BLA Clinical Review Memorandum

Application Type	Efficacy Supplement
STN	125280/235
CBER Received Date	16, Jun 2017
PDUFA Goal Date	16, Apr 2018
Division / Office	CBER/DVRPA
Priority Review (Yes/No)	No
Reviewer Name(s)	Madan Kumar, DO
Review Completion Date / Stamped Date	4/11/18
Supervisory Concurrence	Doran Fink, MD, PhD Team Leader, CRB-2/DVRPA Andrea Hulse, MD Branch Chief, CRB-2/DVRPA
Applicant	Intercell AG
Established Name	Japanese Encephalitis Vaccine, Inactivated Adsorbed
(Proposed) Trade Name	IXIARO
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Purified, inactivated JEV proteins adsorbed to aluminum hydroxide
Dosage Form(s) and Route(s) of Administration	0.5 mL intramuscular injection containing 6 antigen units of JEV proteins
Dosing Regimen	Individuals 3 years of age and older: primary series of two 0.5 mL doses given 28 days apart, single 0.5 mL booster dose at least 12 months after primary series if ongoing exposure or re-exposure to JEV expected; Infants and children 2 months to < 3 years of age: primary series of two 0.25 mL doses given 28 days apart, single 0.25 mL booster dose at least 12 months after primary series if ongoing exposure or re-exposure to JEV expected.
Indication(s) and Intended Population(s)	To allow a booster dose at least 12 months after primary immunization in children who received primary immunization at ages 2 months to < 17 years and who are at risk of ongoing exposure or re-exposure to JEV.
Orphan Designated (Yes/No)	Yes (pediatric usage only)

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GLOSSARY

AE	adverse event
BLA	biologics license application
CBER	Center for Biologics Evaluation and Research
CMC	chemistry, manufacturing, and controls
ELISA	Enzyme-Linked Immunosorbent Assay
GMFR	geometric mean fold rise
GMT	geometric mean titer
ISE	integrated summary of efficacy
ITT	intent-to-treat
JEV	Japanese encephalitis virus
PD	pharmacodynamics
PI	package insert
PK	pharmacokinetics
PLLR	Pregnancy and Lactation Labeling Rule
PMR	postmarketing requirement
PP	Per Protocol
PREA	Pediatric Research Equity Act
$PRNT_{50}$	Plaque Reduction Neutralization Test (50% reduction endpoint)
SAE	serious adverse event
SCR	seroconversion rate

1. Executive Summary

IXIARO is a purified, inactivated Japanese encephalitis virus (JEV) vaccine that is U.S. licensed for active immunization of persons 2 months of age and older for prevention of disease due to JEV. The primary series consists of two 0.25 mL doses 28 days apart for infants and children 2 months to < 3 years of age and two 0.5 mL doses 28 days apart for individuals 3 years of age and older. A single booster dose of 0.5mL is approved for individuals 17 years of age and older who have received a primary immunization series more than one year previously if ongoing exposure or re-exposure to JEV is expected. A 0.5 mL pre-filled syringe presentation is used for all dosing regimens, with instructions to expel 0.25 mL prior to administering the 0.25 mL dose to infants and children 2 months to <3 years of age.

In support of a proposed pediatric booster indication, this BLA supplement contains the final study reports for two pediatric clinical studies. The largest of these studies, IC51-325, was a randomized, open-label, study to evaluate the safety and immunogenicity of an IXIARO booster dose in children and adolescents living in the Philippines, where JEV is endemic. The study enrolled 300 subjects who were 2 months to <18 years of age at primary vaccination and randomized them 1:1 to receive a booster dose vs. no booster dose at 11 months after completion of the primary series. All subjects were followed for a total of three years after primary immunization. Immunogenicity endpoints for this study were $PRNT_{50}$ geometric mean titer (GMT) and the proportion of subjects with $PRNT_{50}$ titer ≥ 1:10 as measured by a 50% plaque reduction neutralization test. A $PRNT_{50}$ titer ≥ 1:10 is generally considered to be reasonable evidence of protection against JEV disease. At one year after primary immunization 89.9% (95% CI [84.1%,93.8%]) of subjects remained above this protective threshold, with GMTs of 45.5 (95% CI [37.8, 54.8]). At one month after the booster dose, 100% of subjects in the booster dose cohort achieved protective titers, with GMTs of 2066.6 (95% CI [1670.8,2556.2]). At three years

after primary immunization, the proportions of subjects with $PRNT_{50}$ titer ≥ 1:10 and $PRNT_{50}$ GMTs were 100% (95% CI [97.4%,100%]) and 350.4 (95% CI [279.2,439.8]), respectively, for the booster dose cohort vs. 90.1% (95% CI [84.1%,94%]) and 59.4 (95% CI [48.4,72.8]), respectively, for the non-booster dose cohort. Safety endpoints included rates of solicited local and systemic adverse events (AEs) following the booster dose (booster dose cohort only) and serious AEs and medically attended AEs throughout the three year study period for the entire study population. Reactogenicity of the booster dose as assessed by solicited AEs was generally mild and comparable to primary immunization. Rates of SAEs and medically attended AEs were low and generally unrelated to IXIARO.

The second study, IC 51-324 was an open label, uncontrolled study to evaluate the longer-term safety and immunogenicity of IXIARO in infants, children, and adolescents living in areas where JEV is not endemic who were 2 months to < 18 years of age at primary immunization prior to travel to JEV-endemic regions (as participants in a previously conducted study, IC51-322). Immunogenicity endpoints evaluated $PRNT_{50}$ GMTs and proportion of subjects with $PRNT_{50}$ titers ≥ 1:10 through three years after primary immunization. A total of 23 subjects were evaluated out of an available pool of 64 subjects who contributed immunogenicity data to IC51-322. Of this small sample size 89.5% of subjects retained protective antibody titers without further vaccinations at both one and three years after their primary series. Safety endpoints evaluated reported AEs throughout the study period, which were few and generally unrelated to IXARO.

This BLA supplement also included the final study report for IC51-322. An interim analysis with data from the first 60 participants enrolled had previously been evaluated to support licensure of the primary series in pediatric age groups given slow recruitment into the study and an urgent public health need for a pediatric JEV vaccine. The final study report provided safety analyses for 100 subjects (as planned) and immunogenicity analyses for 64 subjects (immunogenicity blood draws were discontinued to improve study recruitment). No new safety signals were identified compared to the interim analysis and other pediatric studies of IXIARO. Approximately 90% of subjects maintained $PRNT_{50}$ titers ≥ 1:10 at 7 months after primary immunization.

Taken together the data from these studies demonstrate a favorable safety profile and likelihood of clinical benefit (based on immunogenicity) for an IXIARO booster dose at least 11 months after completion of primary immunization in individuals who were 2 months to < 17 years of age at primary immunization. Although 90% of children appear to maintain protective JEV-neutralizing antibody titers through 3 years after primary immunization, the benefit/risk balance for a pediatric booster dose for children at continued risk of exposure to JEV is favorable given the severity of JE disease, the established safety profile of the vaccine, and lack of standard of care methods for determining which individuals fall into the 10% who may not remain protected at 11 months following completion of the primary series. Consequently this reviewer recommends approval of the proposed IXIARO booster dose in this population.

The PI was revised to include long term immunogenicity data of primary immunization and the safety and immunogenicity data for the booster dose. The PI was also revised to comply with updated PLLR requirements.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The single study evaluating the safety and immunogenicity of the IXIARO booster dose was conducted at three sites in the Philippines with only Asian subjects represented. Long term immunogenicity of the primary series was evaluated in one study (IC 51-324) enrolling U.S children, however only 23 subjects were enrolled.
Booster dose recipients in the 0.25ml group (14 months to 3 years of age) generally achieved higher $PRNT_{50}$ GMTs than subjects in the 0.5ml group (3 years of age and older) – 2910 (95% CI [2235,3791]) versus 1366 (95% CI [988,1889]) one month after booster dose. A similar age stratified response was seen after primary immunization.

2. Clinical and Regulatory Background

2.1 Disease Studied

Japanese encephalitis virus, a mosquito-borne flavivirus, is the most common cause of childhood encephalitis in Asia (pediatric incidence of JEV is 5-50 cases per 100,000 children per year in endemic regions). Infection is frequently asymptomatic, with clinical disease occurring in <1% of infected individuals. However, the case fatality rate for clinical disease is 20-30%, and 30%-50% of survivors are left with serious neurological sequelae.

There are no reports of JEV infection occurring in North America, so the risk to residents of the U.S. occurs from travel to endemic regions. The magnitude of risk depends on several factors, including the specific travel destination, duration of exposure, season, and activities.

The CDC has recorded 12 cases of travel-associated JE cases in travelers from the United States between 1993-2017. The majority (8/12) of these cases occurred with travel greater than 1 month and during the summer months (JE virus transmission season).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

No primary therapies exist for treatment of JEV disease. Supportive therapy (including reduction of intracerebral pressure and prevention of secondary infections) can improve outcomes for clinical disease.

2.3 Safety and Efficacy of Pharmacologically Related Products

Two JEV vaccines have been licensed for use in the U.S (JE-VAX and IXIARO). Both JE-VAX and IXIARO stimulate the production of neutralizing antibodies to JEV. Based on accumulated clinical and nonclinical data, a neutralizing antibody titer of ≥ 1:10 as measured by 50% plaque reduction neutralization test ($PRNT_{50}$) is generally accepted as a threshold for evidence of protective immunity against JEV disease.

JE-VAX was licensed for use in persons 1 year of age and older (efficacy point estimate of 91% against JEV disease in a placebo-controlled, randomized clinical trial in Thai children). The vaccine was generally well tolerated with only rare instances of serious adverse reactions (hypersensitivity, encephalopathy, seizures, and peripheral neuropathy). The product has ceased production, and remaining stocks expired in February 2011.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Initial U.S. licensure of IXIARO in 2009 for use in persons 17 years of age and older was supported by a randomized, controlled study in 867 healthy adults that compared safety and immunogenicity of IXIARO to JE-VAX. In this study, pre-specified noninferiority criteria were met for the primary endpoints of $PRNT_{50}$ geometric mean titer (GMT) and proportion of study participants with $PRNT_{50}$ titer ≥1:10 at 28 days following completion of the primary immunization series. An acceptable safety profile was demonstrated for IXIARO in this study as well as in six other randomized, controlled studies with a total safety database of 3,945 healthy adults. The most common adverse reactions in adults across all studies were headache, myalgia, injection site pain, and injection site tenderness. No specific safety signals (including hypersensitivity reactions and neurologic disorders associated with JE-VAX) have been identified for IXIARO through clinical studies and post-marketing pharmacovigilance. As of April 2017, 984,212 doses of IXIARO have been administered in the United States.

In studies evaluating the safety and immunogenicity of an IXIARO booster dose administered 11 to 22 months after completion of the primary series, JEV-neutralizing antibody responses were robust among adults regardless of whether neutralizing antibodies were detected by $PRNT_{50}$ prior to the booster dose. The most common adverse reactions following the IXIARO booster dose were headache, injection site pain, and injection site tenderness, similar to primary series immunizations. Consequently, a BLA supplement to add a booster dose indication to the IXIARO package insert (PI) was approved in 2010. Long term immunogenicity in traveling adults from non-endemic countries was evaluated with a limited cohort during Phase 2 trials of IXIARO. At 12 months after primary immunization 6/11 subjects (54.6%) maintained a $PRNT_{50}$ titer ≥1:10. A larger cohort was evaluated after Phase 3 trials and showed that 104/134 subjects (83%) maintained a $PRNT_{50}$ titer ≥1:10 at 12 months after primary immunization.

In 2013 the IXIARO primary series was approved for use in infants, children, and adolescents 2 months to < 17 years of age (two 0.25 mL doses 28 days apart for ages 2 months to < 3 years, and two 0.5 mL doses 28 days apart for ages 3 to < 17 years). Clinical benefit of IXIARO in pediatric age groups was demonstrated in two pediatric studies including 1311 recipients residing in the Philippines (where JEV is endemic) and 60 recipients residing in regions where JEV is not endemic. In these studies, nearly 100% of primary series recipients achieved a $PRNT_{50}$ titer ≥1:10 at 1 month after completion of the primary series, and $PRNT_{50}$ GMTs were generally higher than in adults and increased with decreasing age. The safety profile of the IXIARO primary series in pediatric age groups was favorable and included primarily mild injection site reactions in all pediatric age groups, mild muscle pain and fatigue in children and adolescents 3 to <17 years of age, and mild to moderate fever and mild irritability and diarrhea in infants and children 2 months to <3 years of age. Post-vaccination fever occurred most commonly in young infants 2 to <12 months of age (>20% of vaccinees) and was uncommonly associated with febrile convulsion.

In addition to U.S. licensure, IXIARO was granted marketing authorization in 2009 for use in adults in Europe and Australia. Marketing authorization for pediatric use was granted by the European Medicines Agency (EMA) in February 2013 with the same dosing regimen as U.S. licensure. Licensure for an accelerated schedule (two doses seven days apart) for adults was granted by the EMA in July 2015. A single pediatric

booster dose (with a dosing regimen matching sponsor's proposal with this submission) has also been approved by the EMA. As of April 2017 an estimated 984,212 U.S. subjects and 2,532,480 worldwide subjects have been vaccinated with IXIARO.

2.5 Summary of Pre- and Post-Submission Regulatory Activity Related to the Submission

IXIARO was initially approved on 30 March 2009 for active immunization for the prevention of disease caused by JEV in individuals 17 years of age and older. The approval included a partial waiver for infants younger than 1 year of age and a deferral for studies in children and adolescents 1 to <17 years of age.

On 14 October 2010, CBER approved a biologics license supplement to include in the IXIARO package insert long-term immunogenicity data and use of a booster dose for individuals 17 years of age and older who had completed the primary immunization series. PREA requirements for pediatric data relating to long-term immunogenicity and a booster dose were waived for infants younger than 1 year of age and deferred for children and adolescents 1 to <17 years of age. The deferral was to be fulfilled by one PREA PMR study, IC51-325 (included in this submission).
On 25 September 2012 IXIARO was granted Orphan Drug status for use in individuals 2 months to <17 years of age, based on anticipated use in fewer than 200,000 individuals in this age range annually in the US.

Licensure for the primary series was granted on 17 May 2013 for individuals 2 months to <17 years of age, based on the pediatric studies described in Section 2.4. All subjects enrolled into IC51-325 (booster dose and long-term safety and immunogenicity study submitted with this efficacy supplement) were previously participants in IC51-323, the study in the Philippines that primarily supported licensure of the primary series for pediatric use. All subjects enrolled into IC51-324 (long-term safety and immunogenicity study submitted with this efficacy supplement) were previously participants in IC51-322, the study in pediatric travelers from non-endemic countries that also supported licensure of the primary series for pediatric use. IC51-322 was still ongoing at the time of pediatric licensure, with data from only 60 of 100 planned subjects included in the licensure application due to unwillingness of prospective subjects to undergo immunogenicity labs. CBER agreed that the interim data provided sufficient supportive safety and immunogenicity data in pediatric travelers from non-endemic countries and that if the applicant elected to continue enrollment of the study the remaining subjects could undergo evaluation for safety only.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The three studies discussed in this review were conducted at trial sites in the United States, Philippines, and Europe under IND. The study designs adhered to good clinical practices, including elements of informed consent as required by 21 CFR 50.25, and in accordance with acceptable ethical standards.

3.3 Financial Disclosures

Table 1: Financial disclosure information for IC51-322, IC51-324, IC51-325

Covered clinical studies: IC51-325: A Phase III, Long term Immunogenicity and Safety Study for a Booster Dose Following Primary Vaccination with IXIARO in a Pediatric Population in a JEV-endemic Country. IC51-324: Long term immunity and Safety Following Vaccination with the Japanese Encephalitis Vaccine IC51 in a Pediatric Population in Non-endemic Countries. Uncontrolled, Phase 3 Follow-Up Study. IC51-322: Immunogenicity and Safety of the Japanese Encephalitis Vaccine IC51in a Pediatric Population in Non-endemic Countries. Uncontrolled, Open label Phase 3 Study.
Was a list of clinical investigators provided: Yes
Total number of investigators identified: 75
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0

Reviewer comment: The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Not applicable – no changes to chemistry, manufacturing, and controls.

4.2 Assay Validation

Not applicable – no changes to assay validation.

4.3 Nonclinical Pharmacology/Toxicology

Not applicable – no new pharmacology/toxicology information.

4.4 Clinical Pharmacology

Not applicable – no new clinical pharmacology information.

4.5 Statistical

The statistical reviewer verified that the study endpoint analyses cited by the applicant were supported by submitted data. The statistical reviewer independently replicated the sponsor's immunogenicity data analyses and confirmed the sponsor's presented seroconversion rates and GMTs.

4.6 Pharmacovigilance

No changes are proposed to the existing pharmacovigilance plan with this submission. The pharmacovigilance reviewer evaluated the existing pharmacovigilance plan and has no further comments.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The submission includes the results of three pediatric clinical studies. Study IC51-325 (Long term immunogenicity and safety of the primary series and immunogenicity and safety of a booster dose in an endemic population in the Philippines) provides the bulk of the data to support licensure for a pediatric booster dose. This is a follow on study to IC51-323, which provided pivotal data for pediatric licensure of the primary series. A detailed review of this study was performed as it is the only study to evaluate safety and effectiveness of a booster dose in pediatric age groups.

Long term immunogenicity and safety data for the primary series in a population of pediatric travelers from non-endemic areas is provided in IC51-324 (a follow on study to IC51-322). A detailed review was conducted although the sample size was limited.

Interim data from study IC51-322 (N=60 subjects) was included in the efficacy supplement (Amendment 125280.125) to support licensure of the primary series for use in pediatric age groups. The final analysis from IC51-322 is included with this submission and mainly provides additional safety data from an additional 40 subjects through 6 months after completion of the primary series. This clinical review summarizes the final safety and immunogenicity analyses in an abbreviated manner.

The studies were reviewed independently as each were substantially different in purpose and population, with only one study utilizing a booster dose. Subsequently, no integrated discussions of safety and efficacy are presented. As no formal immunobridging statistical hypothesis testing was specified in any of the studies, immunogenicity of a pediatric booster dose was compared descriptively to the endemic non-boosted group from IC51-325, the non-boosted group from IC51-324, and previously submitted immunogenicity data in adult and pediatric populations. A similar descriptive approach previously supported licensure of the primary series for use in pediatric populations.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

This clinical review considered the following documents submitted to the BLA, as listed by electronic common technical document (eCTD) module:

- BLA 125280/235.0 Module 5.3.5.1 (Complete study report for IC51-325)
- BLA 125280/235.0 Module 5.3.5.2.1 (Complete study report for IC51-322)
- BLA 125280/235.0 Module 5.3.5.2.2 (Complete study report for IC51-324)
- BLA 125280/235.1 Module 1.11.3 (Response to CBER information request)
- BLA 125280/235.3 Module 1.3.4 (Financial disclosure form 3454)
- BLA 125280/235.4 Module 1.14.1.3 (draft labeling text)
- BLA 125280/235.5 Module 1.14.1.3 (draft labeling text)

5.3 Table of Studies/Clinical Trials

The clinical studies reviewed in this BLA supplement are summarized in Table 2 below.

Table 2: Clinical Studies Discussed in this Review

Study ID	**IC51-325**	**IC51 -324**	**IC51-322**
NCT Number	NCT 01296360	NCT 01246479	NCT 01047839
Phase	3	3	3
IND study	Yes	Yes	Yes
Trial Dates	12/08/2010 to 10/14/2013	10/20/2010 to 9/15/2014	2/24/2010 to 8/9/2013
Study Location	Philippines	U.S, Europe, Australia	U.S, Europe, Australia
Total Participants	298	23	100
Age Range	Nine months to < 17 years and 7 months of age	Nine months to < 21 years of age	Two months to <18 years
IXIARO Regimen	IXIARO booster dose at 11 months after completion of primary series	None	Two IXIARO IM doses 28 days apart
Comparator Regimen	No IXIARO booster dose	None	None
Follow up Duration	36 months	36 months	7 months
Primary endpoints	% of subjects with $PRNT_{50}$ ≥ 1:10 at 1 month after the booster dose	% of subjects with $PRNT_{50}$ ≥1:10 at 12 months after primary series	SAEs and medically attended AEs through Day 56 (1 month post-dose 2)
Non-primary immunogenicity endpoints	$PRNT_{50}$ GMTs at 1 month after booster dose, $PRNT_{50}$ GMTs and % of subjects with $PRNT_{50}$ ≥ 1:10 at 12, 24, 36 months after primary series	$PRNT_{50}$ GMTs at 12 months after primary series, $PRNT_{50}$ GMTs and % of subjects with $PRNT_{50}$ ≥ 1:10 at 24, and 36 months after primary series	$PRNT_{50}$ GMTs and % of subjects with $PRNT_{50}$ ≥ 1:10 at Day 56 and Month 7
Non-primary safety endpoints	Solicited AEs within 7 days after booster dose; unsolicited AEs, medically attended AEs and SAEs through 1 month after booster dose and through Month 36 after primary series	Unsolicited AEs, medically attended AEs, and SAEs through Month 36 after primary series	Solicited AEs within 7 days after each dose; Unsolicited AEs, medically attended AEs, and SAEs through Month 7

5.4 Consultations

None

5.5 Literature Reviewed

- Hombach *et al.* (2005) Report on a WHO consultation on immunological endpoints for evaluation of new Japanese encephalitis vaccines, WHO, Geneva, 2-3, September, 2004, *Vaccine* 23(45):5205-11.
- Plotkin, Stanley A, Walter A. Orenstein, and Paul A. Offit. *Vaccines*. Philadelphia, PA: Elsevier, 2013. Pp.312-351.
- E. Schuller, B. Jilma, V. Voicu, G. Golor, H. Kollaritsch, A. Kaltenbock, *et al.* Long-term immunogenicity of the new Vero cell-derived, inactivated Japanese encephalitis virus vaccine IC51 Six and 12 month results of a multicenter follow-up phase 3 study, Vaccine, 26 (2008), pp. 4382-4386.

- Fischer, M, *et al.* (2010) Japanese encephalitis vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 59:1-27.
- IXIARO [package insert], Intercell USA Inc, Gaithersburg MD; 2015.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 IC51-325

A Phase III, Long term Immunogenicity and Safety Study for a Booster Dose Following Primary Vaccination with IXIARO in a Pediatric Population in a JEV-Endemic Country.

6.1.1 Objectives

Protocol 325 was an open label, randomized Phase 3 study assessing immunogenicity and safety of a single pediatric booster dose 12 months after primary immunization.

The primary objective was to assess the immune response (JEV-neutralizing antibody GMTs and seroconversion rates [SCRs]) at 28 days after a booster vaccination with the purified inactivated Japanese Encephalitis (JE) vaccine IXIARO administered at 12 months after primary immunization in a pediatric population from JEV endemic regions.

Reviewer comment: A neutralizing antibody titer of ≥ 1:10 as measured by $PRNT_{50}$ is the lower limit of detection for the assay and is considered reasonable evidence of protection against JEV disease. The terms “seroconversion” is used throughout the study report by the sponsor to denote any subject with a detectable $PRNT_{50}$ titer and does not take into account positive vs. negative pre-vaccination antibody titers or fold-rise in antibody titer post-vaccination compared to pre-vaccination. The study report also uses the terms “seroprotection rate” to refer to the proportion of subjects with a detectable JEV-neutralizing antibody response ($PRNT_{50}$ titer of ≥ 1:10). For the purposes of this review, the “seroconversion rate” and “seroprotection rate” endpoints will be described as, “proportion of subjects with $PRNT_{50}$ titers of ≥ 1:10.”

The secondary objectives were as follows:

- To assess persistence of immunity (GMTs and proportions of subjects with $PRNT_{50}$ titers of ≥ 1:10) following primary vaccination with IXIARO in a pediatric population from JEV endemic regions (without booster)
- To assess persistence of immunity (GMTs and proportion of subjects with $PRNT_{50}$ titers of ≥ 1:10) following a booster vaccination with IXIARO in a pediatric population from JEV endemic regions
- To assess the long-term safety profile of IXIARO and the safety profile of a booster dose in a pediatric population from JEV endemic regions
- To assess age-dependent differences in the persistence of the immunity, immune response to a booster dose and the safety profile of IXIARO

6.1.2 Design Overview

IC51-323 was a randomized, open-label, active-controlled study conducted in the Philippines. The study began enrollment in March 2010 and concluded in November 2011. IC51-325 was a Phase 3 follow on study evaluating long term immunogenicity over 36 months after primary immunization in IC51-323 as well as safety and immunogenicity for a booster dose administered 11 months after completion of the primary immunization series. Two booster dose levels (0.25 mL and 0.5 mL) were tested

for ages <3 years and 3 years and older, respectively, as age-appropriate doses derived from previous studies.

6.1.3 Population

A total of 300 children 9 months to < 17 years and 7 months of age who had previously been vaccinated with IXIARO in study IC51-323 were included. Planned enrollment (stratified by age at primary vaccination in IC51-323) included 30 subjects 2 months to < 1 year of age, 130 subjects 1 year to < 2 years of age, 80 subjects 2 years to < 11 years of age, and 60 subjects 11 years to < 17 years of age.

Inclusion criteria:

- Children and adolescents who had completed Study IC51-323 and received both IC51vaccinations according to protocol.
- Children who had received the age-appropriate primary immunization dose for their age group.
- Male or female healthy children and adolescents aged ≥ 9 months to < 17 years and 7 months at the time of enrolment into this study.
- Written informed consent provided by the subject's legal representative(s), according to local requirements, and written informed assent of the subject, if applicable.
- Female subjects with either no childbearing potential or a negative pregnancy test (if after onset of menarche) at Visits 1, 2 and 2a as stipulated by the protocol. For females after menarche, a willingness to practice a reliable method of contraception.

Exclusion criteria:

- Vaccination against JE virus (except within Study IC51-323 and Study IC51-325), yellow fever, West Nile virus and dengue fever at any time prior to, or planned during, the study.
- History of or clinical manifestation of any Flavivirus disease during Study IC51-323 or Study IC51-325.
- Participation in another study with an investigational drug during Study IC51-323 or Study IC51-325.
- Planned active or passive immunization within 2 weeks before and 1 week after the IC51 booster.
- History of or development of any immunodeficiency including post-organ-transplantation after inclusion into Study IC51-323 or Study IC51-325.
- History of or development of an autoimmune disease during Study IC51-323 or Study IC51-325.
- Administration of chronic (defined as more than 14 days) immunosuppressants or other immune-modifying medications started during Study IC51-323 or Study IC51-325.
- Acute febrile infection at Visit 2 (only for the Booster Group).
- Pregnancy (positive pregnancy test at Visit 1 and Visit 2), lactation or unreliable contraception in female subjects after onset of menarche.
- Hypersensitivity reactions to IC51 or AEs in Study IC51-323 requiring withdrawal from further vaccination or anaphylaxis, or severe cases of atopy requiring emergency treatment or hospital admission during Study IC51-323 or Study IC51-325.

- History of urticaria after hymenoptera envenomation, drugs, physical or other provocations or of idiopathic cause during Study IC51-323 or Study IC51-325.
- Known infection with human immunodeficiency virus (HIV), hepatitis B virus
- Illicit drug use and/or current drug or alcohol addiction.
- Inability or unwillingness by the legal representative(s) and/or the subject (where applicable) to provide informed consent/assent and to abide by the requirements of the study.
- Persons who had been committed to an institution (by a court or by an authority).

6.1.4 Study Treatments or Agents Mandated by the Protocol
Subjects were randomized 1:1 to receive an IXIARO booster dose (0.25 mL dose for subjects < 3 years of age, 0.5 mL dose for subjects 3 years or older) or no further immunizations at 11 months after completion of the IXIARO primary series.

Reviewer comment: The study design (open-label without a placebo comparator) allows for reporting bias from both patients and investigators. However, the primary study objective is a descriptive analysis of immunogenicity in the context of an immune response generally accepted to confer protection against disease, rather than a formal comparison between treatment groups. The study design does include randomization to help minimize selection bias.

IXIARO was available as a suspension of 6 µg of purified, inactivated virus per 0.5 mL dose in a pre-filled single-use syringe. Each dose contained 0.1% aluminum hydroxide adjuvant. A single commercial batch: JEV10C48B was used for the study.

Reviewer comment: The antigen content of vaccine at the time of the study was determined as µg/mL. In a subsequent manufacturing supplement, the applicant changed the specifications for antigen content to antigen units per mL, which is roughly equivalent to the antigen content measured as µg/mL The vaccine is currently available at a dose of 6 antigen units per 0.5 mL.

6.1.5 Directions for Use

Study participants $\geq$ 3 years of age were assigned to receive the 0.5 mL dose of IXIARO and were vaccinated with the licensed 0.5 mL pre-filled syringe. For study participants < 3 years of age the assigned 0.25 mL dose of IXIARO was withdrawn from the 0.5 mL pre-filled syringe using a separate tuberculin syringe and then injected from the tuberculin syringe.

Reviewer comment: The method of administration for the 0.25 mL dose differs from the licensed method of administration (expulsion of 0.25 mL from the pre-filled syringe using a half-dose guide mark, followed by injection of the remaining contents). The minor differences are unlikely to significantly affect the resultant safety or immunogenicity data.

6.1.6 Sites and Centers

Three study sites within the Philippines (a JE virus endemic country) were used for this study:

- Research Institute for Tropical Medicine - Clinical Research Division Muntinlupa City, Alabang, Philippines, 1781
- Research Institute for Tropical Medicine

Muntinlupa City, Alabang, Philippines, 1781

- UP-Philippine General Hospital
  Manila, Philippines, 1000

6.1.7 Surveillance/Monitoring

Table 3 summarizes the surveillance and monitoring for study IC51-325

Table 3: Surveillance and Monitoring for IC51 - 325

Visit	**1**	**2**	**2a[2]**	**3**	**4**
Time point after first vaccination in IC51-323	**Month 7**	**Month 12**	**Month 13**	**Month 24**	**Month 36**
PE, Vital Signs	X	X		X	X
Eligibility criteria	X				
PRNT blood sampling	X	X	X	X	X
Hematology	X				
Biochemistry	X				
Urinalysis	X				
Urine pregnancy test	X				
Concomitant medications	X	X		X	X
Adverse events	X	X		X	X
Assessment of injection site[1]		X			
Dispense diary		X			
Collect and review diary				X	
IC 51 Booster vaccination		X			

Adapted from BLA 125280/235, Module 5.3.5.1 – Clinical Study Report IC51-325, Table 9.2 and Table 9.3

[1]Assessed after 60 minutes and 30 days from subjects assigned to receive IXIARO booster dose at these visits

[2]Visit only occurred for subjects randomized to receive the booster dose.

Scheduled follow ups occurred at clinic study sites. For seven days following study vaccination, subjects' parents or guardians used diary cards to record daily temperatures, solicited and unsolicited AEs, and concomitant medications. Safety data was captured using an electronic case report form (eCRF). Captured eCRFs were then regularly reviewed by a designated study safety monitor.

Unsolicited AEs were followed by the investigators until resolution or until the medical condition of the subject was stable. AEs were graded and causality was reported by the investigator according to pre-specified criteria. An independent data safety monitoring board (DSMB) reviewed all cases of suspected serious adverse reactions.

6.1.8 Endpoints and Criteria for Study Success

Two primary endpoints were used to assess the immune response to IXIARO: the GMT for neutralizing antibodies against JEV and the proportion of subjects with neutralizing antibody titer ≥ 1:10 at one month after the booster dose. JEV neutralizing antibody titers were measured by a validated plaque reduction neutralization assay using a 50% plaque reduction endpoint ($PRNT_{50}$)

Secondary endpoints used to assess the immune response to IXIARO included pre-booster dose $PRNT_{50}$ titers to evaluate antibody persistent after primary immunization, and geometric mean increases in individual titers after the booster dose. Serologic evaluations for antibody persistence were performed at months 12, 24 and 36 for all subjects.

Safety endpoints evaluated were the proportions of subjects reporting the following:

- Solicited AEs within 7 days after booster dose
- Unsolicited AEs through Month 36 after the primary series
- SAEs or medically attended AEs throughout the study duration.
- SAEs, medically attended AEs, or unsolicited AEs one month following the booster dose

Reviewer comment: The endpoints for this study were appropriate to evaluate the safety and immunogenicity of IXIARO when administered as a booster dose. No pre-specified criteria for success were provided for immunogenicity endpoints, which mirrors the approach for supporting effectiveness of a booster dose in adults and the primary series in pediatric age groups.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The statistical analysis plan included descriptive analyses only without formal hypothesis testing. The planned sample size of 300 subjects was selected to provide adequate subject numbers for GMT estimates (with an assumed dropout rate of 20%).

All safety analyses were performed on the safety population (subjects who entered into the study and were randomized). The intent-to-treat population was the primary analysis population for immunogenicity (all subjects randomized, analyzed per the treatment group to which they were randomized). These analyses were repeated for the per protocol population (all subjects as treated without major protocol deviation). Major protocol deviations were defined as subjects in the booster group who did not receive the booster dose, subjects with confirmed immunosuppressive or immunodeficient condition, subjects with acute febrile infection, and subjects vaccinated against JE/yellow fever/dengue/West Nile virus at any time.

6.1.10 Study Population and Disposition

Subjects included children ages 9 months to < 17 years and 7 months who were previously enrolled in IC51-323 and who met the eligibility criteria for this study.

6.1.10.1.1 Demographics and Baseline Characteristics
Table 4 below summarizes the demographic data for participants in study IC51-325.

Table 4: Demographics for IC51 - 325

Demographic parameter	Booster (N=150)	Non-booster (N = 150)	Total (N=300)
Mean age at primary vaccination, years (SD)	4.52 (5.05)	4.65 (5.1)	4.58 (5.07)
Age 2 months to 1 year	15	15	30
Age 1 to 3 years	95	92	187
Age 3 to 12 years	11	16	27
Age 12 to 17 years	29	27	56
Gender – female (%)	72 (48%)	79 (52.7%)	151 (50.3%)
Race – Asian (%)	150 (100%)	150 (100%)	300 (100%)

Adapted from BLA 125280/235, Module 5.3.5.1 – Clinical Study Report IC51-325, Table 10.2 and Figure 10.1
*Age represents age at enrollment.

Reviewer comment: There were no major imbalances between treatment groups with respect to gender or ethnicity. Plans for enrollment stratification included greater numbers of subjects 3 to 12 years of age than were actually enrolled. Enrollment was voluntary and limited to subjects previously enrolled in IC51-323, limiting the ability for additional recruitment in this age group. The higher than expected representation of subjects one to three years of age is unlikely to significantly alter the interpretation of resultant immunogenicity data, and some children who were <3 years of age at enrollment were 3 years of age or older at booster vaccination and thus received the 0.5 mL booster dose.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
The majority (66.3%) of subjects reported no medical history. The most frequently reported medical history included a previous history of infections and infestations (28.7% of subjects). No imbalances between treatment groups were noted.

Baseline serostatus for JEV and DENV (prior to primary vaccination) was assessed and summarized in Table 5 below.

Table 5: Baseline JEV and DENV Serostatus for The Safety Population in Study IC51-325

Demographic parameter	Booster n/N (%)	Non-booster n/N (%)	Total n/N (%)
Proportion JEV seropositive	19/150 (12.7)	15/150 (10)	34/300 (11.3)
2 to < 12 months	0/15 (0)	1/16 (6.7)	1/30 (3.3)
1 to < 3 years	3/95 (3.2)	0/92 (0)	3/187 (1.6)
3 to < 12 years	0/11 (0)	4/16 (25)	4/27 (14.8)
12 to <17 years	16/29 (55.2)	10/27 (37)	26/56 (46.4)
Proportion DENV seropositive	41/150 (27.3)	44/150 (29.3)	85/300 (28.3)
2 to < 12 months	2/15 (13.3)	1/15 (6.7)	3/30 (10)
1 to < 3 years	10/95 (10.5)	8/92 (8.7)	18/187 (9.6)
3 to <12 years	6/11 (54.5)	10/16 (62.5)	16/27 (59.3)
12 to <17 years	23/29 (79.3)	25/27 (92.6)	48/56 (85.7)

Adapted from BLA 125280/235, Module 5.3.5.1 – Clinical Study Report IC51-325, Table 10.3

Reviewer comment: Both the ITT and PP populations had similar baseline serostatus data to the safety population detailed above. Age-specific differences between treatment groups in baseline rates of JEV and DENV seropositivity may be due to the small sample sizes. Furthermore, these baseline rates reflect serostatus prior to primary vaccination with IXIARO, which elicited high-titer neutralizing antibody responses in nearly all subjects in study IC51-323. It would therefore be hard to draw clinically meaningful conclusions on the difference in serologic response to booster dosing based on baseline JEV or DENV serostatus.

6.1.10.1.3 Subject Disposition

Of the 300 randomized subjects, 297 subjects presented to visit 2/2a for Month 12 immunogenicity evaluation and administration of IXIARO booster dose (for the treatment group). The study was completed by 95.3% (286) subjects with no withdrawals secondary to adverse events. A total of twenty three subjects from the ITT population (23/300 or 7.7%) were excluded from the per protocol population secondary to major violations (12 from the booster group, 11 from the non-booster group). The majority of these (18 subjects) were lost to follow up (11) or reported for a follow up visit outside of the acceptable range of days (7). The remaining exclusions were due to individual instances of a febrile infection, use of immunosuppressive medication, use of another investigational vaccine, administration of an incorrectly dosed booster for age, and missing GMT results.

Reviewer comment: The number of premature discontinuations and major protocol deviations were generally low and similar between treatment groups.

6.1.11 Efficacy Analyses

Clinical efficacy was not assessed in this study. Efficacy in this study was inferred from analyses of primary immunogenicity endpoints.

6.1.11.1 Analyses of Primary Endpoint(s)

The results of the primary immunogenicity analyses for the intent to treat population are summarized as follows:

The following table shows proportions of subjects with $PRNT_{50}$ titers ≥ 1:10.

Table 6: Proportion of subjects with JEV antibody $PRNT_{50}$ titers ≥ 1:10 by treatment group.

Treatment Group	**0.25 mL booster dose[1]** n/N (%)	**0.5 mL booster dose[2]** n/N (%)	**All Booster recipients** n/N (%)	**Non-booster** n/N (%)
Visit 1 (Month 7)	75/81 (93%)	57/67 (85.1%)	132/148 (89.1%)	129/150 (86%)
Visit 2 (Month 12)	79/81 (97.5%)	60/67 (89.6%)	139/148 (93.9%)	134/149 (89.9%)
Visit 2a (Month 13)	81/81 (100%)	67/67 (100%)	148/148 (100%)	NA*
Visit 3 (Month 24)	80/80 (100%)	67/67 (100%)	147/147 (100%)	130/146 (89%)
Visit 4 (Month 36)	76/76 (100%)	67/67 (100%)	143/143 (100%)	128/142 (90.1%)

Adapted from BLA 125280/235, Module 5.3.5.1 – Clinical Study Report IC51-325, Addendum Month 36 Table 14.2.1.1

[1]Subjects 14 months to < 3 years of age
[2]Subjects 3 years of age or greater
*NA = not assessed

Reviewer Comment: The proportion of subjects with a $PRNT_{50}$ titer ≥ 1:10 remained high in the non-booster group in this endemic population (90.1% at study completion). The booster dose was associated with 100% of subjects achieving $PRNT_{50}$ titers of ≥ 1:10 from 1 month post-booster through the end of the study. Notably at 11 months after completion of primary immunization 92% of all subjects maintained seroprotective titers. This is considerably higher than corollary estimates from studies in adult travelers from non-endemic areas (see Section 2.4). While it is possible that natural boosting from exposure to JEV occurred in these pediatric subjects living in an endemic area, similar proportions of subjects with protective JEV-neutralizing antibody titers at up to three years after completion of the primary series were seen in Study IC51-324, conducted in non-endemic pediatric travelers (see Section 6.2).

The following tables show the immunogenicity results stratified by age group for both dosing regimens:

Table 7: Proportion of subjects with JEV antibody $PRNT_{50}$ titers ≥ 1:10 and GMTs by age group (at primary immunization) for the 0.25 mL booster group.

Visit	Age Group	N	n (%) $PRNT_{50}$ titers ≥ 1:10	GMTs (95% CI)
Visit 2 (Month 12)	2 to < 12 months	15	15 (100)	62.2 (41 – 94))
Visit 2 (Month 12)	1 to < 3 years	66	64 (97)	68.5 (53 – 88))
Visit 2a (Month 13)	2 to < 12 months	15	15 (100)	4075.9 (2403-6912)
Visit 2a (Month 13)	1 to < 3 years	66	66 (100)	2696.4 (1989-3654)
Visit 3 (Month 24)	2 to < 12 months	15	15 (100)	622.54 (270-1432))
Visit 3 (Month 24)	1 to < 3 years	65	65 (100)	561.34 (385-816)
Visit 4 (Month 36)	2 to < 12 months	14	14 (100)	534.64 (248-1152)
Visit 4 (Month 36)	1 to < 3 years	62	62 (100)	406.43 (286-576)

Adapted from BLA 125280/235, Module 5.3.5.1 – Clinical Study Report IC51-325, Table 11.4

Table 8: Proportion of subjects with JEV antibody $PRNT_{50}$ titers ≥ 1:10 and GMTs by age group (at primary immunization) for the 0.5 mL booster group.

Visit	Age Group	N	n (%) $PRNT_{50}$ titers ≥ 1:10	GMTs (95% CI)
Visit 2 (Month 12)	1 to < 3 years	28	22 (78.6)	32.2 ()
Visit 2 (Month 12)	3 to < 12 years	11	10 (90.9)	26.2 (14 - 49)
Visit 2 (Month 12)	12 to <17 years	28	28 (100)	60.1 (40-90)
Visit 2a (Month 13)	1 to < 3 years	28	28 (100)	2029.3 (1214-3393)
Visit 2a (Month 13)	3 to < 12 years	11	11 (100)	1483.9 (673-3271)
Visit 2a (Month 13)	12 to <17 years	28	28 (100)	889.9 (537-1474)
Visit 3 (Month 24)	1 to < 3 years	28	28 (100)	417.4 (233-747)
Visit 3 (Month 24)	3 to < 12 years	11	11 (100)	263.5 (112-618)
Visit 3 (Month 24)	12 to <17 years	28	28 (100)	230.7 (134-395)
Visit 4 (Month 36)	1 to < 3 years	28	28 (100)	350.8 (191-644)
Visit 4 (Month 36)	3 to < 12 years	11	11 (100)	254.1 (121-533)
Visit 4 (Month 36)	12 to <17 years	28	28 (100)	231.5 (143-374)

Adapted from BLA 125280/235, Module 5.3.5.1 – Clinical Study Report IC51-325, Table 11.4

Reviewer Comment: The proportion of subjects with a $PRNT_{50}$ titer ≥ 1:10 following the booster dose was 100% across all age subgroups for the duration of the study. GMTs waned over time but remained notably above pre-booster GMTs through 24 months after booster dosing. Results in the per-protocol analysis mirrored the data from the ITT population presented above. In general, the magnitude of booster response was lower with increasing age, similar to antibody responses to primary vaccination. Please see Section 6.1.11.3 for further discussion.

6.1.11.2 Analyses of Secondary Endpoints

Persistence of JEV-neutralizing antibodies is demonstrated above in Table 5. GMTs after primary immunization and booster dose through the last study visit, comparing the booster group and non-booster group are demonstrated in Table 9 below:

Table 9: GMTs with and without a booster dose through study window (ITT population)

Visit	Booster Group GMTs (95% CI) (N)	Non-booster Group GMTs (95% CI) (N)
1 (Month 7)	51.96 (42.5 – 63.5) (N= 150)	41.85 (34.5 – 50.9) (N= 150)
2 (Month 12)	53.41 (44.7 – 63.8) (N= 148)	45.53 (37.8 – 54.8) (N= 148)
2a (Month 13)	2066.6 (1670.8 – 2556.2) (N= 150)	NA*
3 (Month 24)	427.73 (335.1 – 546)) (N= 147)	49.8 (40.6 – 61.1) (N= 146)
4 (Month 36)	350.40 (279.2 – 439.8) (N= 143)	59.36 (48.43 – 72.8) (N= 142)

Adapted from BLA 125280/235, Module 5.3.5.1 – Clinical Study Report IC51-325 Addendum Month 36, Table 14.2.2.1
*NA = not assessed

6.1.11.3 Subpopulation Analyses

Analyses were performed stratifying GMTs by gender. JEV-neutralizing antibody titers were nominally higher for females compared to males at all time points; however differences were statistically non-significant with overlapping 95% CI. No stratifications by ethnicity were possible given the uniform study population of Asian subjects. In the booster group, older age groups demonstrated lower post-booster GMTs at the Month 13, Month 24 and Month 36 visits (Tables 6 and 7 above), consistent with the more rapidly diminishing immune response seen in older age groups following primary immunization in study IC51-323. Age related differences were also seen in GMTs for subjects in the non-booster dose group. Month 36 GMT point estimates were 81.49 for subjects 2 months to < 1 year, 58.1 for subjects 1 year to < 3 years, 80.15 for subjects 3 years to < 12 years, and 44.8 for subjects 12 to 17 years of age, continuing the trend seen through Month 7 in study IC51-323. The effects of baseline JEV and DENV serostatus on $PRNT_{50}$ GMTs are difficult to interpret and not included here given the extraordinarily low (2 subjects receiving 0.25mL and 7 subjects receiving 0.5mL booster doses of IXIARO) seronegative rate prior to booster dosing. In general GMTs trended higher for subjects who were DENV baseline seropositive (similar to observations for the primary series), with unclear clinical significance.

6.1.11.4 Dropouts and/or Discontinuations

The limited and balanced number of discontinuations and dropouts did not likely impact immunogenicity evaluations.

6.1.12 Safety Analyses

6.1.12.1 Methods

All safety analyses were conducted on the safety population, consisting of all subjects randomized to treatment assignment. Diary cards were used to record daily temperatures and solicited AEs over seven days post booster dose vaccination. Solicited AEs included injection site reactions (pain, itching, tenderness, hardening, swelling, and redness) as well as the following systemic symptoms: irritability, nausea, vomiting, diarrhea, flu-like symptoms, excessive fatigue, muscle pain, rash, headache, loss of

appetite, and fever. Unsolicited AEs were collected during a 1-hour observation period following study vaccination and at clinic follow-up visits.

6.1.12.2 Overview of Adverse Events

An overview of safety data through Month 36 is presented below stratified by age group. These analyses include primary safety endpoints of proportion of participants with at least one SAE or medically attended AE after booster dose.

Table 10: Safety Data through Month 36 for subjects in IC51-325 (Booster Group)

Age at booster	9 months to < 3 years (N = 80) n (%)	3 to < 12 years (N = 39) n (%)	12 to < 18 years (N = 29) n (%)
Death	0	0	0
SAE	4 (5)	1(2.5)	2(6.9)
Related SAE	0	1 (2.5)	0
Medically attended AE	34 (42.5)	13 (31.6)	5 (17.2)
Related medically attended AE	0	1 (2.5)	0
Solicited AE	11 (13.8)	11 (26.3)	7 (24.1)
Unsolicited AE	48 (60)	23 (58)	13 (44.8)
Probably related	0	0	0
Possibly related	0	1	0
Solicited or unsolicited AEs by severity grade			
Grade 1	35 (43.8)	21 (55.3)	13 (44.8)
Grade 2	12 (15)	5 (13.2)	2 (6.9)
Grade 3	2 (2.5)	1 (2.5)	1 (3.4)
Grade 4	0	0	0

Adapted from BLA 125280/235, Module 5.3.5.1 – Clinical Study Report IC51-325, Table 12.5

Table 11: Safety Data through Month 36 for study IC51-325 (Non-Booster Group)

Age at primary series	2 to < 12 months (N = 15) n (%)	1 to < 3 years (N = 92) n (%)	3 to < 12 years (N = 16) n (%)	12 to < 17 years (N = 27) n (%)
Death	0	0	0	0
SAE	0 (0)	1 (2.5)	0	2 (7.4)
Related SAE	0	1 (2.5)	0	0
Medically attended	10 (66.7)	13 (31.6)	5 (17.2)	7 (25.9)
Related medically attended	0	1 (2.5)	0	0
Unsolicited AE	12 (80)	66 (71.7)	9 (56.3)	13 (48.1)
Probably related	0	0	0	0
Possibly related	0	0	0	0
Unsolicited AEs by severity grade				
Grade 1	10 (66.7)	57 (62)	9 (56.3)	9 (33.3)
Grade 2	2 (13.3)	7 (7.6)	0	3 (11.1)
Grade 3	0	2 (2.2)	0	1 (3.7)
Grade 4	0	0	0	2 (7.4)

Adapted from BLA 125280/235, Module 5.3.5.1 – Clinical Study Report IC51-325, Table 12.3

Solicited AEs stratified by dosing group are presented below in Table 12.

Table 12. Rates of Solicited Adverse Reactions on Days 0-7 After IXIARO Booster Dose, by Treatment Group

Injection Site Reactions	0.25 mL booster recipients n/N (%)	0.5 mL booster recipients n/N (%)
Pain	0/56	6/64 (9.4)
Itching	0/56	0/64
Tenderness	1/81 (1.2)	3/67 (4.5)
Hardening	0/81	1/67 (1.5)
Swelling	3/81 (3.7)	1/67 (1.5)
Redness	1/81 (1.2)	0/67
Solicited Systemic Reactions		
Irritability	2/81 (2.5)	0/67
Nausea	0/57	0/63
Vomiting	0/81	1/67 (1.5)
Diarrhea	0/81	1/67 (1.5)
Flu-like symptoms	1/57 (1.8)	0/67
Excessive fatigue	1/81 (1.2)	0/67
Muscle pain	0/56	2/63 (3.2)
Rash	1/81 (1.2)	1/67 (1.5)
Headache	0/56	3/67 (4.5)
Loss of appetite	3/81 (3.7)	3/67 (4.5)
Fever	6/81 (7.4)	6/67 (9.0)

Adapted from BLA 125280/235.7, Table 1 – Response to Questions 0279

Rates of Solicited AEs were low (14.8% of subjects receiving 0.25mL dosage and 25.4% of subjects receiving the 0.5mL dosage). In the 0.25 mL dosage group the most common solicited AEs were fever (7.4%), swelling (3.7%), and loss of appetite (3.7%). In the 0.5 mL dosage group the most common solicited AEs were pain (9.4%), fever (9.0%), and headache (4.8%). Most of these solicited AEs were rated as Grade 1 in severity, and no Grade 4 solicited AEs were reported. In the 0.25mL dosage group five Grade 3 solicited AEs were reported (singular reports of Grade 3 redness, swelling, flu-like symptoms, excessive fatigue, and loss of appetite). In the 0.5mL dosage group there were no reported Grade 3 solicited AEs.

Overall 56% of subjects receiving a booster dose versus 66.7% of subjects in the non-booster group reported at least one unsolicited AE through month 36. Infections/Infestations predominated with a majority in both treatment arms with a large majority constituting upper respiratory infections. Other unsolicited AEs with an incidence > 10% were pyrexia and injury. Only one unsolicited AE (lumbar abscess) was assessed as "possibly related" and was the sole related medically attended AE (details below in 6.1.12.4). No Grade 4 unsolicited AEs were reported with only three total Grade 3 events in the booster group, all unrelated to vaccination: One subject was diagnosed with dengue fever 12 months after vaccination, another was diagnosed with pneumonia 13 months after vaccination, a third subject was also diagnosed with pneumonia 11 months after vaccination. Two Grade 4 unsolicited AEs secondary to injury were reported in the non-booster group in a single subject (stabbing requiring hospitalization and traumatic pneumothorax).

Reviewer Comment: The overall reactogenicity profile of the booster dose was milder when compared to data presented in study IC51-323, which supported licensure of the primary series. Reported fevers were almost entirely Grade 1 (11/12 episodes, with a single instance of Grade 2 fever). No febrile seizures were reported after immunization. Overall, rates of solicited and unsolicited AEs are nominally reduced from those in the primary series, and no new safety signals were observed.

6.1.12.3 Deaths

There were no deaths in this study.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 10 subjects (7 in the booster group and 3 in the non-booster group) each reported a single SAE during the study period. None were assessed by the sponsor as possibly, probably, or definitely related to the study product.

- A three year old male received his booster dose in the left deltoid area on 26 May 2011. The subsequent day he developed fever and back pain. A mass was noted by his mother on his right flank the next week prompting admission to the hospital on June 6. The subject underwent incision and drainage of his lumbar abscess and was treated successfully with drainage and antibiotics. Review by DSMB suggested that given the remote location from vaccination the product was unlikely to have caused the abscess. However, due to the close temporal relationship, the SAE was assessed by the investigator as possibly related to the study product but assessed by the DSMB and the sponsor as unrelated to the study product.

- A one year old female suffered a traumatic distal fingertip amputation from an accident playing near a power drill.
- A thirteen year old male in the non-boosted group suffered intermittent muscle weakness and pain almost three years after primary series. The patient developed loss of distal motor strength and was found to be severely hypokalemic. There was no evidence of demyelinating axonal disease, and his symptoms resolved with fluid resuscitation and potassium repletion.
- A two year old female developed pneumonia requiring hospitalization two months after receiving her booster dose. She was discharged in 48 hours to complete oral antibiotics.
- A fourteen year old girl developed a urinary tract infection two months after receipt of her booster dose. An incidental adnexal mass was noted, which was no longer seen on repeat ultrasounds.
- A 2 year old female developed diarrhea and vomiting 22 months after her booster dose. She was subsequently found to have amoebic dysentery and treated with resolution.
- A 14 month old female developed vomiting and diarrhea six months after her booster dose and was diagnosed with gastroenteritis, with ameobiasis seen on fecal examination. She was treated with antiparasitic drugs with resolution of her symptoms.
- A 16 year old male who did not receive a booster dose was involved in a street fight and obtained a penetrating chest trauma and pneumothorax requiring hospitalization.
- A 16 year old male developed fever, anorexia, malaise, muscle pain and vomiting one month after receiving the booster dose. He was hospitalized for mucosal bleeding and subsequently diagnosed with dengue fever. His symptoms resolved with symptomatic care over 72 hours.
- A two year old male who did not receive the booster dose was hospitalized after an acute fall with associated emesis. The patient was diagnosed with a concussion after negative neuroimaging.

Reviewer comment: The majority of SAEs were infections of clear bacterial, parasitic, or viral etiology remote in pathology and temporally to the study product. There were also instances of unrelated trauma. The single instance deemed possibly related to the study product is a remote skin/soft tissue infection at the time of vaccination. Improperly sanitized injection sites may cause a skin/soft tissue infection. However, these infections would be expected to be anatomically related to the injection site. The single SAE assessed by the investigator as likely related represents a discrete infection (lumbar abscess) that was in this reviewer's opinion unlikely related to vaccination in the left deltoid. Thus, this reviewer agrees with the sponsor's assessments for that all reported SAEs were unrelated to IXIARO.

6.1.12.5 Adverse Events of Special Interest (AESI)

Based on prior experience with JE-VAX AESIs include neurological disorders and hypersensitivity reactions. These reactions were thought to be related to gelatin used in production of JE-VAX. IXIARO does not contain gelatin as an excipient and prior monitoring during vaccine development and post-marketing surveillance has not demonstrated significant increased risk for hypersensitivity events or neurological disorder. IXIARO does contain protamine sulfate, and known allergies to protamine sulfate are a contraindication. MedDRA terms used for analysis for hypersensitivity

included anaphylactic reactions, rash, dermatitis, pruritus, wheezing, angioedema, asthma. MedDRA terms used for analysis for neurological disorders included Guillain-Barre Syndrome, neuritis, paresthesia, neuralgia, encephalitis, meningitis, and convulsion. No potential AESIs (including neurological AEs) were reported during the study.

6.1.12.6 Clinical Test Results

There were no reported AEs associated with vital signs or clinically significant changes in hematology and chemistry parameters.

6.1.12.7 Dropouts and/or Discontinuations

The rate of discontinuation was very low and was unlikely to affect safety evaluations. No participants discontinued participation due to an AE.

6.1.13 Study Summary and Conclusions

This was a randomized, open-label study to assess the safety and immunogenicity of an IXIARO booster dose 11 months after completion of the primary series in infants, children, and adolescents 2 months to < 17 years of age living in a region endemic for JEV. The design of the study was appropriate, and the quality of the data appears to be adequate.

Immunogenicity was used as an indirect measure of vaccine effectiveness. The majority of subjects remained above an accepted threshold for protection ($PRNT_{50}$ titer ≥ 1:10) without a booster dose (86-90% throughout study period) overall GMTs increased substantially after a booster dose (100% of boosted subjects with a $PRNT_{50}$ titer ≥ 1:10 throughout study period) and demonstrated persistence of higher overall titers, suggesting that the booster dose could extend the duration of protective immunity. There were no clinically significant differences in immunogenicity measures when results were stratified by JEV or DENV serostatus. There was a minimal and not clinically significant difference in these same measures when stratified by gender.

In terms of safety, IXIARO was generally well tolerated as a single booster dose with an acceptable safety profile similar to or better tolerated than the IXIARO primary series and other U.S.-licensed vaccines. Only one SAE was deemed by the sponsor as possibly related to the study vaccine and was assessed by this reviewer as unlikely vaccine related.

In conclusion, this study supports the safety and immunogenicity of an IXIARO booster dose in infants, children, and adolescents 2 months to < 17 years of age at one year after the primary series. Although the long term immunogenicity data obtained after primary vaccination shows that ~90% of individuals in pediatric age groups maintain protective JEV-neutralizing titers through 1-3 years after completion of the primary series, the severity of Japanese encephalitis disease and benign safety profile of the booster dose support licensure of a booster dose for pediatric use to cover the ~10% of children who may not be protected 1 year or later after primary vaccination and who are expected to have continued exposure to JEV. Even so, we acknowledge that titers below the level of detection may still be protective, and data from this trial does not provide sufficient information to definitively determine what proportion of children are susceptible to JEV disease at one year after primary vaccination. A detailed discussion of the

risk/benefit of an additional booster dose to primary immunization is discussed in Section 11.

6.2 Trial #2 IC51 - 324

Long term immunity and Safety Following Vaccination with the Japanese Encephalitis Vaccine IC51 in a Pediatric Population in Non-Endemic Areas, Uncontrolled, Phase 3 Follow-Up Study.

6.2.1 Objectives (Primary, Secondary, etc)

IC51-324 was a Phase 3 study to assess the long term immunity and safety following primary vaccination with IXIARO in infants, children, and adolescents 9 months to < 21 years of age in non-endemic regions. The study consisted of the long term follow up of subjects enrolled in IC51-322 (a Phase 3 safety and immunogenicity study evaluating non-endemic subjects vaccinated with IXIARO primary series).

The primary objective was to assess immunogenicity of IXIARO by JEV $PRNT_{50}$ GMTs and proportion of participants with $PRNT_{50}$ titer ≥ 1:10 in children from areas where JE is not endemic.

Secondary objectives included assessing the long term safety of IC51 in a pediatric population where JE is not endemic and evaluating for age-dependent differences on persistence of immunity.

6.2.2 Design Overview

The study encompassed four visits for subjects previously enrolled in IC51-322. These subjects received two doses of IC51 at the now licensed primary series dosage and interval prior to travel to JEV-endemic areas. Additional visits were scheduled at 12, 24, and 36 months (+/- 1 month) with study enrollment occurring concomitantly with the final IC51-322 visit at 7 months (or within one month later). Additional blood samples for determination of JEV antibodies, updated medical histories, and recording of AEs were performed at each visit.

6.2.3 Population

Healthy male and female children and adolescents were enrolled at multiple clinic sites in the U.S., Europe, and Australia.

Inclusion criteria:

- Subjects who have received 2 vaccinations of IC51 in study IC51-322.
- Subjects who were enrolled as part of the immunogenicity subgroup of study IC51- 322.
- Male or female healthy subjects ≥ 9 months to < 21 years of age at the time of enrollment into this study.
- Written informed consent by the subject, subject's legal representative(s), according to local requirements, and written informed assent of the subject, if applicable.

Exclusion criteria:

- Clinical manifestation or history of any Flavivirus disease during study IC51-322.
- Vaccination against JE (except within IC51).

- Participation in another study with an investigational drug during study IC51-322 or IC51-324.
- History or development of immunodeficiency including post-organ-transplantation after inclusion into study IC51-322.
- History or development of an autoimmune disease during study IC51-322.
- Administration of chronic (defined as more than 14 days) immunosuppressants or other immune-modifying drugs started during study IC51-322 up to first visit of study IC51-324. (For corticosteroids, this meant prednisone, or equivalent, ≥ 0.05 mg/kg/day. Topical and inhaled steroids were allowed).
- Known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV).
- Illicit drug use, and/or a history of drug or alcohol addiction, and/or current drug or alcohol addiction.
- Inability or unwillingness by the legal representative(s) and/or the subject (where applicable) to provide informed consent/assent and to abide by the requirements of the study.
- Persons who had been committed to an institution (by a court or by an authority).

6.2.4 Study Treatments or Agents Mandated by the Protocol

No investigational medicinal product was administered in this study. The parent study (IC51-322) administered IXIARO as a 0.25mL or 0.5mL dose to subjects 2 months to < 3 years of age and 3 years to < 18 years of age, respectively, at Days 0 and 28.

6.2.5 Directions for Use

Vaccination procedures in the parent study were the same as described for IC51-325 detailed above.

6.2.6 Sites and Centers

Six study sites in Germany (2), Australia (2) and the U.S. (2) were used. All sites were included form the parent study.

6.2.7 Surveillance/Monitoring

The safety monitoring for study IC51-324 was conducted as a review at each follow up visit. No solicited AEs or diary cards were provided.

Reviewer comment: Given the absence of any investigational products in this study, the limited monitoring provided was appropriate.

Table 13: Surveillance and Monitoring for IC51 - 324

Visit	1	2	3	4
Time point after first vaccination in IC51-323	**Month 7**	**Month 12**	**Month 24**	**Month 36**
PE, Vital Signs	X	X	X	X
Eligibility criteria	X	X		
PRNT blood sampling	X	X	X	X
Hematology	X			
Biochemistry	X			
Urinalysis	X			
Urine pregnancy test	X			
Concomitant medications	X	X	X	X
Adverse events	X	X	X	X
Medical/Social history	X	X	X	X

Adapted from BLA 125280/235, Module 5.3.5.2.2 – Clinical Study Report IC51-324, Table 9.1

6.2.8 Endpoints and Criteria for Study Success

The primary endpoint for this study was the proportion of subjects with $PRNT_{50}$ titer ≥ 1:10 at Month 12 (11 months after completion of the primary series).

Secondary endpoints included:

- GMTs for JEV neutralizing antibodies using $PRNT_{50}$ at Month 12.
- GMTs for JEV neutralizing antibodies using $PRNT_{50}$ and proportion of subjects with $PRNT_{50}$ titer ≥ 1:10 at Months 24 and 36.
- Rates of subjects with AEs, SAEs, and medically-attended AEs throughout study period.

No statistical success criteria were specified as there was no formal hypothesis testing.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The SAP included descriptive analyses only. No formal sample size calculations were performed. The study was intended to enroll 20 to 80 subjects as feasible.

6.2.10 Study Population and Disposition

Twenty-three subjects who were previously enrolled in IC51-322 and who met the eligibility criteria for this study were included.. The majority of subjects (19/23 or 82.6%) were in the 12 to < 18 years of age subgroup.

6.2.10.1 Populations Enrolled/Analyzed

The safety and ITT populations are identical and included all subjects who entered into the study. The PP population excluded all subjects with a major protocol deviation (e.g., immunosuppressive condition, intercurrent vaccination against JE, yellow fever, dengue fever, or West Nile virus, or visit outside of allowable window). Seven subjects (30.4%) were excluded from the Per Protocol population before the 12 month visit. Of these, two had received prohibited immunosuppressive medications, four subjects were lost to follow up, one subject's original vaccination was improperly stored, and three were instances of visits outside of the allowable window.

6.2.10.1.1 Demographics
Table 14 below summarizes the demographic data for Study IC51-324.

Table 14: Demographic Information for Study IC51 - 324

Age at enrollment in IC51-322	**2 months to < 3 years**	**3 years to < 12 years**	**12 years to < 18 years**	**Total**
N	1	3	19	23
Mean Age	2.9	6.9	15.8	14.3
Median (min, max)	2.9	7 (5,8)	16 (13,18)	16 (3, 18)
Gender – female n (%)	1 (100)	1 (33)	9 (47.36)	11 (47.8)
Race: n (%)				
Asian	1 (100)	0	0	1 (4.3)
Caucasian	0	3(100)	19(100)	22(95.7)
Black	0	0	0	0

Adapted from BLA 125280/235, Module 5.3.5.2.2 – Clinical Study Report IC51-324, Table 10.1

Reviewer comment: Blacks were underrepresented compared to the U.S. population, and no Hispanics were enrolled. No infants were enrolled in this study, with the majority 12 to 18 years of age (19/23). The remaining subjects under twelve years of age were 2 years (one subject), 7 years (two subjects), and 8 years old (one subject). Males and females were relatively evenly divided.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Eight subjects (34.8%) reported a medical history, including four with history of seasonal allergies and three subjects with nervous system disorders.

6.2.10.1.3 Subject Disposition
No subjects discontinued participation due to AEs. There were a number of major/minor protocol violations including seven subjects with eleven total major protocol deviations (detailed in Section 6.2.10).

Reviewer comment: The high rate of major protocol deviations in this small study significantly limited the usable data points in the PP analysis set. These data are included in the ITT population analyses.

6.2.11 Efficacy Analyses

Clinical efficacy was not assessed in this study. As previously discussed, evaluation of IXIARO effectiveness was based on JEV-neutralizing antibody responses.

6.2.11.1 Analyses of Primary Endpoint(s)

The primary endpoint for study IC51-324 was $PRNT_{50}$ GMTs and proportion of subjects with $PRNT_{50}$ titer ≥ 1:10 at Month 12. The results of this primary analysis for the ITT population are summarized below.

Table 15: Proportion of subjects with $PRNT_{50}$ titer ≥ 1:10 through the study window of Study IC51-324 by dose group, ITT population

Visit	IC51 0.25mL (N=1) n/N (%)	IC51 0.5 mL (N=22) n/N (%)	Total (N=23) n/N (%)
Visit 1 (Month 7)	1/1 (100)	20/22 (90.9)	21/23(91.3)
Visit 2 (Month 12)	NA	17/19 (89.5)	17/19 (89.5)
Visit 3 (Month 24)	1/1 (100)	20/22 (90.9)	21/23 (91.3)
Visit 4 (Month 36)	1/1 (100)	16/18 (88.9)	17/19 (89.5)

Adapted from BLA 125280/235, Module 5.3.5.2.2 – Clinical Study Report IC51-324, Table 11.4
NA = not available

Reviewer comment: Despite the limitations imposed by the sample size, overall approximately 90% of subjects maintained protective JEV $PRNT_{50}$ titers (≥ 1:10) one to three years after primary immunization. This proportion is similar to the endemic population evaluated in IC51-325.

6.2.11.2 Analyses of Secondary Endpoints

GMTs by age group over the study period was evaluated as a secondary endpoint and detailed in the table below.

Table 16: JEV GMTs for Study IC51-324 by age of enrollment in 322, ITT population

Visit (time point)	2 months to < 3 years GMTs (95% CI) (N)	3 years to < 12 years GMTs (95% CI) (N)	12 years to < 18 years GMTs (95% CI) (N)	Total GMTs (95% CI) (N)
1 (Month 7)	115 (N=1)	150.9 (12.8 – 1772.9) (N= 3)	58.5 (33.6 – 102.1) (N=19)	68.2 (41.7 – 111.6) (N=23)
2 (Month 12)	NA	140 (N=1)	45.1 (26.6 – 76.3) (N=18)	47.8 (28.7 – 79.8) (N=19)
3 (Month 24)	193 (N=1)	136 (45.9 – 402.9) (N=3)	65.3 (36.5 – 116.9) (N=19)	75.4 (45.9 – 123.7) (N=23)
4 (Month 36)	136 (N=1)	102 (N=1)	56.2 (30.3 – 104.2) (N=17)	60.8 (34.8 – 106.1) (N=19)

Adapted from BLA 125280/235, Module 5.3.5.2.2 – Clinical Study Report IC51-324, Table 11.7
NA = not available

Reviewer comment: There is a small increase in GMTs between Month 12-24 in the age group between 12 to 18 years. Review of travel data demonstrates travel to endemic countries in 18/23 subjects. Two subjects in this age group had notably higher titers on Month 24 after interim visits to Manila and Borneo for 7 and 30 days respectively, suggesting the potential for natural boosting with exposure to JEV or related flavivirus. Alternatively, it is possible that neither the subjects in this study nor subjects in the endemic population study (IC51-325) experienced natural boosting, and the vaccine-attributable seropositive rate through three years following primary vaccination is truly 90% in children.

Despite the limitations imposed by the sample size, the general trend demonstrates stable GMTs although notably lower than results elicited in the immediate period after vaccination.

6.2.11.3 Subpopulation Analyses

No subpopulation analyses were provided given the minimal sample size and limited racial parity.

6.2.11.4 Dropouts and/or Discontinuations

The significant number of discontinuations and minimal overall study population makes the resultant immunogenicity data somewhat limited in interpretation.

6.2.12 Safety Analyses

6.2.12.1 Methods

The safety population included all participants included in the overall study (identical to the ITT population). Safety data collection was performed at interval follow up visits given the absence of new investigational product administration.

6.2.12.2 Overview of Adverse Events

An overview of safety data through month 36 is presented below.

Table 17: Safety Data through Month 36 for subjects in IC51-324

Category	**Number of Subjects**
Death	0
SAE	2 (8.7)
Related SAE	0
Medically attended AE	7 (30.4)
Related medically attended AE	0
AE	8 (34.8)
Probably related	0
Possibly related	0
AEs by severity grade	
Grade 1	2 (8.7)
Grade 2	4 (17.4)
Grade 3	2 (8.7)
Grade 4	0

Adapted from BLA 125280/235, Module 5.3.5.2.2 – Clinical Study Report IC51-324, Table 12.1

Eight subjects reported AEs (35 total) throughout the study period, none of which were considered related to the study vaccine by the investigator. The majority of these were predominantly infectious with URIs, Otitis media, and Pharyngitis most highly represented.

Reviewer comment: The reported AEs were reviewed, and this reviewer agrees with the assessment that none of the reported AEs were related to study vaccination.

6.2.12.3 Deaths

There were no deaths in the study period.

6.2.12.4 Nonfatal Serious Adverse Events

There were two SAEs reported in the study period, both deemed unrelated to the study product, as follows:

- An 18 year old female subject developed tonsillitis seven months after completion of her vaccination series. This subject had a history of recurrent tonsillitis and was treated with a tonsillectomy six months after this episode.
- An 18 year old female subject developed a "pimple" on her left neck one year after vaccination. This developed into a MRSA positive abscess treated with resolution with oral antibiotics after a hospital visit.

Reviewer comment: The two SAEs were well delineated as independent of study vaccination. The reviewer agrees with the sponsor's assessment.

6.2.12.5 Adverse Events of Special Interest (AESI)

Neurological and hypersensitivity related AEs were assessed similarly to the previous studies. No AESIs were reported.

6.2.12.6 Clinical Test Results

There were no reported AEs associated with vital signs or clinically significant changes in hematology and chemistry parameters.

6.2.12.7 Dropouts and/or Discontinuations

No participants discontinued participation due to an AE. The protocol deviations documented above were unlikely to affect the overall safety profile observed in this study.

6.2.13 Study Summary and Conclusions

This was a Phase 3 study to assess the long term immunity and safety following primary vaccination with IXIARO in infants, children, and adolescents from 9 months to < 18 years of age in non-endemic regions who had been vaccinated with IC51 in study IC51-322.

In terms of long term safety, there were very few SAEs and medically attended AEs, none of which were likely related to previous administration of IXIARO.

In terms of immunogenicity, subjects with available immunogenicity data demonstrated high rates of continued seroprotection ($PRNT_{50}$ titer ≥ 1:10) from 12 to 36 months after primary immunization. No conclusions can be drawn for the persistence of antibodies in different subgroups (including age, race, gender) given the limited and skewed number of participants. The immunogenicity findings were similar to those among pediatric subjects living in an endemic area who participated in IC51-325.

In summary, this limited study provided some data on the high rate of persistence of JEV neutralizing antibodies in a non-endemic population 36 months after a primary series and show that at 1-3 years after completion of the primary series up to 10% of non-endemic pediatric subjects lack detectable JEV-neutralizing antibody titers.

6.3 Trial # 3 IC51-322

In addition to the above two studies, the sponsor has submitted a final study report for IC51-322 (previously submitted as an interim study report to support pediatric licensure of the primary series). This was a phase 3 study to assess the safety and immunogenicity of the IXIARO primary series in infants, children, and adolescents 2 months to < 18 years of age living in regions non-endemic for JEV.

For full details please refer to the clinical review of the first pediatric efficacy supplement (STN 125280/125). At that time, 60 of the planned 100 subjects had been enrolled and had safety and immunogenicity data available through Month 7 (6 months after completion of the primary series). Forty additional subjects are included in the final analysis submitted to this efficacy supplement, although immunogenicity blood draws were discontinued following the 64th subject to improve recruitment into the study. Similar to the interim analysis the majority of enrolled patients were white adolescents (mean age 11.6 years, 53% female, 83% white).

In terms of additional safety data very few SAEs and medically attended AEs were reported. These were reviewed by the investigator, and none were likely related to IXIARO. Local and systemic reactogenicity was generally mild, and rates of solicited adverse reactions were similar to those reported in the interim analysis and considerably less frequent than those observed in study IC51-323. The final analysis included 37 more solicited or unsolicited AEs that followed a similar trend of primarily respiratory infections. Two additional SAEs were reported (Type 1 diabetes mellitus with complications, and self-harm behavior), both unrelated to the study vaccine by the investigators and the sponsor No new safety signals or hypersensitivity or neurologic AESIs were identified.

Reviewer Comment: The reviewer agrees with the investigators' assessments for the unrelated SAEs

In terms of immunogenicity, limited additional data is presented. Protocol version 10 (September 2011) changed the primary objective to "safety" alone, and immunogenicity assessments were discontinued. The data presented here from the final analysis includes 10 additional subjects overall compared to the interim analysis. The rate of subjects with a $PRNT_{50}$ titer ≥ 1:10 was slightly reduced at 91.2% of subjects (as opposed to 100% of subjects) for those with a $PRNT_{50}$ titer result available at Month 7. Month 7 GMTs for both doses were comparable at 47.96 for the 0.25 mL dose and 51.05 for the 0.5mL group. Comparisons remain limited with a high dropout rate (only 34 subjects available at month 7 for immunologic testing, with only two of these subjects in the 0.25mL group). Comparative immunogenicity data is presented in the tables below:

Table 18: Proportion of subjects with a $PRNT_{50}$ titer ≥ 1:10 by dose group from Interim Analysis through Month 7 of Study IC51-322, ITT Population

Visit	IXIARO 0.25mL n/N (%)	IXIARO 0.5 mL n/N (%)	Total n/N (%)
Visit 0	0/5 (0)	0/49 (0)	0/54 (0)
Visit 3 (Month 2)	5/5 (100)	46/46 (100)	51/51 (100)
Visit 4 (Month 7)	2/2 (100)	16/16 (100)	18/18 (100)

Adapted from BLA 125280/235, Module 5.3.5.2.2 – Interim Study Report IC51-322, Table 11.4

Table 19: Proportion of subjects with a $PRNT_{50}$ titer ≥ 1:10 by dose group from Final Analysis through Month 7 of Study IC51-322, ITT Population

Visit	IXIARO 0.25mL n/N (%)	IXIARO 0.5 mL n/N (%)	Total n/N (%)
Visit 0	0/5 (0)	0/59 (0)	0/64 (0)
Visit 3 (Month 2)	5/5 (100)	57/57 (100)	62/62 (100)
Visit 4 (Month 7)	2/2 (100)	29/32 (90.6)	31/34 (91.2)

Adapted from BLA 125280/235, Module 5.3.5.2.2 – Clinical Study Report IC51-322, Table 11.4

Table 20: GMTs by dose group from Interim Analysis through Month 7 of Study IC51-322, ITT Population

Visit	IXIARO 0.25mL GMTs (95% CI) (N)	IXIARO 0.5 mL GMTs (95% CI) (N)	Total GMTs (95% CI) (N)
Visit 0	0 (0 – 0) (N=5)	0 (0- 0) (N=49)	0 (0 - 0) (N=54)
Visit 3 (Month 2)	216.18 (105.9 – 441) (N=5)	332.1 (251.2 – 439.1) (N=46)	318 (246.1 – 411.9) (N=51)
Visit 4 (Month 7)	47.96 (0 – 3.2 x 10^6) (N=2)	84 (56.3 – 125.4) (N=16)	78.9 (53.3 – 116.8) (N=18)

Adapted from BLA 125280/235, Module 5.3.5.2.2 – Interim Study Report IC51-322, Table 11.4

Table 21: GMTs by dose group from Final Analysis through Month 7 of Study IC51-322, ITT Population

Visit	IXIARO 0.25mL GMTs (95% CI) (N)	IXIARO 0.5 mL GMTs (95% CI) (N)	Total GMTs (95% CI) (N)
Visit 0	0 (0 - 0) (N=5)	0 (0 - 0) (N=59)	0 (0 - 0) (N=64)
Visit 3 (Month 2)	216.18 (105.9 – 441) (N=5)	340.74 (269.8 – 430.3) (N=46)	328.5 (263.7 – 409.1) (N=51)
Visit 4 (Month 7)	47.96 (0 – 3.2 x 10^6) (N=2)	57.12 (38.4 – 84.9) (N=16)	56.5 (38.6 – 82.7) (N=18)

Adapted from BLA 125280/235, Module 5.3.5.2.2 – Clinical Study Report IC51-322, Table 11.4

Reviewer comment: The final analysis for IC51-322 does not alter the known safety/immunogenicity profile of the IXIARO primary series.

7. INTEGRATED OVERVIEW OF EFFICACY

No integrated overview of safety is presented because only one study (IC51-325) evaluated effectiveness of the IXIARO booster dose and persistence of immune response in boosted vs. non-boosted subjects.

8. INTEGRATED OVERVIEW OF SAFETY

No integrated overview of safety is presented because only one study (IC51-325) evaluated safety of the IXIARO booster dose.

9.1.1 Human Reproduction and Pregnancy Data

No pregnancies occurred during the submitted studies. There is little data available from clinical trials or post-marketing experience on vaccine associated risks with human pregnancy. The supplement includes label revisions to Section 8 of the PI to comply with the Pregnancy and Lactation Labeling Rule (PLLR).

9.1.2 Use During Lactation

This IXIARO supplement does not inform any changes or revisions to labeling with regards to use during lactation. However, label revisions with respect to use during lactation will comply with the PLLR.

9.1.3 Pediatric Use and PREA Considerations

The Pediatric Research Equity Act (PREA) of 2003 requires that each application for licensure contain data on the safety and efficacy of the product in relevant pediatric subpopulations. Studies IC51-323 and IC51-322 were conducted to fulfill post marketing requirements with initial licensure in 2009. IC51-325 was conducted to fulfill a PREA post marketing requirement after approval of the booster dose in adults. A partial waiver was granted for infants younger than two months of age. Licensure was obtained for infants, children, and adolescents 2 months to < 17 years of age. This BLA supplement includes an assessment of the safety and effectiveness of a booster dose for pediatric

age groups covered by the PREA PMR and updates the PI to allow use of a booster dose in pediatric populations. This BLA supplement thereby fulfills the PREA PMR.

9.1.4 Immunocompromised Patients

IXIARO has not been evaluated in specifically immunocompromised individuals. IXIARO is manufactured from inactivated virus, so there is no specific safety concern for use in immunocompromised populations. However, protective immunity as elicited by the vaccine in healthy populations cannot be assured for immunocompromised populations.

10. CONCLUSIONS

The clinical data submitted with this BLA supplement support the safety and immunogenicity of an IXIARO booster dose administered 11 months after completion of the primary series in individuals who were 2 months to <17 years of age at time of primary immunization. Clinical benefit was demonstrated by neutralizing antibody responses with a titer of at least 1:10 as measured by $PRNT_{50}$ assay one month after receipt of the booster dose (All 148 subjects evaluated after a booster dose met this threshold for protection). The safety profile of the booster dose appears to be favorable and less reactogenic than that of the primary vaccination series, and no new potential safety signals were identified in long-term follow-up of pediatric study subjects.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

A comparison of the risks and benefits for inclusion of the proposed package insert revisions is presented in Table 14 below and discussed in Section 11.2 following the table.

Table 22: Risk-Benefit Considerations for Revised Package Insert of IXIARO

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• JEV disease is associated with a mortality rate of 20-30% and serious permanent neurologic disability. • U.S. children traveling to JEV endemic areas generally lack pre-existing neutralizing antibodies.	• JEV disease is life threatening
Unmet Medical Need	• IXIARO is the only available U.S. licensed JEV vaccine approved for pediatric use. • There is no available therapy for JEV disease beyond supportive care. • Approximately 10% of subjects who have undergone primary immunization have undetectable ($PRNT_{50}$ < 10) titers after one to three years. • Some subjects with $PRNT_{50}$ titers < 10 may have neutralizing antibodies below the lower limit of detection and may be protected from disease, but it is unknown whether this is the case.	• There is a small but existent subset of children who who may not be protected from ongoing exposure or re-exposure to JEV despite primary immunization with IXIARO.
Clinical Benefit	• A JEV $PRNT_{50}$ neutralizing antibody titer ≥ 1:10 is regarded as evidence of protection against clinical disease. • In a clinical trial with 1311 children living in a region endemic for JEV, 96-100% of subjects obtained this neutralizing antibody titer threshold. • In a follow up trial of 300 children from this same population 86-90% demonstrated titers above this threshold of protection at 1-3 years after primary immunization. • Of the 148 subjects receiving a single booster dose, $PRNT_{50}$ GMTs increased substantially, and 100% had protective titers through two years following the booster dose. • Approximately 90% of subjects who have undergone primary immunization have detectable ($PRNT_{50}$ ≥ 10) titers after one to three years. • It is unclear whether the 10% of subjects without detectable titers ($PRNT_{50}$ < 10) are susceptible to JEV disease.	• There is evidence of clinical benefit of a booster dose of IXIARO 11 months after completion of the primary series based on neutralizing antibody response. • The primary series remains effective for approximately 90% of subjects up to three years after immunization. • A 0.5 mL dose booster dose is appropriate for children and adolescents 3 to < 18 years of age, while a 0.25 mL dose is appropriate for infants and children 2 months to < 3 years of age.
Risk	• The primary risks of vaccination with IXIARO among children and adolescents 3 to <18 years of age are mild injection site pain, tenderness, muscle pain, and fatigue. • The primary risks of vaccination with IXIARO among infants and children 2 months to < 3 years of age are mild to moderate fever, injection site redness, irritability, and diarrhea. • The risk profile of the IXIARO booster dose is favorable compared to primary immunization.	• All the evidence indicates that the risks of vaccination with IXIARO are minor, including the risks associated with an additional booster dose.
Risk Management	• There is no safety signal related to hypersensitivity and neurological adverse events of special interest in children vaccinated with IXIARO (including in the booster dose). • The current label indicates IXIARO contains protamine sulfate, a compound known to cause hypersensitivity reactions in some individuals. IXIARO is contraindicated in individuals with known allergies to protamine sulfate or reactions to prior administrations of IXIARO.	• Planned routine pharmacovigilance following licensure of IXIARO for use in children is adequate to manage expected risks.

11.2 Risk-Benefit Summary and Assessment

The data submitted to this BLA supplement support the clinical benefit of an IXIARO booster dose in infants, children, and adolescents (14 months to < 17 years of age) who may be at risk of JEV disease 11 months or longer after completion of the primary series (based on serostatus). The likelihood of clinical benefit is demonstrated by the complete proportion of study participants with a JEV neutralizing antibody titer of ≥ 1:10 at one month through two years after the booster dose (100% of subjects in IC51-325) in an endemic population. This threshold is generally regarded as conferring protection against clinical disease. This seroresponse was demonstrated in all subgroups regardless of gender, age, or previous JEV neutralizing antibody titers. The booster dose also substantially increased $PRNT_{50}$ GMTs from pre-booster values, and $PRNT_{50}$ GMTs at two years after the booster dose suggest that protective immunity conferred by the booster dose will be durable for many years and therefore may outlast protective immunity conferred by primary series alone.

Subjects in an endemic population not provided a booster dose demonstrated persistent protective antibody response in the vast majority of subjects through one to three years after primary vaccination, although 10-14% did not have detectable JEV neutralizing antibody titers during this timeframe. It is not known whether lack of detectable neutralizing antibodies in these children predicts susceptibility to JEV disease, but it is a possibility. Similarly, the limited immunogenicity data from non-endemic populations suggests an approximately 90% rate of continued seroprotection seven months to three years after primary immunization.

The proposed IXIARO booster dose of 0.5mL for children and adolescents 3 to < 18 years of age and 0.25 mL for infants and children 14 months to < 3 years of age is supported by the available immunogenicity data. The booster dose was only evaluated at one time point (11 months after completion of primary vaccination). However, a booster dose given more remotely after primary vaccination would likely elicit a similar immune response.

The risk profile associated with a JEV booster dose was favorable compared to the age associated safety profile seen with primary immunization. Although overall rates of AEs were low, a typical pattern was seen with associated pain, tenderness, fatigue, irritability, and/or diarrhea that resolved within a few days. There remain no safety signals in pediatric study participants related to hypersensitivity reactions or neurological adverse events following IXIARO.

There is only one available JEV vaccine licensed for pediatric use in the U.S., and there remains no available specific therapy for JEV disease (which is fatal in 30% of cases and may cause permanent neurologic disability in nonfatal cases). Although over 90% of individuals who have undergone primary vaccination with IXIARO appear to be protected one to three years later, the risks of JEV disease are significant enough to make available the option for a booster dose if exposure to JEV is possible. Consequently, ensuring prolonged protective antibody titers in children with risk of JEV exposure would fill an unmet medical need. In the opinion of this reviewer, the substantial benefit of prevention of JEV disease in pediatric travelers to JEV endemic areas outweighs the risks of generally mild adverse reactions.

Although 90% of children appear to maintain protective JEV-neutralizing antibody titers through 3 years after primary immunization, the benefit/risk balance for a pediatric booster dose for children at continued risk of exposure to JEV is favorable given the severity of JE disease, the established safety profile of the vaccine, and lack of standard of care methods for determining which individuals fall into the 10% who may be uncertain to remain protected at 11 months following completion of the primary series.

11.3 Discussion of Regulatory Options

The regulatory options include approval of the proposed changes to the IXIARO PI to allow a booster dose for pediatric age groups (and to add longer-term immunogenicity data following the primary series and booster dose) vs. not to approve these changes. As noted above, the data submitted support the proposed changes.

11.4 Recommendations on Regulatory Actions

In the opinion of this review, the clinical data supports approval of this BLA supplement.

11.5 Labeling Review and Recommendations

The applicant provided a draft version of extensive revisions to the PI, including adding dosing instructions for a pediatric booster dose, adding safety and immunogenicity data for the pediatric booster dose and long-term immunogenicity data for the primary series in pediatric age groups, and updating Section 8 to comply with the PLLR. A final version of the revised PI was agreed upon by the applicant and CBER following labeling negotiations with the following substantive changes:

A. Highlights and Section 2 – Inclusion of the following language regarding use of a booster dose: “A booster dose (third dose) may be given at least 11 months after completion of the primary immunization series if ongoing exposure or re-exposure to JEV is expected.”

B. Section 2 – Dosing instructions added regarding use of a pediatric booster dose.

C. Section 6 – Safety data included in the final CSR for IC51-322 was updated. Safety data derived from study IC51-325 was added.

D. Section 8 – Updated to comply with the Pregnancy Lactation and Labeling Rule. Available clinical data was noted to be insufficient to establish the presence or absence of drug associated risk during pregnancy, and therefore no human data is included in the label.

E. Section 14 – Immunogenicity data from IC51-325 was added in a Table combining Table 6 and Table 9 of this review. Immunogenicity data from IC51-324 was added in textual format.

11.6 Recommendations on Postmarketing Actions

Routine pharmacovigilance is adequate to manage expected risks. No changes in the pharmacovigilance plan are recommended.