008 by measuring the JE-specific IFNγ T-cell response.

7.2 Criteria Used in Studies in Pediatric Populations

Immunogenicity endpoints used in the development in pediatric populations (studies H-040-004, JEC01, and JEC02) included both seroconversion and post-vaccination neutralizing antibody titers as described above for adults. In addition to the absolute PRNT50 titer threshold (1:10) for subjects who were seronegative (titer <1:10) at baseline, seroconversion for seropositive (titer ≥1:10) subjects was defined as a four-fold increase of titers.

In study H-040-004, the primary immunogenicity outcome was the proportion of JE naïve subjects who seroconverted 28 days after vaccination to homologous JE virus (i.e. the JE-CV virus for subjects receiving JE-CV and the Nakayama strain for subjects receiving MBDV).

JE-CV and MBDV were also compared using the same challenge viruses (i.e. JE-CV virus, Nakayama strain, or a wild-type JE virus strain).

For children in study JEC01, the main immunogenicity endpoint was the proportion of subjects having completed a two-dose primary immunization schedule with an inactivated JE vaccine who seroconverted 28 days after vaccination, as assessed using the JE-CV virus.

For toddlers in both studies JEC01 and JEC02, the main immunogenicity endpoint was the proportion of JE naïve subjects who seroconverted 28 days after vaccination, as assessed using the JE-CV virus.

In addition, the immune response against wild-type JE viruses originating from different Asian countries and belonging to the four main genotypes was evaluated in study JEC01.

Long-term persistence of immune response up to 5 years post-vaccination is being assessed in two ongoing studies; results up to one year post-vaccination from study JEC01 are available to date

8. Criteria for Analysis of Vaccine Reactogenicity and Safety in Individual Clinical Trials

8.1 Criteria Used in Studies in Adult Populations

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 (hematology, 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.

The durations of serious adverse events (SAEs) follow-up was different from one study to another: one month in study H-040-001, 2 months in study H-040-003, 6 months in studies H-040-006 and H-040-010, 7 months in study H-040-009, 12 months in studies H-040-007 and H-040-008, and 60 months in study H-040-005.

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 analysis of safety includes analyses by study and pooled analyses where appropriate.

8.2 Criteria Used in Studies in Pediatric Populations

The safety of JE-CV was investigated in all three studies in the pediatric clinical development.

The methodology of safety data collection differed between study H-040-004 and JEC01 and JEC02.

In study H-040-004, 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 (hematology and biochemistry). The subjects' parents were required to complete a diary card after vaccination to record daily signs and symptoms, oral temperature, and any new medications. A DSMB assessed safety data during the stepwise inclusion.

In studies JEC01 and JEC02, the clinical safety was assessed based on reported AEs, which included solicited AEs (injection site and systemic reactions) pre-defined and listed in diary cards given to the subjects' parents, and spontaneously reported events. Physical examination and assessment of viremia in case of specific clinical symptoms were performed in both studies.

Viremia and routine laboratory (hematology and biochemistry) testing were performed in study JEC01. A Safety Review Committee (in study JEC01) or an Independent Data Monitoring Committee (IDMC) (in study JEC02) monitored the safety on an ongoing basis.

9. Studies Ongoing or Planned at the Time of Submission

9.1 Studies Ongoing or Planned in Adult Populations

The clinical development of JE-CV in adults is completed and no more studies are planned.

9.2 Studies Ongoing or Planned in Pediatric Populations

Ongoing Studies at the Time of the Submission

Three studies are currently ongoing in pediatric populations.

- Study H-040-004 is a Phase II study investigating the safety and immunogenicity of JE-CV in infants, toddlers and children aged between 9 months and 10 years. To date the vaccinations with JE-CV (and placebo) or two doses of MBDV have been completed in the three age groups, and the 24-month follow-up is ongoing. Interim results up to 28 days after vaccination are presented in the clinical sections of this application.
- Study JEC01 is a Phase II study of safety and immunogenicity of JE-CV in children aged 2 to 5 years and toddlers aged 12 to 24 months. Interim results up to one year after vaccination are presented in the clinical sections of this application. A 5-year follow-up to evaluate the yearly persistence of immune response to JE and to collect confirmed cases of JE through passive surveillance is still ongoing.
- Study JEC05 is a Phase III long-term follow-up study of immunogenicity (up to 5 years post-vaccination) in a subset of subjects from study JEC02. Results are not yet available.

Studies Planned at the Time of the Submission

At the time of submission of this application, four additional studies in pediatric populations are planned to start in 2010:

- Study JEC04 is a Phase III study designed to assess the co-administration of JE-CV and the measles mumps rubella (MMR) vaccine.

- Study JEC06 is a Phase III study in India of immunogenicity and safety.
- Study JEC07 is a Phase III study of immunogenicity and safety of JE-CV in comparison with SA14-14-2 in infants and toddlers.
- Study JEC11 is a Phase III study designed to assess the co-administration of JE-CV and a pediatric combination vaccine (including diphtheria, tetanus and pertussis).

10. Conclusions, risk/benefit assessment and recommendations

Efficacy

The pivotal clinical study of IMOJEV, designed according to recommendation of WHO (3) (2), demonstrated that JE-CV provides high seroconversion rates and is as immunogenicity as JE-VAX®.

Safety

The safety profile of JE-CV has shown to be comparable to JE-VAX®. The number of adverse reactions or severe, serious or related adverse reactions was similar after administration of JE-CV, JE-VAX® or placebo and did not raise any safety concerns. No related serious adverse reactions have been observed. The most common adverse reactions reported for JE-CV were malaise, fever, headache, myalgia, vomiting, appetite loss, abnormal crying, pyrexia, irritability, injection site pain/tenderness and injection site erythema..

From the safety database all the adverse reactions reported in clinical trials have been included in the summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, TFDA considered that the proposed activities are adequately addressed.

Benefits

The availability of an effective vaccine to protect those who are at risk from Japanese encephalitis is necessary. So far the JE-VAX® prepared from suckling mouse brains have shown to be efficacious. Therefore, the JE-CV which showed high seroconversion rates and as immunogenicity as JE-VAX® is considered acceptable.

Recommendations

The TFDA and external experts have reviewed quality, safety, toxicology and clinical studies data and found them evidently supportive; therefore positive opinion was given toward the approval of marketing authorization of IMOJEV with one condition requesting the applicant to conduct a clinical phase IV study as under Safety Monitoring Program (SMP) for a period of two years.

The applicant submitted a synopsis of clinical phase IV study on 10,000 subjects and gave commitment to report the progress of the study to TFDA. Final study report should be submitted for further consideration after completion of the study. The applicant also committed to perform the safety monitoring program as part of the pharmacovigilance plan.