Post-licensure, phase IV, safety study of a live attenuated Japanese encephalitis recombinant vaccine in children in Thailand

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Background: Japanese encephalitis is a mosquito-borne viral disease endemic in most countries in Asia. A recombinant live, attenuated Japanese encephalitis virus vaccine, JE-CV, is licensed in 14 countries, including Thailand, for the prevention of Japanese encephalitis in adults and children.

Methods: This was a prospective, phase IV, open-label, multicentre, safety study of JE-CV conducted from November 2013 to April 2015, to evaluate rare serious adverse events (SAEs). JE-CV was administered to 10,000 healthy children aged 9 months to <5 years in Thailand as a primary (Group 1) or booster (Group 2) vaccination. Serious AEs (SAEs), including AEs of special interest, up to 60 days after administration were evaluated. Immediate Grade 3 systemic AEs up to 30 min after JE-CV administration were also described.

Results: The median age of participants was 1.1 years in Group 1 and 3.8 years in Group 2. SAEs were reported in 204 (3.0%) participants in Group 1 and 59 (1.9%) participants in Group 2. Among a total of 294 SAEs in 263 participants, only three events occurring in two participants were considered related to vaccination. All three cases were moderate urticaria, none of which met the definition of AEs of special interest for hypersensitivity. AEs of special interest were reported in 28 (0.4%) participants in Group 1 and 4 (0.1%) participants in Group 2; none were considered related to vaccination. Febrile convulsion was the most frequently reported AE of special interest: 25 (0.4%) participants in Group 1; and 2 (<0.1%) in Group 2. There were no cases of Japanese encephalitis reported. No Grade 3 immediate systemic AEs were reported after any JE-CV vaccination.

Conclusions: Our study did not identify any new safety concerns with JE-CV and confirms its good safety profile.

This study was registered on www.clinicaltrials.gov (NCT01981967; Universal Trial Number: U1111-1127-7052).

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1. Introduction

Japanese encephalitis (JE) is a mosquito-borne viral disease that is endemic in most countries in Asia [1]. JE belongs to the same genus (Flavivirus) as yellow fever (YF) and dengue viruses [2]. The greatest burden of disease occurs in childhood with 66% of cases occurring in those under 15 years of age and an overall case fatality rate of up to 35% [3]. In Thailand during the 1970s and 1980s, 1500–2500 cases of encephalitis were reported annually [3]; following the introduction of a national JE vaccination programme in 1990, the number of cases declined to 297–418 cases per year between 2002–2008, reflecting the large proportion of cases caused by JE virus [4].

There is no specific antiviral treatment for JE. The World Health Organization recommends that JE vaccination should be integrated into national immunisation schedules in endemic areas [5]. A live, attenuated JE vaccine (JE-CV; IMOJEVTM, Sanofi Pasteur) has been developed using the YF virus vaccine vector YF17D with the cDNA encoding the envelope proteins of YF virus replaced with that of the attenuated JE SA-14-14-2 virus strain [6,7]. A number of phase II and phase III studies conducted in adults and children have demonstrated the safety and immunogenicity of JE-CV [5,8–13]. The vaccine was first registered in Australia and Thailand in 2010 in children aged 12 months to 5 years and has subsequently been licensed in 12 other countries to date, for the prevention of JE in both children and adults. For children, the current recommended dosing schedule for JE-CV is a single dose as primary vaccination from 9 months of age followed by a booster dose 12–24 months later [14]. In adults, a booster dose is not required for up to 5 years after administration of a single dose of JE-CV [14].

Previous safety evaluation in non-clinical studies showed no evidence of viscerotropism or neurotropism [15]. We undertook this large prospective phase IV post-marketing safety study to further characterise the safety profile of JE-CV to evaluate rare (>1/10,000 and <1/1000) serious adverse events (SAEs) in a large population. Here we describe Grade 3 systemic, immediate adverse events (AEs) and SAEs, including AEs of special interest (AESIs), of JE-CV following administration to 10,000 children, 70% of whom received JE-CV for the first time.

2. Methods

2.1. Study design

This study was a prospective, phase IV, open-label, multicentre, safety study of the live attenuated JE vaccine, JE-CV, administered to 10,000 healthy children in Thailand either as a primary vaccination (Group 1) or as a booster ≥1 year after primary immunization with inactivated JE vaccine or JE-CV (Group 2). The study was conducted between 03 November 2013 and 09 April 2015 in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on the Harmonization-Good Clinical Practice guidelines. In addition, the study protocol, including any amendments, was approved by each study site’s Institutional Review Board and Independent Ethics Committee. Written informed consent was obtained from the parents/guardians of all children before study entry. This trial has been registered at www.clinicaltrials.gov (identifier NCT01981967; Universal Trial Number: U1111-1127-7052).

At study initiation, children aged 12 months to less than 5 years were eligible for inclusion, however, this criteria was later modified in 2014 to include children from 9 months of age, following a change in the age indication for JE-CV. Participants were physically examined to assess general health at the time of inclusion; all participants required vaccination against JE. Children who had received medications such as high dose systemic corticosteroids, antiviral drugs, immunosuppressive drugs (usually chemotherapy) and immunoglobulins/blood products containing immunoglobulins within the last three months were excluded. Other exclusion criteria included: any contraindications to JE-CV vaccination, participation in another clinical trial in the four weeks preceding the vaccination or at any time during the study period, a medical procedure or receipt of any vaccine in the four weeks preceding the study vaccination, planned vaccination in the four weeks following the study vaccination, previous vaccination with another live attenuated JE vaccine (CD-JEVAX®, Chengdu Institute of Biological Products, Chengdu, China) or prior receipt of JE-CV earlier in this study as primary vaccination (Group 2 only).

The proportions of participants included in the study to receive JE-CV either as primary vaccination (Group 1) or as a booster (Group 2) were approximately 70% and 30%, respectively. Group 1 was defined as follows: participants who never received a JE vaccine; participants who received a single dose of inactivated JE vaccine; and participants whose JE vaccination history was unknown or not documented. Group 2 was defined as follows: participants who received at least 2 doses of inactivated JE vaccine (at least 1 year earlier since the last dose); participants who received a single dose of JE-CV as part of the routine vaccination schedule at least 1 year earlier.

2.2. Vaccine

The JE-CV vaccine (IMOJEVTM, Sanofi Pasteur) was supplied as powder and solvent for injection. The solvent for reconstitution consisted of sterile 0.4% sodium chloride solution. Two batches of JE-CV (batch numbers 08A1201BF and 08A1305BB) were used in the study. Each 0.5 mL dose of reconstituted vaccine contained 4.0 (batch 08A1201BF) or 5.8 log10 (batch 08A1305BB) plaque forming units of lyophilised virus vaccine. The vaccine was administered subcutaneously into the anterolateral aspect of the thigh or the deltoid region of the upper arm.

2.3. Safety

Participants were kept under observation for 30 min after vaccination to monitor the appearance of any immediate Grade 3 systemic AE. Systemic reactions were graded as follows: for fever, Grade 3 AEs were defined as a body temperature >39.5 °C for participants aged <2 years or ≥39.0 °C for participants aged ≥2 years. For any other AE, Grade 3 was defined as a significant AE that prevents normal activity.

Parents/guardians were provided with cards to record information and events during the 60-day follow-up period. Parents/guardians were interviewed by telephone on four occasions during the 60-day follow-up period using a questionnaire to capture SAEs (including AESIs); relevant information was transcribed onto case report forms. A SAE was defined as any untoward medical occurrence following the dose (including overdose) that: resulted in death; was life-threatening; required inpatient hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect; or was an important medical event. AESIs were selected based on events previously reported with licensed JE mouse-brain derived vaccines and related YF17D vaccines, or events typically expected after vaccination with a live-attenuated vaccine. These included: hypersensitivity reactions (severe [Grade 3] allergic reaction, regardless of the relationship to the vaccine, anaphylactic/anaphylactoid reaction); neurological disorders such as convulsions.
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