

ASSESSMENT REPORT
FOR
THAIJEV

Common Name: Japanese Encephalitis Vaccine (recombinant)

Application No. 1 A 90002/52(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, THAIJEV 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.

THAIJEV is also referred to in the application as ChimeriVa-JE or JE-CV. THAIJEV corresponds to the multidose presentation of IMOJEV and same product, same formulation. IMOJEV, THAIJEV use the same Drug Substance, Non Clinical data and Clinical data

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
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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
- After the In dept assessment the external experts agreed on the consolidated List of Questions to be sent to the applicant.
 - **Quality:** 8 Oct 2010, 14 Mar 2011
 - **Non Clinic:** 21 Jun 2010
 - **Clinic:** 6 Oct 2010, 14 Jul 2011, 10 Aug 2011
- Final draft of English SPC, labeling and package leaflet was sent by applicant to the TFDA PTL on 30 Sep 2011
- TFDA adopted the decision on marketing authorization on 13 Oct 2011

2. SCIENTIFIC DISCUSSION

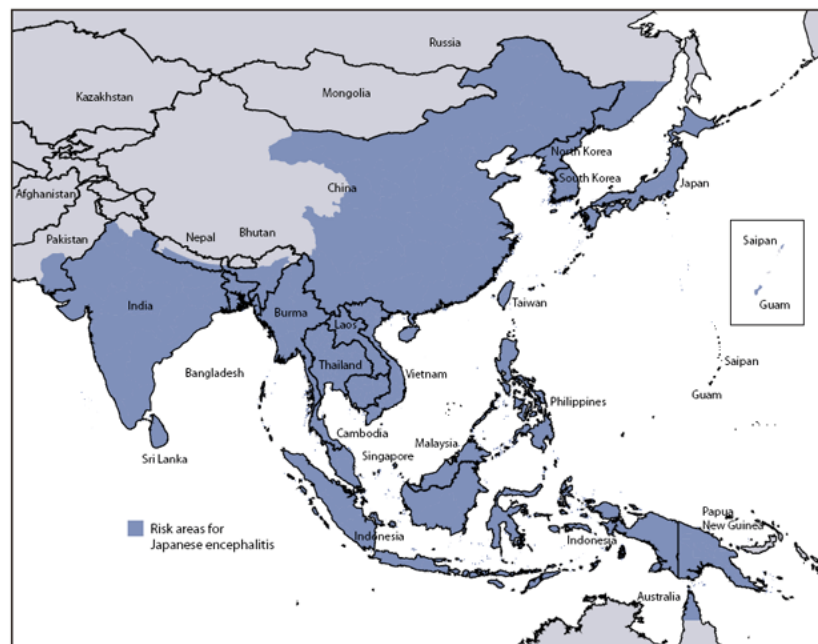
2.1 Introduction

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 envelope glycoprotein 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.

THAIJEV 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

THAIJEV™, 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 virus was obtained via recombinant DNA technology and is based on two well-characterized live attenuated vaccine viruses, the yellow fever (YF) 17D vaccine virus and the JE SA14-14-2 vaccine virus.

JE-CV virus is propagated in Vero cells grown in serum-free conditions. It is purified and then formulated in a stabilizer constituted of lactose, mannitol, histidine, glutamic acid, human serum albumin and salts. The JE-CV liquid formulation is then freeze-dried.

The vaccine comprises a freeze-dried powder and 0.9% NaCl diluents for reconstitution in multidose (4-dose) presentation.

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) 241 Moo 7, Gateway City Industrial Estate, Tambon Huasamrong, Amphoe Plaengyao, Chachoengsao 24190, Thailand.	- Manufacture of the Drug Product, - Manufacturing of 0.4 sodium chloride diluent solution - 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 THAIJEV vaccine.

Drug substance

1. The JE-CV virus genomes sequencing of Pre master seed, Master seed, Working seed, Virus harvest for the Identity test

2. Update the stability study of Drug substance

3. The Analytical procedure for the all process of Drug substance manufacturing
Drug product

1. There are Neurovirulence of MSL, WSL and DP but couldn't be found in Commercial lot of DP, which from WHO guideline TRS number 910, 2002 stated that must be tested in mice in the final bulk

2. The summanry production protocol of 3 consecutive batches

3. The Study data of Shipment validation and packaging validation of final product

4. The details of the standard antibody preparing which used in the testing of Adventitious agent of the Quality control
5. The stability data of Drug product (validated batch) and commercial batch
6. The Human albumin content in every batch of the final product
7. The Analytical procedure for the all process of Drug product manufacturing
8. The stability data of the Diluent (0.9 % NaCl) batch no. 1281101, 1281102, 1281103 Which used in Sterilization $F_0 \geq 12$ and batch no. 129704, 129705, 129706 of new sterilization $F_0 \geq 15$ which used in the commercial lot.
9. The company should provide the thermal stability study test of DP.

The company responded to the above recommendations as the followings:

1. The company showed the JE-CV virus genome sequencing (cDNA sequence) of the seed virud (from uncloned Pre master seed, Working seed, Drug substance which has nothing changed. This is satisfactory
2. The stability study of Drug substance is updated. This is satisfactory
3. The Analytical procedure for the all process of Drug substance manufacturing has shown and the company added more information(SOP) such as Sterility testing using the Millipore sterile, Potency testing of ChimericVax Sample by Plaque Forming Units. This is satisfactory
4. The company informed that regarding the Neurovirulence of MSL, WSL and DP couldn't be found. Because of the potency of drug substance is higher than drug product and the virus in the drug substance and drug product are not added. This is satisfactory
5. The company showed the the summanry production protocol of 3 consecutive batches. This is satisfactory
6. The company showed the Study data of Shipment validation and packaging validation of the Commercial Hepatitis vaccine which has not only the same packaging and shipment condition but also the same size of vial and pack size. This is satisfactory
7. The company showed the stability data (shelf life 24 months at $5+/- 3$ C) of Drug product (validated batch) and commercial batch and the stability data (shelf life 24 months at $5+/- 3$ C) of the diluents (0.9 % NaCl). This is satisfactory
8. The company committed to provide the stability data of the commercial batch. This is satisfactory
9. The company committed to provide Human albumin content in the preparation of final bulk vaccine of Summanry production protocol in every batch of the final product. This is satisfactory.
10. The company committed to provide the thermostability data as soon as available. 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 tetravalent 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 THAIJEV 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

Introduction

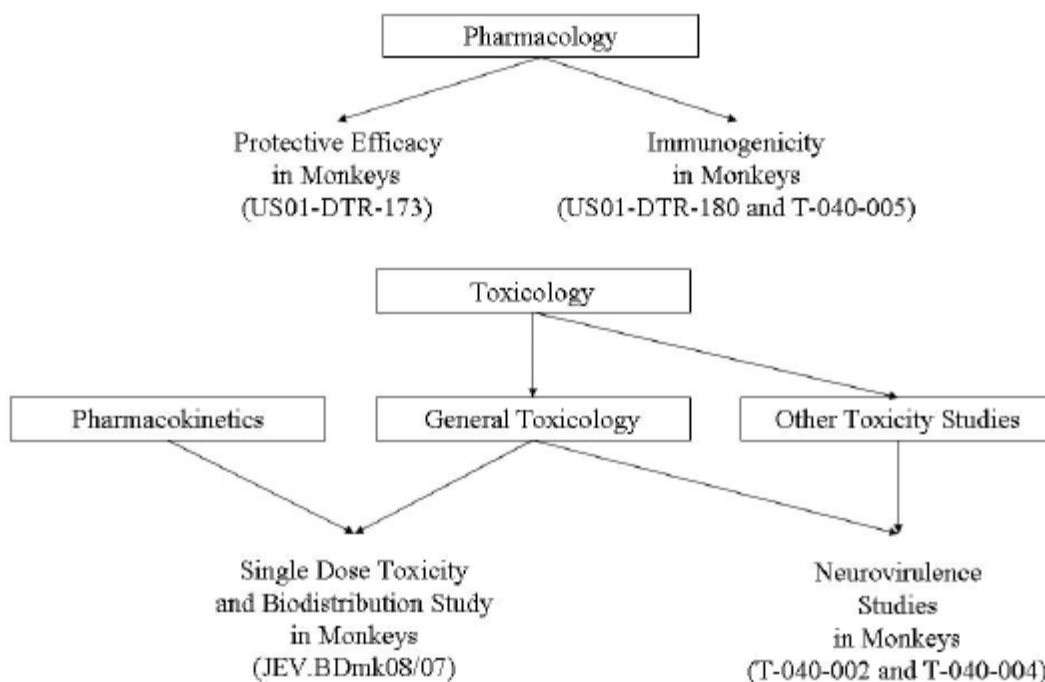
THAIJEV is a live, attenuated, recombinant Japanese encephalitis chimeric virus vaccine (JE CV) for s.c. administration. It contains between 4.0 and 5.8 log PFU of freeze-dried viral powder for reconstitution per dose (using 0.9 % Sterile NaCl diluent) in 4 dose/vial package. THASIJEV is indicated for prophylaxis of Japanese encephalitis caused by the Japanese encephalitis virus in subject from 18 years of age and over.

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.

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.

- **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)

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 transmembrane 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.

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 2)

- 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 2: 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 = xth passages in Vero cells
† Vaccine Lot
‡ PFU = Plaque Forming Unit
§ Master Seed Lot
** Vaccine Bulk
†† Working Seed Lot

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.

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.

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 local toxicity of JE-CV by s.c. route was also conducted in monkeys using large scale JE-CV lot. There was no injection site reaction.

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 conducted 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

OVERALL CONCLUSIONS ON NON-CLINICAL ASPECTS

1. From pharmacodynamic 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 2: 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	<p>JE-CV</p> <p>- 5.0 log₁₀ PFU† in 0.5 mL or - 4.0 log₁₀ PFU in 0.5 mL</p> <p>Control vaccine: YF-VAX® 5.04 PFU in 0.5 mL</p> <p>One dose at D1 Subcutaneous injection</p>	<p>36 included 36 randomized</p> <ul style="list-style-type: none"> ● 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 3: 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	<ul style="list-style-type: none"> • Characterize the safety of the administration of JE-VAX® in subjects who were vaccinated at least 6 months Previously with JE-CV • Characterize the 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: <ul style="list-style-type: none"> • 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 4: 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	<p>JE-CV</p> <p><i>5 dose levels for groups 1–5:</i></p> <ul style="list-style-type: none"> - 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 <p>Two doses: at D0 and D30</p> <p><i>1 dose level for groups 6–9:</i></p> <ul style="list-style-type: none"> - 4.8 log₁₀ PFU in 0.5 mL <p>One dose: at D0 or D30</p> <p>Control vaccine: YF- VAX <input type="checkbox"/></p> <p>5.04 PFU in 0.5 mL</p> <p><i>Group 6:</i> one dose at D30</p> <p><i>Group 7:</i> one dose at D0</p> <p>Placebo</p> <p>0.5 mL</p> <p><i>Group 8:</i> one dose at D0</p> <p><i>Group 9:</i> one dose at D30</p> <p>Subcutaneous injection</p>

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 5: 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	<ul style="list-style-type: none"> • 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	<u>Primary Vaccination Series</u> JE-CV <ul style="list-style-type: none"> • <u>Group A</u> 3.8 log₁₀ PFU in 0.5 mL. One dose at Day 0 • <u>Group B</u> 3.8 log₁₀ PFU in 0.5 mL. One dose at Day 28 JE-CV Diluent (placebo) <ul style="list-style-type: none"> • <u>Group A</u> 0.5 mL at Day 28 • <u>Group B</u> 0.5 mL at Day 0 <u>Booster injection</u> JE-CV 0.5 mL at M6 Subcutaneous injection in the deltoid region of the arm	202 included 202 randomized <u>Primary Vaccination Series</u> 101 in Group A 101 in Group B <u>Booster Injection</u> 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-040-007: Randomised, double-blind, placebo-controlled Phase II dose-ranging study of the safety, tolerability and immunogenicity of live attenuated ChimeriVax™-JE vaccine (lyophilised)

Table 7: 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 Diagnosis Of Patients	Study Status; Type of Report
H-040-007	5.3.4.1	<ul style="list-style-type: none"> • 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	<p>JE-CV</p> <ul style="list-style-type: none"> • <u>Group 1</u> - 3.0 log₁₀ PFU in 0.5 mL (effective administered dose 3.3 log₁₀ PFU) One dose at Day 0 • <u>Group 2</u> - 4.0 log₁₀ PFU in 0.5 mL (effective administered dose 4.3 log₁₀ PFU) One dose at Day 0 • <u>Group 3</u> - 5.0 log₁₀ PFU in 0.5 mL (effective administered dose 5.3 log₁₀ PFU) One dose at Day 0 <p>JE-CV Diluent (placebo)</p> <ul style="list-style-type: none"> • <u>Group 4</u> 0.5 mL One dose at D0 Subcutaneous injection in the deltoid region of the upper arm 	<p>128 included 128 randomized in 4 groups:</p> <p>JE-CV</p> <ul style="list-style-type: none"> • 3.0 log₁₀ PFU: 32 • 4.0 log₁₀ PFU: 32 • 5.0 log₁₀ PFU: 32 <p>Diluent : 32</p>	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 8: 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	<ul style="list-style-type: none"> ● 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	<p>JE-CV Diluent</p> <p>One dose at D0 and D7 followed by</p> <p>JE-CV</p> <p>One dose at D28, 4.0 log₁₀ PFU in 0.5 mL (effective administered dose 4.3 log₁₀ PFU)</p> <p>JE-VAX®</p> <p>One dose at D0, D7 and D28 1.0 mL</p> <p>Subcutaneous injection in the deltoid region of the upper arm</p>	<p>60 included</p> <p>60 randomized:</p> <ul style="list-style-type: none"> ● 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 9: 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	<ul style="list-style-type: none"> ● 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	<p>JE-CV</p> <ul style="list-style-type: none"> - 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 <p>JE-VAX®: 1.0 mL</p> <ul style="list-style-type: none"> - at D0 and D7: single vaccination - at D30: concomitant injection with placebo 0.5 mL <p>Subcutaneous injection(s) in the deltoid region of the upper arm; at D30, simultaneous injections into different arms</p>	<p>820 included</p> <p>820 randomized:</p> <ul style="list-style-type: none"> ● 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	<p>Completed; Full CSR</p> <p>Addendum to CSR for additional analyses</p>

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 10: 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	<ul style="list-style-type: none"> Comparative safety data 30 days after a single vaccination of JE-CV or placebo 	Phase III, randomized, double-blind, placebo-controlled, multicentre	<p>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</p> <p>Placebo 0.5 mL One dose at D0</p> <p>Subcutaneous injection into the deltoid region of the upper arm</p>	<p>2004 included 2004 randomized:</p> <ul style="list-style-type: none"> 1601\$: JE-CV 403: Placebo 	<p>Australia – USA</p> <p>10 Oct 2005 to 01 May 2006</p> <p>Last visit for the month 6 follow-up: 15 Nov 2006</p>	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 11: 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	<ul style="list-style-type: none"> 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	<p>JE-CV Group</p> <p>Placebo 0.5 mL One dose at D0</p> <p>JE-CV 4.0 log₁₀ PFU (effective administered dose: 4.5 log₁₀ PFU, 4.8 log₁₀ PFU, 4.9 log₁₀ PFU) One dose at D14</p> <p>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</p> <p>All vaccinations subcutaneous in 1.0 mL for subjects ≥3 years in 0.5 mL for subjects <3 years</p> <p>Subjects >12 months: the deltoid region of the upper arm For subjects ≤12 months: the anterolateral aspect of the thigh</p>	<p>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</p> <p>MBDV: 48 - :≥5 to <10 years: 16 - ≥2 to <5 years: 16 - ≥9 months to <2 years: 16</p>	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 12: 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	<ul style="list-style-type: none"> ● 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 <p>To describe the yearly persistence of immune response to JE after a single dose of JE-CV (5-year follow-up)</p>	Phase II trial, randomized, crossover, open, active controlled (hepatitis A vaccine), multicenter	<p>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</p> <p>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)</p>	<p>301 included 301 randomized Sequential enrolment in two age cohorts:</p> <ul style="list-style-type: none"> ● 101 children ed 2 to 5 years <ul style="list-style-type: none"> - 50 in group 1 (JE-CV/Hepatitis A) - 51 in group 2 (Hepatitis.A/JE-CV) ● 200 toddlers ed 12 to 24 months <ul style="list-style-type: none"> - 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 13: 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	<ul style="list-style-type: none"> ● 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 GPO-MBP. ● Descriptive safety of vaccination in all subjects 	Phase III, randomized, controlled (hepatitis A vaccine), observer - blind multicenter	<p>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 GPO-MBP lots</p> <p>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</p> <p>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</p>	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 (EMA) "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 (IFN γ) 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 $\geq 50\%$ 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 thresholds. In addition to the absolute PRNT50 thresholds for subjects who were seronegative (titer $< 1:10$) at baseline, seroconversion for seroprotected subjects (titer $\geq 1:10$) 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 $\geq 1:10$) 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 $\geq 1:10$ 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 IFN γ 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 \geq 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 THAIJEV, 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

THAIJEV is also referred to in the application as ChimeriVa-JE or JE-CV. THAIJEV corresponds to the multidose presentation of IMOJEV and same product, same formulation. IMOJEV, THAIJEV use the same Drug Substance, Non Clinical data and Clinical data

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 THAIJEV 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.