Application Type	Efficacy Supplement
STN	125280/125
CBER Received Date	July 18, 2012
PDUFA Goal Date	May 18, 2013
Division / Office	DVRPA /OVRR
Priority Review	No
Reviewer Name(s)	Doran Fink; Doran Fink
Review Completion Date / Stamped Date	May 16, 2013
Supervisory Concurrence	
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 mcg JEV proteins
Dosing Regimen	Children and adolescents 3 to <17 years of age: two 0.5 mL doses given 28 days apart; Infants and children 2 months to <3 years of age: two 0.25 mL doses given 28 days apart.
Indication(s) and Intended Population(s)	Prevention of Japanese encephalitis in children ages 2 months to <17 years.

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GLOSSARY

AE	adverse event
AESI	adverse event of special interest
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CRF	case report form
DE	Division of Epidemiology
DENV	Dengue virus
DIS	Division of Inspections and Surveillance
DSMB	data safety monitoring board
FDA	Food and Drug Administration
GMT	geometric mean titer
HDM	half-dose mark
ITT	intent-to-treat
JEV	Japanese encephalitis virus
KD	Kawasaki disease
MAAE	medically attended adverse event
mL	milliliter
OBE	Office of Biostatistics and Epidemiology
PeRC	Pediatric Review Committee
PI	package insert
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PREA	Pediatric Research Equity Act
PRNT	plaque reduction neutralization test
$PRNT_{50}$	PRNT with 50% plaque reduction endpoint
SAE	serious adverse event
U.S.	United States
VAERS	Vaccine Adverse Event Reporting System

1. EXECUTIVE SUMMARY

IXIARO, manufactured by Intercell AG, is a purified, inactivated Japanese encephalitis virus (JEV) vaccine that is U.S. licensed for active immunization of persons 17 years of age and older for prevention of disease due to JEV. A primary series consisting of two 0.5 mL doses administered intramuscularly 28 days apart was approved in 2009, and a 0.5 mL booster dose was approved in 2010 for use in persons 17 years of age and older with potential re-exposure to JEV more than 1 year after completion of the primary series. On 18 July 2012, Intercell submitted a biologics license application (BLA) supplement requesting approval of an IXIARO primary immunization series for infants, children, and adolescents 2 months to <17 years of age. A primary series consisting of two 0.25 mL doses administered intramuscularly 28 days apart is proposed for infants and children 2 months to <3 years of age, while the currently licensed primary series is proposed for children and adolescents 3 to <17 years of age. The licensed 0.5 mL pre-filled syringe presentation will be used to administer both IXIARO dosing regimens.

In support of the proposed pediatric indication, this BLA supplement contains the final study reports for three pediatric clinical studies. The largest of these studies, IC51-323, was a randomized, open-label, active controlled study to evaluate the safety and immunogenicity of IXIARO in infants, children, and adolescents 2 months to <18 years of age living in the Philippines, where JEV is endemic. This study was a post-marketing requirement (PMR) mandated by the Pediatric Research Equity Act (PREA) as a condition of the initial approval of IXIARO in 2009. In this study, 1,311 participants received the IXIARO primary series according to the proposed age-dependent dosing regimen. An additional 458 participants received U.S.-licensed active comparator vaccines: 64 infants 2 to <12 months of age who received Prevnar (pneumococcal conjugate vaccine) and 394 children and adolescents 1 to <18 years who received HAVRIX720 (Hepatitis A vaccine).

Immunogenicity endpoints for study IC51-323 were the proportion of participants with JEV-neutralizing antibody titer ≥1:10, as measured by a 50% plaque reduction neutralization test ($PRNT_{50}$), and $PRNT_{50}$ geometric mean titer (GMT). A $PRNT_{50}$ titer ≥1:10 is generally considered to be reasonable evidence of protection against JEV disease. At baseline 85% of participants were seronegative for JEV ($PRNT_{50}$ titer <1:10). Among 396 participants who received an age-appropriate dose of IXIARO and who were randomized to the immunogenicity subgroup, 99-100% (depending on the age subgroup) had a $PRNT_{50}$ titer ≥1:10 at 28 days after completion of the primary series and 85-100% had a $PRNT_{50}$ titer ≥1:10 at 6 months after completion of the primary series. $PRNT_{50}$ geometric mean titers (GMTs) and proportions of participants with $PRNT_{50}$ titer ≥1:10 were similar at both time points to those observed in prior studies with adults.

Safety endpoints included rates of combined serious adverse events (SAEs) and medically attended adverse events (MAAEs) in the 56 days or 7 months following the first study vaccination, unsolicited adverse events in the 56 days or 7 months following the first study vaccination, and solicited adverse events in the 7 days following each study vaccination. Rates of combined SAEs and MAAEs and rates of unsolicited adverse events were similar following IXIARO vs. active comparator vaccination. The most common SAE was febrile convulsion (12 instances), none of which were plausibly related to study vaccination, and which occurred among 1.3% of IXIARO recipients 1 to

<3 years of age, 1.4% of HAVRIX720 recipients 1 to <3 years of age, and 1.6% of Prevnar recipients (1 infant). The most common unsolicited adverse events were unrelated infections. Solicited adverse events were mostly mild and occurred at similar rates following IXIARO vs. active comparator vaccines. The most common solicited adverse events (rate ≥10% in an age subgroup) were injection site redness, fever ≥37.7˚C, irritability, and diarrhea among participants 2 months to <3 years of age, fever ≥37.7˚C among children 1 to <12 years of age, and injection site pain and injection site tenderness among adolescents 12 to <18 years of age.

The second study, IC51-322, was an open-label, uncontrolled study to evaluate the safety and immunogenicity of IXIARO in infants, children, and adolescents 2 months to <18 years of age residing in a region where JEV is not endemic but planning travel to a region where JEV is endemic. This study was also a PREA PMR and was originally designed to enroll 100 participants. Due to slower than expected recruitment of participants, an urgent public health need for a pediatric JEV vaccine resulting from expiration of remaining stocks of JE-VAX, and the availability of final study results from IC51-323, CBER recommended that this BLA supplement include analyses of available data from study IC51-322. The submitted analyses included data from 60 participant (55 of whom were 3 to <18 years of age) who received the IXIARO primary series according to the proposed age-dependent dosing regimen.

Immunogenicity endpoints for study IC51-322 were the same as for study IC51-323. Immunogenicity data was available for 54 participants (49 of whom were 3 to <18 years of age) at 28 days following completion of the IXIARO primary series and for 18 participants (16 of whom were 3 to <18 years of age) at 6 months following completion of the primary series. At both time points, all participants with available immunogenicity data had a $PRNT_{50}$ titer ≥1:10. $PRNT_{50}$ GMTs at both time points were similar to those observed in study IC51-323 and to those observed in prior studies with adults.

Safety endpoints for study IC51-322 were the same as for study IC51-323. Rates of combined SAEs and MAAEs and rates of unsolicited adverse events through 56 days or 7 months following the first study vaccination were lower in study IC51-322 compared to study IC51-323. Only two SAEs occurred, neither of which was plausibly related to IXIARO. Solicited adverse events were mostly mild, and the most common (rate ≥10% in an age subgroup) were injection site hardening, injection site redness, and diarrhea among participants 2 months to <3 years of age and injection site pain, injection site tenderness, excessive fatigue, and muscle pain among participants 3 to <18 years of age.

The third study, IC51-221, was a randomized, open-label study to evaluate the safety and immunogenicity of two dosing regimens of IXIARO in children 1 to <3 years of age residing in Bangalore, India. Twenty-four participants completed an IXIARO primary series consisting of two 0.5 mL doses, and an additional 24 participants completed an IXIARO primary series consisting of two 0.25 mL doses. Using the same immunogenicity endpoints as studies IC51-322 and IC51-323, 96% of participants in each treatment group had a $PRNT_{50}$ titer ≥1:10 at 28 days after completion of the primary series, and $PRNT_{50}$ GMTs at this time point were similar between treatment groups. Few adverse events (and no SAEs) were reported, and rates of adverse events were similar between treatment groups.

Taken together, the data from studies IC51-323 and IC51-322 satisfy the PREA post-marketing requirements and demonstrate a favorable safety profile and likelihood of clinical benefit (based on immunogenicity) of IXIARO in individuals 2 months to <17 years of age. The 0.25 mL dose proposed for infants and children 2 months to <3 years of age is to be administered using the licensed 0.5 mL syringe presentation, following expulsion of 0.25 mL from the syringe while using a guide mark printed on a label affixed to the syringe barrel. Validation studies of the label affixation process demonstrated acceptable consistency of label placement on the syringe barrel but also indicate that the mean volume remaining in the syringe after completing the proposed preparation procedure will be ----------(b)(4)----------. Although the IXIARO dose administered to infants and children 2 months to <3 years of age will be on average ----------(b)(4)-- than the intended dose, data from study IC51-221 suggest that the dose range likely to be administered to this age group will be associated with a favorable safety profile and adequate immunogenicity. The applicant has committed to conduct post-marketing studies to assess the impact of human factors issues on preparation and administration of the 0.25 mL dose, though based on prior experience with internationally marketed vaccines and U.S.-licensed drug products administered using a similar presentation, human factors are unlikely to significantly affect the safety risks or clinical benefit of the vaccine. In the opinion of this reviewer, when travel activities result in potential exposure to JEV, the clinical benefit of IXIARO outweighs its risks for all pediatric age groups 2 months and older. Consequently, this reviewer recommends approval of the proposed IXIARO primary immunization series for infants, children, and adolescents 2 months to <17 years of age.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Japanese encephalitis virus (JEV) is a mosquito-borne flavivirus that causes viral encephalitis. 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[1,2]. JEV is the most common cause of viral encephalitis in Asia, with a pediatric incidence of 5-50 cases per 100,000 children per year in endemic regions.

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[2]. From 1973-2011, 58 cases of travel-associated JEV disease among individuals from non-endemic areas have been reported in the literature[3,4]. Seven of these cases (12%) occurred among individuals 1 to 19 years of age.

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

No specific therapy exists for treatment of JEV clinical disease. Individuals with symptomatic JEV infection are managed using supportive measures.

2.3 Safety and Efficacy of Pharmacologically Related Products

JEV vaccines act by inducing antibodies that neutralize JEV. Based on accumulated data from animal studies, clinical trials of other JEV vaccines, and human epidemiological studies, a neutralizing antibody titer of ≥1:10 as measured by 50%

plaque reduction in a plaque reduction neutralization test ($PRNT_{50}$) is generally accepted as a reasonable threshold for evidence of protective immunity[5,6].

Prior to IXIARO, the only JEV vaccine licensed for use in the U.S. was JE-VAX, a mouse-brain derived vaccine manufactured by Biken (Japan). JE-VAX was licensed for use in individuals 1 year of age and older based on demonstration of clinical efficacy in Thai children (efficacy point estimate of 91% for protection against JEV disease). The most common adverse reactions following JE-VAX were tenderness, redness, and swelling at the injection site and fever, headache, malaise, rash, chills, dizziness, myalgia, nausea, vomiting and abdominal pain. Less common but potentially serious adverse reactions included hypersensitivity and rare instances neurologic disorders such as encephalitis, encephalopathy, seizures, and peripheral neuropathy (rate of 1 to 2.3 per million vaccines). Production of JE-VAX ceased in 2006, and by February 2011 all remaining stocks had expired.

2.4 Previous Human Experience with the Product (Including Foreign Experience)
IXIARO is a purified, inactivated JEV vaccine (Vero cell culture derived) licensed in the U.S. for active immunization of persons 17 years of age and older for prevention of disease due to JEV. The approved primary immunization series is two 0.5 mL doses administered intramuscularly 28 days apart.

Initial U.S. licensure of IXIARO in 2009 for use in persons 17 years of age and older was supported by a randomized, controlled pivotal study in 867 healthy adults that compared safety and immunogenicity of IXIARO to JE-VAX. In this study, pre-specified non-inferiority criteria were met for the primary endpoints of $PRNT_{50}$ geometric mean titer 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.

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.

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. The approved pediatric doses in Europe are 0.25 mL for infants and children 2 months to <3 years of age and 0.5 mL for children and adolescents 3 to <18 years of age (using a 0.5 mL pre-filled syringe to administer either dose).

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

2.5.1 Prior Approval of IXIARO and Pediatric Post-Marketing Requirements

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. To address the requirements of the Pediatric Research Equity Act (PREA), 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. The deferral was to be fulfilled by two PREA post-marketing requirement (PMR) studies. The first PREA PMR study, IC51-322, would be an open-label uncontrolled study to evaluate the safety and immunogenicity of IXIARO in 100 children and adolescents 1 to <17 years of age residing in countries not endemic for JEV. The second PREA PMR study, IC51-323, would be an open-label, randomized, active controlled study to evaluate the safety and immunogenicity of IXIARO in 1400 children and adolescents 1 to <17 years of age residing in a JEV-endemic region (the Philippines), with 3:1 randomization of treatment assignment to IXIARO vs. HAVIRX (Hepatitis A vaccine) active comparator. Neither study would include pre-specified success criteria but rather would use descriptive statistics assess vaccine effectiveness based on neutralizing antibody responses, as measured by $PRNT_{50}$.

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. Similar to the initial approval of IXIARO, 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, an open-label, randomized follow-up study to evaluate long-term immunogenicity and use of a booster dose of IXIARO administered to a subset of study participants in the Philippines who had received a primary series of IXIARO in study IC51-323. Although not specified as a PREA PMR, the applicant planned another study of long-term immunogenicity (IC51-324) among study participants in non-endemic regions who had received their primary series of IXIARO in study IC51-322.

2.5.2 Pre-Submission Regulatory Activity

Following development of the pediatric plan to satisfy licensure requirements of the EMA, the study populations for IC51-322 and IC51-323 were expanded to include infants, children, and adolescents 2 months to <18 years of age, with 2:1 randomization of treatment assignment among infants 2 months to <1 year of age in study IC51-323 to receive IXIARO vs. Prevnar (heptavalent pneumococcal conjugate vaccine) active comparator. Based on immunogenicity results from dose-ranging studies conducted during Phase 2 and during a run-in phase for study IC51-323, children and adolescents 3 to <18 years of age enrolled into studies IC51-323 and IC51-322 would receive an IXIARO dose of 0.5 mL, while infants and children 2 months to <3 years of age enrolled into these studies would receive an IXIARO dose of 0.25 mL.

On 14 February 2011, the applicant informed CBER that although study IC51-323 (in the Philippines) had fulfilled its enrollment goal and was projected to reach completion in July 2011, study IC51-322 (in non-endemic regions) had enrolled only 24 participants

out of its goal of 100, including only 2 participants younger than 3 years. Concomitantly, CBER learned that all remaining stocks of JE-VAX (JEV vaccine manufactured by Sanofi Pasteur) would expire in May 2011. JE-VAX was the only JEV vaccine licensed for pediatric use in the U.S. but had not been manufactured since 2006. On May 2, 2011, in response to the logistical issues affecting enrollment of subjects into study IC51-322 and the impending public health need resulting from the unavailability of JE-VAX, CBER advised the applicant to submit a biologics license application (BLA) supplement for use of IXIARO in infants, children and adolescents 2 months to <17 years of age as soon as the data from IC51-323 were available and to include in the supplement the available safety and immunogenicity data from study IC51-322.

During February through May 2012, as the applicant was preparing to submit the pediatric efficacy supplement, CBER and the applicant discussed options for the presentation of the 0.25 mL dose of IXIARO intended for infants and children 2 months to <3 years of age. The applicant contended that since the market demand for the 0.25 mL presentation would be only several hundred doses per year, it would be financially prohibitive to develop a dedicated 0.25 mL pre-filled syringe presentation, a new graduated pre-filled syringe presentation, or a new 0.5 mL vial presentation from which either a 0.5 mL dose or a 0.25 mL dose could be withdrawn. The applicant therefore proposed adding a half-dose mark (HDM) to the barrel of its licensed 0.5 mL pre-filled syringe presentation. Actuation of the plunger to the HDM would result in expulsion of 0.25 mL from the 0.5 mL pre-filled syringe, leaving a 0.25 mL dose remaining in the syringe for injection. Due to financial considerations, the HDM would be printed on a label applied to the syringe rather than imprinted directly on the syringe barrel.

Although there was no precedent among U.S.-licensed vaccines for the applicant's proposed presentation for the 0.25 mL dose of IXIARO, several influenza vaccinations employing this type of presentation had been licensed for adult and pediatric use in Europe (Agrippal, Vaxigrip) or Canada (AGRIFLU). Furthermore, the applicant planned to propose the same 0.25 mL dose presentation as part of its request for pediatric marketing authorization to the EMA. However, the applicant had not yet completed validation studies for the process affixing the label with the HDM to the syringe barrel, nor had they planned studies to assess human factors issues that might affect reliable administration of the 0.25 mL dose as intended. CBER discussed recommendations for such studies with reviewers in FDA's Center for Devices and Radiologic Health (CDRH), Office of Device Evaluation (Human Factors Team) and Office of Compliance. Following these discussions, CBER determined that these recommended studies could substantially delay the pediatric efficacy supplement, which was otherwise ready for submission, and further prolong the unfilled need for a JEV vaccine licensed for pediatric use in the U.S.

During a teleconference on 20 June 2012, CBER advised the applicant that pediatric licensure of IXIARO might be achieved most expediently with the 0.5 mL dose for children and adolescents 1 to <17 years of age. This advice was based on the following considerations:

- Data from studies IC51-323 and IC51-323 could potentially support use of the 0.5 mL dose in children and adolescents 3 to <17 years of age.
- Data from a Phase 2 dose-ranging study conducted in Bangalore, India (IC51-221), which evaluated safety and immunogenicity of the 0.5 mL dose of IXIARO in 24 children 1 to <3 years of age, could potentially support use of the 0.5 mL dose in children 1 to <3 years of age.
- Licensure of IXIARO for use in children and adolescents 1 to <17 years of age would fulfill the PREA post-marketing requirements, since a partial waiver had been granted for infants younger than 12 months of age.
- Lack of a U.S.-licensed JEV vaccine for use in infants younger than 12 months of age would not represent a critical unfilled need due to the very small number of U.S. infants who might be expected to travel to endemic areas and be at risk for exposure to JEV.

Consequently, the applicant submitted a BLA supplement on 13 July 2012 requesting licensure of the 0.5 mL dose for active immunization for prevention of disease due to JEV in children and adolescents 1 to <17 years of age.

2.5.3 Post-Submission Regulatory Activity

Clinical review of safety data from study IC51-323 revealed higher than expected rates of solicited fever in the 7 days after vaccination with IXIARO, in particular among infants and children <3 years of age (see details in Section 6.1). While the risk-benefit assessment remained favorable for use of IXIARO in infants and young children at risk of exposure to JEV (see discussion in Section 11), the rates of fever observed in study IC51-323 following vaccination with the 0.25 mL dose of IXIARO raised the concern of potentially greater rates of fever and reactogenicity in general following vaccination of children 1 to <3 years of age with the 0.5 mL dose of IXIARO. Fever and other symptoms of reactogenicity were uncommon among the 24 children 1 to <3 years of age who were vaccinated with the 0.5 mL dose of IXIARO in study IC51-211 (see details in Section 6.3), but the small sample size of this study and overall low rates of adverse events compared to studies IC51-322 and IC51-323 called into question whether the safety data for this study accurately reflected the safety profile of the 0.5 mL dose among children 1 to <3 years of age.

The CBER mid-cycle meeting for this BLA supplement occurred on 27 November 2012 and focused on licensure considerations for infants and children 2 months to <3 years of age. Discussions around this issue included the following considerations:

- The risk-benefit balance for the 0.5 mL dose in children 1 to <3 years of age was not as favorable as originally assessed due to uncertain potential for reactogenicity in this age subgroup, as described above.
- The risk-benefit balance for the 0.25 mL dose in infants and children 2 months to <3 years of age remained favorable based on evaluation of safety and immunogenicity data from studies IC51-323 and IC51-322.
- Although full validation of the HDM label affixation process was close to completion at this time, the applicant had not yet planned human factors assessments of the preparation and administration of the 0.25 mL dose. Lack of

human factors assessments imparted some risk of incorrect administration of the 0.25 mL dose, but based on experience with similar vaccine presentations licensed for pediatric use in foreign markets, this risk was likely to be small and outweighed by the benefit of having a JEV vaccine licensed for use in infants and children 2 months to <3 years in the U.S. market (see discussion in Section 11).

- If the 0.25 mL dose were to be approved for infants and children 2 months to <3 years of age prior to validation of the half-dose mark affixation process and human factors studies, these studies could be completed post-marketing.
- Approval of the 0.25 mL dose for infants and children 2 months to <3 years of age, to be administered using the proposed presentation and following the proposed instructions, would maintain consistency between the licensed indications in the U.S. and Europe. EMA approval of the proposed pediatric doses and presentation was expected soon at the time of CBER's mid-cycle meeting and was ultimately granted in February 2013.

Consequently, CBER advised the applicant on 7 December 2012 to submit an amendment to modify the BLA supplement and proposed package insert by eliminating the 0.5 mL dose for children 1 to <3 years of age, adding the 0.25 mL dose for infants and children 2 months to <3 years of age, and adding instructions for preparation of the 0.25 mL dose using the HDM affixed to the syringe barrel as a guide. The applicant submitted the recommended modifications on 13 December 2012 as Amendment 8.

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 without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

All of the pediatric studies discussed in this review were conducted under the applicant's original IND 8589. The study designs adhered to good clinical practices, including elements of informed consent as required by 21 CFR 50.25 and pediatric ethical considerations as outlined in 21 CFR 50.51-54.

Two of the three clinical sites for study IC51-323 in the Philippines (sites 103 and 104, both in Muntinlupa City) were selected for bioresearch monitoring audit because these sites did not have previous experience conducting clinical studies under U.S. IND and were responsible for enrollment of 70% of the participants in the entire study. The audit report was completed by the Division of Inspections and Surveillance (DIS) on 1 March 2013 and identified no specific concerns. The DIS review memorandum stated that there were no sponsor issues, monitoring issues, or deviations from applicable regulations at either site.

3.3 Financial Disclosures

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*[1]. No potential conflicts of interest were reported. Financial

1 See http://www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm.

disclosure information for the three clinical studies submitted to this BLA supplement is summarized in Tables 1-3 below.

Table 1. Financial disclosure information for study IC51-323

Covered clinical study (name and/or number): IC51-323; Safety and Immunogenicity of the Japanese Encephalitis Vaccine IC51 (IXIARO®) in a Pediatric Population. Open Label, Randomized, Active Controlled, Phase 3 Study.		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 18		
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		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Table 2. Financial disclosure information for study IC51-322

Covered clinical study (name and/or number): IC51-322; Immunogenicity and Safety of the Japanese Encephalitis Vaccine IC51 (IXIARO®, JESPECT®) in a Pediatric Population in Non-endemic Countries. Uncontrolled, Open label Phase 3 Study.		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 28		
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		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Table 3. Financial disclosure information for study IC51-221

Covered clinical study (name and/or number): IC51-221; A Single Centre Open Label Phase II Clinical Study To Evaluate The Immunogenicity & Safety Of Inactivated Japanese Encephalitis Vaccine In 60 Healthy Indian Subjects In The Age Group Of ≥ 1 To <3 Years – A Dose Response Study.		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 2		
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		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

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

4.5 Statistical
The statistical reviewer verified that the primary study endpoint analyses cited by the applicant were supported by the submitted data.

4.6 Pharmacovigilance
The pharmacovigilance plan for post-licensure safety monitoring following initial approval of IXIARO in 2009 included: routine pharmacovigilance to detect adverse reactions related to hypersensitivity (dermatitis, dyspnea, erythema, eye pruritus, flushing, hypersensitivity, pruritus, rash, and urticaria) and to neurologic disorders (convulsion, acute disseminated encephalomyelitis, acute encephalitis, acute myelitis, central nervous system inflammation, and Guillain-Barre Syndrome); an enhanced surveillance study in adult military recruits (IC51-401); and a pregnancy registry.

The proposed pharmacovigilance plan following pediatric licensure of IXIARO includes: continued routine pharmacovigilance for hypersensitivity and neurologic adverse reactions; intensified post-marketing surveillance of pregnancy within the spontaneous reporting system and study IC51-401 using a questionnaire; and evaluation of long-term safety data from the ongoing pediatric studies (IC51-324, a long-term follow-up study with children vaccinated during participation in IC51-322, and IC51-325, a long-term follow-up study with children vaccinated during participation in IC51-323).

On 14 March 2013, the reviewer from the Office of Biostatistics and Epidemiology, Division of Epidemiology (OBE/DE), completed her review of the proposed pharmacovigilance plan and available pre- and post-licensure safety data in adults and children. Her recommendations were as follows:

- Continue routine pharmacovigilance, as proposed by the sponsor.
- Enhanced pharmacovigilance to provide expanded AE reporting to the Vaccine Adverse Event Reporting System (VAERS) for three years following product licensure: as 15 day reports, all serious events, whether expected/labeled or unexpected/unlabeled; and as 30 day reports all reports of pregnancy not previously filed as 15 day reports.
- Intensified Post Marketing Surveillance within the spontaneous reporting system: Pregnancy Questionnaire as proposed by the sponsor.
- Review of the final reports for all ongoing studies, including pediatric studies (IC51-322, IC51-324, and IC51-325) and the enhanced surveillance study in adult military recruits (IC51-401, with emphasis on the pregnancy questionnaire and pregnancy registry).

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The results of three pediatric clinical studies are included in this BLA supplement. Study IC51-323 (conducted in the Philippines, where JEV is endemic) provides the bulk of safety and immunogenicity data to support of licensure of IXIARO in infants, children, and adolescents 2 months to <17 years of age. The other two pediatric studies are smaller but provide important safety and immunogenicity data to support pediatric licensure of IXIARO. Data from study IC51-322 provides safety and immunogenicity observations from participants residing in non-endemic regions. Study IC51-221 includes an assessment of the safety and immunogenicity of IXIARO among children 1 to <3 years of age when administered as a 0.5 mL dose that is higher than the 0.25 mL dose intended for use in this age group (which may be relevant to the dose volume actually administered when following the instructions for preparation of the 0.25 mL dose). Since the three pediatric studies were substantially different in size and purpose, they are reviewed here independently without integrated discussions of safety and efficacy.

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 125280/125.0, Module 5.3.5.1.3 (final study report for IC51-221)
- BLA 125280/125.6, Module 5.3.5.1.3 (revised final study report for IC51-323)
- BLA 125280/125.6, Module 5.3.5.2.3 (revised final study report for IC51-322)
- BLA 125280/125.7, Module 1.11.3 (response to CBER information request)
- BLA 125280/125.7, Module 5.3.5.1.3 (post-hoc analyses for IC51-323 submitted in response to CBER information request)
- BLA 125280/125.7, Module 5.3.5.2.3 (post-hoc analyses for IC51-322 submitted in response to CBER information request)
- BLA 125280/125.8, Module 1.14.1.3 (draft prescribing information)
- BLA 125280/125.9, Module 1.11.3 (response to CBER information request)
- BLA 125280/125.9, Module 5.3.5.1.3 (post-hoc analyses for IC51-323 submitted in response to CBER information request)
- BLA 125280/125.10, Module 1.11.3 (response to CBER information request)
- BLA 125280/125.10, Module 5.3.5.1.3 (post-hoc analyses for IC51-323 submitted in response to CBER information request)

5.3 Table of Studies/Clinical Trials

The clinical studies reviewed in this BLA supplement are summarized in Table 4 below.

Table 4. Clinical Studies Discussed in this Review

Study ID	**IC51-323**	**IC51-322**	**IC51-221**
NCT number	NCT01041573	NCT01047839	-
Phase	3	3	2
IND study	Yes	Yes	Yes
Study location(s)	Philippines	U.S., Europe, Australia	India
Total participants	1869	60	60
IXIARO recipients	1411	60	24
Age range	2 months to <18 years	2 months to <18 years	1 to <3 years
IXIARO dosage	0.25 mL: <3 years 0.5 mL: ≥ 3 years	0.25 mL: <3 years 0.5 mL: ≥ 3 years	0.25 mL vs. 0.5 mL
IXIARO regimen	2 intramuscular doses 28 days apart	2 intramuscular doses 28 days apart	2 intramuscular doses 28 days apart
Comparator treatments	2 months to <1 year of age: Prevnar 1 to <18 years of age: HAVRIX720	None	JenceVac
Follow-up duration	7 months	7 months	56 days
Primary endpoint*	SAEs, medically attended AEs through Day 56	$PRNT_{50}$ GMT and % ≥1:10 at Day 56	$PRNT_{50}$ % ≥1:10 at Day 56
Non-primary immunogenicity endpoints*	$PRNT_{50}$ GMT and % ≥1:10 at Day 56 and Month 7	$PRNT_{50}$ GMT and % ≥1:10 at Month 7	$PRNT_{50}$ GMT at Day 56; $PRNT_{50}$ GMT and % ≥1:10 at Day 28
Non-primary safety endpoints*	SAEs, medically attended AEs through Month 7; Unsolicited AEs through Day 56 and Month 7; Solicited AEs through 7 days after each study vaccination	SAEs, medically attended AEs through Day 56 and Month 7; Unsolicited AEs through Day 56 and Month 7; Solicited AEs through 7 days after each study vaccination	

*AE = adverse event; SAE = serious adverse event; $PRNT_{50}$ = plaque reduction neutralization test with a 50% plaque reduction endpoint; GMT = geometric mean titer; % ≥1:10 = proportion of participants with $PRNT_{50}$ titer ≥1:10.

5.4 Consultations

5.4.1 Pre-Filled Syringe Presentation

The applicant proposed not to develop a new presentation for the 0.25 mL IXIARO dose intended for use in infants and children 2 months to <3 years of age and instead proposed to alter its 0.5 mL single dose pre-filled syringe presentation by affixing a label with a red half-dose mark (HDM). The HDM indicates the position at which actuation of the plunger would expel 0.25 mL from the syringe and leave 0.25 mL (extractable volume) remaining in the syringe for injection. (b)(4) qualification runs of (b)(4) syringes each were performed to determine the optimal position for affixing the label on the syringe barrel so that following the instructions for preparation of the 0.25 mL dose would most consistently result in the intended extractable volume (as determined by weight) remaining in the syringe.

Based on these qualification runs, the applicant selected a label position for which the lower edge of the label is 9.5 mm from the finger flange. Using syringes filled with 0.5 mL saline solution, actuating the plunger to the HDM at this position resulted in a mean extractable volume of ----------(b)(4)----------. Subsequent validation runs were performed with (b)(4) syringes on each of two labeling machines to demonstrate consistency of the label affixation process. Extractable volumes were evaluated for (b)(4) syringes labeled during the validation runs. The mean extractable volume was ----------(b)(4)----------. For comparison, a label position of (b)(4) resulted in instances of extractable volumes below the intended dose (mean volume (b)(4), range ---------(b)(4)----------), while a label position of (b)(4) resulted in larger extractable volumes (mean volume (b)(4), range ----------(b)(4)---------).

Reviewer comment: Clinical implications of the extractable volume range are discussed further in Section 9.2 (Additional Clinical Issues, Preparation for Administration of the 0.25 mL Dose).

On 17 December 2012 CBER consulted the Office of Compliance in the Center for Devices and Radiologic Health (CDRH/OC) regarding the adequacy of validation for the HDM label affixation process. After reviewing the validation data initially submitted by the applicant on 13 December 2012 in Amendment 8, the consultant from CDRH/OC recommended on 16 January 2013 to request additional validation data for the labeling machines. This additional data was submitted by the applicant on 18 February 2013 as Amendment 11. Following review of the additional data, the consultant from CDRH/OC recommended on 13 March 2013 that the HDM label validation appeared to be adequate.

CBER consulted the CDRH Human Factors Team (HFT) prior to submission of the BLA supplement and again on 1 April 2013 regarding recommendations for studies to assess the potential impact of human factors on preparation and administration of the 0.25 mL dose. The HFT recommended that the applicant complete the following assessments:

- An analysis of the intended user population to describe who the intended users are and the essential characteristics of all intended users.
- A use-related analysis to systematically consider each aspect of use and known use issues with similar devices, identify all potential use errors and failures, estimate the likelihood of each error, describe any potential effect on the delivery

of an effective dose and identify corrective measures for the most likely human errors.

- A validation study to demonstrate that representative users can read, understand and follow the instructions and perform necessary tasks to administer the correct pediatric dose.

5.5 Literature Reviewed

1. Diagana, M, *et al.* (2007) Japanese encephalitis revisited. *J. Neurol. Sci.*15:262(1-2);165-70.

2. Fischer, M, *et al.* (2010) Japanese encephalitis vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 59:1-27.

3. Hills, S, *et al.* (2010) Japanese encephalitis in travelers from non-endemic countries, 1973-2008. *Am. J. Trop. Med. Hyg.* 82(5):930-6.

4. Centers for Disease Control and Prevention. (2011) Japanese encephalitis in two children – United States, 2010.

5. Hoke *et al.* (1988) Protection against Japanese encephalitis by inactivated vaccines. *N. Engl. J. Med.* 319(10);608-14.

6. 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.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: IC51-323

Title: Safety and Immunogenicity of the Japanese Encephalitis Vaccine IC51 (IXIARO) in a Pediatric Population. (NCT01041573)

6.1.1 Objectives (Primary, Secondary, etc)

IC51-323 was a Phase 3 study to assess the safety and immunogenicity of IXIARO in infants, children, and adolescents 2 months to <18 years of age living in a region endemic for JEV.

The primary objective was to assess the systemic and local safety profile of IXIARO, administered in 2 doses in a 28-day interval, up to 7 months after the first IXIARO vaccination, in a pediatric population from endemic regions.

The secondary objectives were as follows:

- To assess immunogenicity of IXIARO in terms of geometric mean titer (GMT) and proportion of participants with $PRNT_{50}$ titer ≥1:10 at 56 days following the first IXIARO vaccination (28 days following completion of the primary series).
- To determine the appropriate dose of IXIARO in children 3 to <12 years of age (0.5 mL vs. 0.25 mL).
- To assess age-dependent differences in the immunogenicity and safety profile of IXIARO.
- To assess differences in safety and immunogenicity profile of IXIARO for subjects with no baseline immunity against JEV or Dengue virus and subjects with pre-existing immunity against JEV or Dengue virus.

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. Study participants were followed for 7 months from the first vaccination.

Reviewer comment: This study was conducted as a pediatric post-marketing requirement intended to serve as the primary source of safety and immunogenicity data to support licensure of IXIARO for use in children. Both the U.S. Food and Drug Administration and the European Medicines Agency provided input into the design of the study. Although the intended use population in the United States differs in some respects from the study population (e.g., in terms of ethnicity and prior exposure to Japanese encephalitis virus) an endemic population was selected for this study because pediatric use of Japanese encephalitis virus vaccine in non-endemic regions is ethically limited to a relatively small number of children whose travel activities result in a high risk of exposure. Consequently, it would have been impractical to generate definitive data from a non-endemic pediatric population.

6.1.3 Population

Healthy children and adolescents were enrolled at three clinical sites in the Philippines. Enrollment was completed using a gender-balanced, age-stratified approach.

Inclusion criteria:

- Age 2 months to <18 years at the time of first vaccination.
- Written informed consent by the participant's legal representative(s) and written informed assent, if applicable.
- Post-menarchal females were required to have a negative pregnancy test prior to enrollment and be willing to practice a reliable method of contraception.

Exclusion criteria:

- Clinical manifestation of Japanese encephalitis or known seropositivity for Japanese encephalitis virus neutralizing antibodies at screening.
- Prior vaccination against Japanese encephalitis, yellow fever, West Nile virus, or dengue virus.
- Prior vaccination with Prevnar (age <1 year only) or HAVRIX720 (all ages).
- For infants and children 6 months of age and older, active or passive immunization within 2 weeks before the first IXIARO vaccination through 1 week after the second IXIARO vaccination. For infants <6 months of age, active or passive immunization within 1 week before through 1 week after each IXIARO vaccination.
- Immunodeficiency, including post-organ transplantation or a family history of congenital or hereditary immunodeficiency.
- History of autoimmune disease.
- Receipt of ≥ 14 days of immunosuppressant or immune-modifying drug therapy (including corticosteroids at prednisone dose equivalent of ≥ 0.05 mg/kg/day) within 4 weeks prior to the first IXIARO vaccination.
- Pregnancy, lactation, or unreliable contraception in post-menarchal females.
- History of hypersensitivity reaction to vaccines or investigational vaccine components, or history of urticaria.
- Any contraindication to HAVRIX720 or Prevnar.
- Known infection with HIV, hepatitis B virus, or hepatitis C virus.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Study participants were randomized in an age stratified manner to receive either IXIARO or active control. The randomization ratio was 3:1 for children 1 year of age or older at the time of the first vaccination and 2:1 for infants <1 year of age at the time of the first vaccination. All vaccinations were administered intramuscularly. The doses and dosing regimens for IXIARO and active controls are summarized by age group in Table 5 below.

Table 5. Study IC51-323 Treatment Assignments

Age at first vaccination	IXIARO Days 0 and 28 (N=1411)	Prevnar (see schedule[1]) (N=64)	HAVRIX720 Day 0 and Month 7 (N=394)
2 months to <1 year	0.25 mL (3 µg) N=131	0.5 mL N=64	–
1 year to <3 years	0.25 mL (3 µg) N=640	–	0.5 mL N=213
3 years to <12 years[2]	0.25 mL (3 µg) N=100	–	–
3 years to <12 years[2]	0.5 mL (6 µg) N=300	–	0.5 mL N=101
12 years to <18 years	0.5 mL (6 µg) N=240	–	0.5 mL N=80

[1]Participants 2 to <6 months of age assigned to Prevnar treatment were vaccinated on Days 0, 28, and 56, with an optional 4th dose at age 12-15 months, which may have occurred outside of the study. Participants 6 to <12 months of age assigned to Prevnar treatment were vaccinated on Days 0, 56, and 210.
[2]A dose-finding run-in phase randomized the first 200 participants 3 to <12 years of age to receive IXIARO 0.25 mL or IXIARO 0.5 mL at a 1:1 ratio.

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. Three commercial batches were used for this study: JEV08K16A, JEV09K35A, and JEV10C48B.

HAVRIX720 is an inactivated hepatitis A vaccine manufactured by GlaxoSmithKline Biologicals and contains 720 EL.U antigen and 0.25 mg aluminum hydroxide adjuvant per 0.5 mL dose. Commercial batch AHAVB332AA was used for this study and was supplied as single-dose vials or pre-filled single-use syringes.

Prevnar is a 7-valent pneumococcal conjugate vaccine manufactured by Pfizer Inc. Each 0.5 mL dose contains 2 µg of capsular saccharide for each of the *Streptococcus pneumoniae* serotypes 4, 9V, 14, 18C, 19F, and 23F, and 4 µg of capsular saccharide for serotype 6B, conjugated to a total of 20 µg diphtheria CRM_{197} carrier protein and adjuvanted with 0.125 mg aluminum phosphate. Commercial batches 37667 and D14317 were used for this study and were supplied as single-use syringes.

Concomitant vaccinations were prohibited for participants assigned to IXIARO treatment as described in the exclusion criteria above. Following the active treatment period (Study Days 0 to 28) and through the end of study participation, vaccinations unless part of national immunization program.

Reviewer comment: Due to restrictions on concomitant vaccinations, there is no data to assess whether immune interference may occur between IXIARO and routine childhood immunizations. Use of IXIARO in children will be limited to those who will be at high risk for exposure to Japanese encephalitis vaccine due to travel activities, but the potential need for concomitant administration with other vaccines will be increased in infants and younger children (<19 months of age) who are completing their primary immunization

series. No immune interference was observed in adults when IXIARO was administered concomitantly with HAVRIX720.

6.1.5 Directions for Use

Study participants who were assigned to receive the 0.5 mL dose of IXIARO were vaccinated directly with the licensed 0.5 mL pre-filled syringe. For study participants assigned to receive the 0.25 mL dose of IXIARO, this dose 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 (used for all pediatric studies of IXIARO discussed in this review) differs from the intended licensed method of administration, which involves expulsion of 0.25 mL from the 0.5 mL pre-filled syringe using a half-dose guide mark printed on the syringe label, followed by injection of the contents remaining in the pre-filled syringe (see Section 5.4, Consultations). Consequently, the intended use method of administration for the 0.25 mL dose may result in injection volumes that are slightly higher on average and slightly more variable than those administered to Phase 3 study participants. However, these minor differences are unlikely to significantly affect safety or immune response to the vaccine.

6.1.7 Surveillance/Monitoring

Table 6 summarizes the surveillance and monitoring for study IC51-323.

Table 6. Surveillance and Monitoring for Study IC51-323

Visit	**0**	**1**	**2**	**3**	**4**
Study Day (± range)	**Day -14 (-14 to -1)**	**Day 0**	**Day 28 (± 4 d)**	**Day 56 (± 7 d)**	**Day 210 (± 14 d)**
HIV, HBsAg, HCV tests	X				
Eligibility criteria	X	X	X	X[1]	X[1]
Medical history	X	X			
Physical exam/vital signs	X	X	X	X	X
Hematology/biochemistry	X		X	X	X
Urinalysis	X	X	X	X	X
Urine pregnancy test[2]		X	X	X	X
Concomitant medications	X	X	X	X	X
Immediate adverse events (60 min after vaccination)		X[3]	X[3]	X[3]	X[3]
Assessment of previous injection site			X	X[4]	X[4]
Dispense diary		X	X[3]	X[3]	
Collect and review diary			X	X[4]	X[4]
Adverse event collection		X	X	X	X

Adapted from BLA 125280/125, 5.3.5.1.3 – Clinical Study Report IC51-323, Table 9.1 Schedule of Events, p. 43
[1]Participants assigned to receive Prevnar or HAVRIX720 at these visits.
[2]Post-menarchal female participants.
[3]Participants scheduled to receive study vaccine at these visits (see treatment schedule in Table 5 above).
[4]Participants who were vaccinated at the previous scheduled visit.

All scheduled follow-up occurred at clinic study sites. For 7 days following each study vaccination (except for Prevnar and HAVRIX720 vaccinations administered at Visit 4, Day 210), the study participants' parents or guardians used diary cards to record daily otic temperatures (obtained with infrared thermometers), solicited and unsolicited adverse events (AEs), and concomitant medications. Safety data collected from diary cards and interviews at each follow-up clinic visit was captured using an electronic case report form (eCRF), with regular review of eCRFs by a designated study safety monitor.

An independent data safety monitoring board (DSMB) reviewed all cases of suspected unexpected serious adverse reactions, as well as all cases of febrile convulsions, and also conducted at their request a partially blinded interim review of all safety data early in the study. Furthermore, the DSMB conducted a formal interim analysis of safety and immunogenicity data from the dose-finding run-in phase for participants 3 to <12 years of age (N=100 for each of the 0.25 mL and 0.5 mL doses) to determine the most appropriate dose with which to move forward for this age subgroup.

6.1.8 Endpoints and Criteria for Study Success

The primary study endpoint was the proportion of participants who experienced a serious adverse event (SAE) or medically attended adverse event (MAAE) in the 56 days following the first study vaccination. There were no pre-specified criteria for study success.

Secondary endpoints related to safety included the rates of participants who experienced:

- A SAE or MAAE in the 7 months following the first study vaccination.
- Solicited AEs over 7 consecutive days following each study vaccination (except active comparator vaccines administered at Month 7).
- Unsolicited AEs in the 56 days and 7 months following the first study vaccination.
- Laboratory abnormalities in the 56 days and 7 months following the first study vaccination.

Secondary endpoints related to immunogenicity included geometric mean titers (GMTs) for neutralizing antibodies against JEV and proportion of participants with neutralizing antibody titer ≥1:10 at baseline (Day 0) and at 28 days and 6 months following completion of the IXIARO primary immunization series. JEV neutralizing antibody titers were measured by a validated plaque reduction neutralization assay using a 50% plaque reduction endpoint ($PRNT_{50}$).

Reviewer comment: The endpoints for this study were appropriate to evaluate the safety of IXIARO in children and to evaluate the immunogenicity of IXIARO in children as a predictor of vaccine effectiveness. As described previously in Section 2, a neutralizing antibody titer of ≥1:10 as measured by $PRNT_{50}$ is considered to be reasonable evidence of protection against JEV disease. The immunologic measures of $PRNT_{50}$ GMT and proportion of participants with $PRNT_{50}$ titer ≥1:10 were the primary endpoints used to infer vaccine effectiveness of IXIARO by non-inferiority comparison to the licensed JE-VAX vaccine. Although the term "seroconversion" appears throughout the IC51-323 study report to refer to a $PRNT_{50}$ titer ≥1:10, this term is meaningful only in the context of a negative pre-vaccination antibody titer and only for the first measurement of neutralizing antibody response following completion of the primary immunization series.

Therefore, this review will not reference seroconversion rates and will instead describe the proportion of participants with $PRNT_{50}$ titer ≥1:10.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The Statistical Analysis Plan included descriptive analyses only without formal hypothesis testing. The study sample size was calculated to provide a total pediatric safety database of 1,500 IXIARO recipients throughout all clinical studies. Sample sizes for immunogenicity analyses (which were conducted on a subset of all IXIARO recipients) were designed to provide a sufficient amount of data from initially JEV-naïve participants in each age subgroup, assuming that 10% of participants assigned to undergo immunogenicity testing would be excluded from the per-protocol analysis set due to a major protocol violation.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

All safety analyses were conducted on the Safety Populations for each study vaccination, which consisted of all participants who received at least one vaccination and who had evaluable safety data in the time period of interest.

Immunogenicity analyses were conducted for recipients of IXIARO only using the following defined populations:

- Intent-to-treat (ITT) population, consisting of all participants who received at least one dose of IXIARO and who were assigned to the immunogenicity subgroup.
- Per Protocol (PP) population, consisting of all participants who completed the immunization schedule without a major protocol violation, who were assigned to the immunogenicity subgroup and who had evaluable immunogenicity data at the time point of interest.

6.1.10.1.1 Demographics and Baseline Characteristics

Table 7 summarizes the demographic data for the participants enrolled in study IC51-323.

Table 7. Demographic Information for Study IC51-323

Demographic parameter	**IXIARO 0.25 mL (N=871)**	**IXIARO 0.5 mL (N=540)**	**Prevnar (N=64)**	**HAVRIX720 (N=394)**	**Total (N=1869)**
Mean age, years (SD)	2.4 (2.2)	10.6 (4.1)	0.7 (0.2)	6.0 (5.2)	5.5 (5.1)
2 to <6 months	30	0	15	0	45
6 to <12 months	101	0	49	0	150
1 to <3 years	640	0	0	213	853
3 to <12 years	100	300	0	101	501
12 to <18 years	0	240	0	80	320
Gender – male (%)	422 (48.5%)	291 (53.9%)	34 (53.1%)	197 (50.0%)	944 (50.5%)
Ethnicity – Asian (%)	871 (100%)	540 (100%)	64 (100%)	394 (100%)	1869 (100%)

Adapted from BLA 125280/125, 5.3.5.1.3 – Clinical Study Report IC51-323, Table 10.2

Reviewer comment: There were no obvious imbalances between treatment groups with respect to gender or ethnicity, and gender distribution for the entire study was evenly split between males and females. Differences between treatment groups with respect to mean age reflect the different age stratifications for each treatment assignment. The demographic data for the ITT and PP populations were similar to those for the safety population. The study population is similar to the intended use population in the U.S. with respect to age and gender but is significantly different with respect to ethnicity (100% Asian) due to the study location in the Philippines.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
The majority of enrolled participants (68.2%) reported no medical history. The most frequently recorded medical conditions included a previous history of infections and infestations (25.3%). There were no imbalances between treatment groups with respect to baseline medical history. Baseline characteristics for pre-existing positive serology for Japanese encephalitis virus (JEV) and Dengue virus (DENV) were assessed because natural immunity to JEV and DENV could potentially influence the immune response to IXIARO. Baseline JEV and DENV serostatus data are summarized in Table 8 with stratification by age subgroup.

Table 8. Baseline JEV and DENV Serostatus for Participants in Study IC51-323

Demographic parameter	IXIARO 0.25 mL (N=871)	IXIARO 0.5 mL (N=540)	Prevnar (N=64)	HAVRIX720 (N=394)	Total (N=1869)
% JEV seropositive	4.5	31.3	9.4	20.1	15.7
2 to <6 months	23.3	n/a	20.0	n/a	22.2
6 to <12 months	1.0	n/a	6.1	n/a	2.7
1 to <3 years	3.0	n/a	n/a	2.8	2.9
3 to <12 years	12.0	22.3	n/a	33.7	22.6
12 to <18 years	n/a	42.5	n/a	48.8	44.1
% DENV seropositive	17.7	67.4	29.7	41.1	37.4
2 to <6 months	56.7	n/a	93.3	n/a	68.9
6 to <12 months	7.9	n/a	10.2	n/a	8.7
1 to <3 years	12.0	n/a	n/a	16.4	13.1
3 to <12 years	52.0	59.7	n/a	70.3	60.3
12 to <18 years	n/a	77.1	n/a	70.0	75.3

Adapted from BLA 125280/125, 5.3.5.1.3 – Clinical Study Report IC51-323, Table 10.4
n/a = not applicable (no participants in this age subgroup for the study treatment).

Reviewer comment: Baseline serostatus for JEV and DENV was similar for the ITT and PP populations compared to the safety population. The observed differences between treatment groups in rates of baseline positive serology for both JEV and DENV were expected due to the specific age stratifications for each treatment assignment and reflect persistence of maternal antibody for the youngest age subgroup, followed by loss of maternal antibody and then increasing frequency of natural exposure to JEV and DENV with age. Baseline positive serology for DENV was uniformly higher compared to baseline positive serology for JEV, reflecting the comparative epidemiology of these two viruses and higher likelihood of exposure to DENV in the Philippines.

6.1.10.1.3 Subject Disposition
Table 9 summarizes the disposition of participants in study IC51-323.

Table 9: Disposition of Participants in Study IC51-323.

Randomized to treatment assignment	IXIARO 0.25 mL (N=871)	IXIARO 0.5 mL (N=541)	Prevnar (N=64)	HAVRIX720 (N=393)	Total (N=1869)
Vaccinated at least once[1]	871	540	64	394	1869
Completed study	858 (98.5%)	535 (99.1%)	62 (96.9%)	387 (98.2%)	1842 (98.6%)
Premature discontinuation	13 (1.5%)	5 (0.9%)	2 (3.1%)	7 (1.8%)	27 (1.4%)
Consent withdrawn	5	2	0	2	9
Lost to follow-up	1	0	1	2	4
Discontinued due to AE	2	0	0	0	2
Died	0	1	0	0	1
Other reason[2]	5	2	1	3	11
Protocol violation/ deviation[3]	73 (8.4%)	19 (3.5%)	5 (7.8%)	24 (6.1%)	121 (6.5%)
Major violation/ deviation	36 (4.1%)	14 (2.6%)	2 (3.1%)	11 (2.8%)	63 (3.4%)
Minor violation/ deviation	40 (4.6%)	5 (0.9%)	3 (4.7%)	15 (3.8%)	63 (3.4%)

Adapted from BLA 125280/125, 5.3.5.1.3 – Clinical Study Report IC51-323, Figure 10.1
[1]One participant was randomized to IXIARO 0.5 mL but received HAVRIX720.
[2]The most common reason given was relocation away from the study site.
[3]Some participants committed both major and minor protocol violations or deviations but are counted only once in this row.

Reviewer comment: The number of premature discontinuations and major protocol violations or deviations were generally low (well within the statistical assumptions of the study's sample size calculation) and were similar between treatment groups.

6.1.11 Efficacy Analyses

Clinical efficacy was not assessed in this study. As discussed previously, evaluation of IXIARO vaccine effectiveness was based on JEV-neutralizing antibody responses, which provide reasonable evidence of protection against clinical disease.

6.1.11.1 Analyses of Primary Endpoint(s)

The sole primary endpoint for study IC51-323 related to safety. All immunogenicity analyses involved secondary endpoints.

6.1.11.2 Analyses of Secondary Endpoints

The immunogenicity endpoints for study IC51-323 were JEV $PRNT_{50}$ geometric mean titer (GMT) and proportion of participants with $PRNT_{50}$ titer ≥1:10 at Day 0, Day 56 (28 days after completion of the immunization series), and Month 7 (6 months after completion of the immunization series). The results of the immunogenicity analyses for the ITT population are summarized in Tables 10 and 11 with stratification by age subgroup and IXIARO dose.

Table 10. $PRNT_{50}$ Geometric Mean Titers Following IXIARO (Intent to Treat Population), Study IC51-323

Age subgroup	IXIARO dose	Day 0 GMT[1] [95% CI] N	Day 56 GMT[1] [95% CI] N	Month 7 GMT[1] [95% CI] N
2 to <6 months	0.25 mL	8.4 [4.3, 16.7] N=10	687.4 [263.2, 1795.1] N=9	159.3 [110.0, 230.7] N=10
6 to <12 months	0.25 mL	5 [5.0, 5.0] N=20	377.8 [210.3, 678.8] N=19	64.0 [39.4, 104.1] N=18
1 to <3 years	0.25 mL	5.5 [5.0, 6.1] N=124	258.9 [214.4, 312.6] N=121	38.9 [31.8, 47.7] N=125
3 to <12 years	0.25 mL	6.1 [5.4, 6.8] N=100	113.9 [89.9, 114.3] N=98	28.8 [22.6, 36.5] N=96
3 to <12 years	0.5 mL	6.5 [5.8, 7.4] N=101	213.7 [175.6, 260.0] N=100	43.6 [35.6, 53.4] N=100
12 to <18 years	0.5 mL	13.1 [10.7, 16.1] N=140	175.6 [147.8, 208.7] N=137	86.6 [70.7, 106.4] N=137

Adapted from BLA 125280/125.6, 5.3.5.1.3 – Clinical Study Report IC51-323, Section 14, Table 14.2.2.13
[1]Reciprocal $PRNT_{50}$ titers <10 were imputed to a value of 5.

Excluding the data for the age subgroup 3 to <12 years vaccinated with IXIARO 0.25 mL, $PRNT_{50}$ GMTs at Day 56 were inversely correlated with age subgroup and were generally similar to or higher than Day 56 GMTs in previous studies of IXIARO in adults. $PRNT_{50}$ GMTs at Month 7 were similar to GMTs in previous studies in adults at 5 months after completion of the primary immunization series. There were no significant differences between $PRNT_{50}$ GMTs for the ITT and PP populations.

Reviewer comment: The Day 56 $PRNT_{50}$ GMT in the 3 to <12 year-old age subgroup vaccinated with IXIARO 0.25 mL was clearly inferior to that observed in the same age subgroup vaccinated with IXIARO 0.5 mL. Consequently, following the initial dose-finding run-in phase the 0.5 mL dose was selected for the remainder of enrollees in this age subgroup.

Table 11. Proportion of participants with $PRNT_{50}$ titer ≥1:10 following IXIARO (Intent to Treat Population), Study IC51-323

Age subgroup	IXIARO dose	Day 0 %$PRNT_{50}$ ≥1:10 (n/N) [95% CI]	Day 56 %$PRNT_{50}$ ≥1:10 (n/N) [95% CI]	Month 7 %$PRNT_{50}$ ≥1:10 (n/N) [95% CI]
2 to <6 months	0.25 mL	30% (3/10) [10.8, 60.3]	100% (9/9) [70.1, 100.0]	100% (10/10) [72.2, 100.0]
6 to <12 months	0.25 mL	0% (0/20) [0.0, 16.1]	100% (19/19) [83.2, 100.0]	100% (18/18) [82.4, 100.0]
1 to <3 years	0.25 mL	3% (4/125) [1.3, 7.9]	99% (119/120) [95.4, 99.9]	85.5% (106/124) [78.2, 90.6]
3 to <12 years	0.25 mL	12.0% (12/100) [5.6, 18.4]	96% (94/98) [90.0, 98.4]	77% (74/96) [67.7, 84.4]
3 to <12 years	0.5 mL	17% (17/101) [10.8, 25.3]	100% (100/100) [96.3, 100.0]	91% (91/100) [83.8, 95.2]
12 to <18 years	0.5 mL	46% (64/140) [37.7, 54.0]	100% (137/137) [97.3, 100.0]	97.1% (133/137) [92.7, 98.9]

Adapted from BLA 125280/125.6, 5.3.5.1.3 – Clinical Study Report IC51-323, Section 14, Tables 14.1.4.2 and 14.2.1.11

Excluding the data for the age subgroup 3 to <12 years vaccinated with IXIARO 0.25 mL, the proportions of participants with $PRNT_{50}$ titer ≥1:10 at Day 56 were 99-100%. The proportions of participants with $PRNT_{50}$ titer ≥1:10 at Month 7 were 85-100%, with no distinguishable pattern of relationship to age subgroup. There were no significant differences between seroprotection rates for the ITT and PP populations. By historical comparison, the proportions of adults with $PRNT_{50}$ titer ≥1:10 at Day 56 and Month 6 following the first dose of IXIARO were 96.4% and 95%, respectively.

Reviewer comment: Persistence of neutralizing antibodies appears to be somewhat lower in the middle pediatric age subgroups (1 to <12 years) compared to the other age subgroups and to data from previous studies in adults, although the significance of these difference is unclear due to small sample sizes. An ongoing extension phase of study IC51-323 (IC51-325) will assess long-term immunogenicity of IXIARO in children living in a JEV-endemic area. If the proportion of children with $PRNT_{50}$ titer ≥1:10 declines significantly through 1 year after completion of the primary immunization series, a booster dose for children with continued exposure may be warranted earlier than is recommended for persons 17 years of age and older.

6.1.11.3 Subpopulation Analyses

A post-hoc analysis requested by CBER evaluated $PRNT_{50}$ GMTs and proportion of participants with $PRNT_{50}$ titer ≥1:10 stratified by gender. $PRNT_{50}$ GMTs were nominally higher for females compared to males at both Day 56 and Month 7 and across all age subgroups, although these differences were not statistically significant. The proportions

of participants with $PRNT_{50}$ titer ≥1:10 were similar for males compared to females at both Day 56 and Month 7 for all age subgroups.

Immunogenicity analyses stratified by ethnicity were not possible due to the homogenous study population (uniformly Asian).

Reviewer comment: The observed higher $PRNT_{50}$ GMTs in females compared to males are reminiscent of similar observations in adult studies of IXIARO immunogenicity but may also be due to chance, as the differences were not statistically significant. These differences are also unlikely to be clinically significant, since seroprotection rates were similar between males and females.

Planned analyses evaluated the effect of baseline JEV and DENV serostatus on $PRNT_{50}$ GMTs and proportion of participants with $PRNT_{50}$ titer ≥1:10. The results of these analyses are summarized in Tables 12 and 13 and exclude data for participants in the 3 to <12 year-old age subgroup who received IXIARO 0.25 mL.

Table 12. $PRNT_{50}$ Geometric Mean Titers and Proportion of Participants with $PRNT_{50}$ titer ≥1:10 Stratified by Baseline JEV Serostatus* (Intent to Treat Population), Study IC51-323

IXIARO 0.25 mL	**Day 56 – Seropositive at Baseline**	**Day 56 – Seronegative at Baseline**	**Month 7 – Seropositive at Baseline**	**Month 7 – Seronegative at Baseline**
GMT [95% CI] N	734.7 [251.5,2146.4] N=6	281.3 [235.1,336.6] N=142	111.55 [44.1,281.9] N=7	44.0 [36.5,53.0] N=145
%$PRNT_{50}$ ≥1:10 (n/N) [95% CI]	100% (6/6) [61.0,100.0]	99.3% (141/142) [96.1,99.9]	100% (7/7) [64.6,100.0]	87.6% (127/145) [81.2,92.0]
IXIARO 0.5 mL	**Day 56 – Seropositive at Baseline**	**Day 56 – Seronegative at Baseline**	**Month 7 – Seropositive at Baseline**	**Month 7 – Seronegative at Baseline**
GMT [95% CI] N	168.1 [133.1,212.3] N=79	203.3 [173.9,237.5] N=158	97.9 [75.6,126.9] N=79	52.8 [44.1,63.1] N=158
%$PRNT_{50}$ ≥1:10 (n/N) [95% CI]	100% (79/79) [95.4,100.0]	100% (158/158) [97.6,100.0]	98.7% (78/79) [93.2,99.8]	92.4% (146/158) [87.2,95.6]

Adapted from BLA 125280/125.7, 5.3.5.1.3 – Response to Information Request, Table 19

*Seropositive = $PRNT_{50}$ titer ≥1:10; seronegative = $PRNT_{50}$ titer <1:10.

Table 13. $PRNT_{50}$ Geometric Mean Titers and Proportion of Participants with $PRNT_{50}$ titer ≥1:10 Stratified by Baseline DENV Serostatus* (Intent to Treat Population), Study IC51-323

IXIARO 0.25 mL	**Day 56 – Seropositive at Baseline**	**Day 56 – Seronegative at Baseline**	**Month 7 – Seropositive at Baseline**	**Month 7 – Seronegative at Baseline**
GMT [95% CI] N	250.3 [157.3,398.2] N=23	297.5 [244.9,361.3] N=122	62.2 [36.3,106.6] N=24	42.7 [35.0,52.0] N=125
%$PRNT_{50}$ ≥1:10 (n/N) [95% CI]	100% (23/23) [85.7,100.0]	99.2% (121/122) [95.5,99.9]	91.7% (22/24) [74.2,97.7]	87.2% (109/125) [80.2,92.0]
IXIARO 0.5 mL	**Day 56 – Seropositive at Baseline**	**Day 56 – Seronegative at Baseline**	**Month 7 – Seropositive at Baseline**	**Month 7 – Seronegative at Baseline**
GMT [95% CI] N	154.4 [132.2,180.3] N=153	285.6 [229.9,354.8] N=81	68.8 [57.2,82.7] N=153	57.9 [44.3,75.9] N=81
%$PRNT_{50}$ ≥1:10 (n/N) [95% CI]	100% (153/153) [97.6,100.0]	100% (81/81) [95.5,100.0]	96.7% (148/153) [92.6,98.6]	90.1% (73/81) [81.7,94.9]

Adapted from BLA 125280/125.7, 5.3.5.1.3 – Response to Information Request, Table 19

*Seropositive is defined as $PRNT_{50}$ titer ≥1:10. Seronegative is defined as $PRNT_{50}$ titer <1:10.

For participants 2 months to <3 years of age vaccinated with IXIARO, negative baseline JEV serostatus was associated with lower $PRNT_{50}$ antibody titers at Day 56 and Month 7 and a marginally lower proportion of participants with $PRNT_{50}$ titer ≥1:10 at Month 7 compared to positive baseline JEV serostatus. These differences were not statistically significant. Half of the baseline seropositive participants in this treatment group were 2 to <6 months old, indicating that presence of maternal antibody to JEV does not adversely affect the immune response to IXIARO. Among baseline JEV seropositive participants, a four-fold increase in PRNT50 titer at Day 56 compared to baseline was observed for 58.8% (10/17) of participants who were treated with IXIARO 0.25 mL and for 54.4% (43/79) of participants who were treated with IXIARO 0.5 mL. Negative baseline DENV serostatus was associated with higher $PRNT_{50}$ antibody titers at Day 56. This difference was not statistically significant and disappeared by Month 7.

For participants 3 years of age or older vaccinated with IXIARO, negative baseline JEV serostatus was associated with higher $PRNT_{50}$ antibody titers at Day 56 but lower $PRNT_{50}$ antibody titers and a lower proportion of participants with $PRNT_{50}$ titer ≥1:10 at Month 7. The difference in $PRNT_{50}$ GMTs at Month 7 was the only statistically significant difference for this treatment group and is unlikely to be clinically significant. Negative baseline DENV serostatus was associated with significantly higher $PRNT_{50}$ antibody titers at Day 56, but this difference disappeared by Month 7.

Reviewer comment: U.S. travelers to endemic areas are likely to be JEV and DENV seronegative at baseline, so immune response to IXIARO among pediatric recipients in

the U.S. will probably be most similar to the responses observed for the baseline JEV and DENV seronegative study participants.

6.1.11.4 Dropouts and/or Discontinuations

There were relatively few dropouts, discontinuations, and major protocol violations leading to exclusion of participants from immunogenicity analyses, so there was likely minimal impact of these exclusions on the immunogenicity observations and conclusions.

6.1.12 Safety Analyses

6.1.12.1 Methods

All safety analyses were conducted on the safety population, consisting of all subjects who received were randomized to treatment assignment, received at least 1 study vaccination, and for whom safety data was available.

For 7 days following each study vaccination, diary cards were used to record daily temperatures and solicited AEs. 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 each study vaccination and at clinic follow-up visits on Days 28 and 56 and at Month 7. No safety data was collected following Prevnar or HAVRIX720 administered at Month 7.

Reviewer comment: Subjective solicited AEs including injection site pain, injection site itching, flu-like symptoms, muscle pain, and headache were not recorded for participants whose cognitive or language development were not sufficient to assess for the presence or absence these symptoms.

6.1.12.2 Overview of Adverse Events

An overview of safety data through day 56 is presented in Table 14 for participants 2 months to <1 year of age and in Table 15 for participants 1 year to <18 years of age. These analyses include the primary safety endpoint of proportions of participants with at least one SAE or medically attended AE (MAAE) through Day 56 following the first study vaccination.

Table 14. Overview of Safety Data through Day 56 for Participants 2 Months to <1 Year of Age in Study IC51-323

Rate (%) of participants reporting ≥1:	IXIARO (N=131)	Prevnar (N=64)
Death	0	0
SAE	0	1.6
Related SAE	0	0
Medically attended AE	38.2	42.2
Related medically attended AE	2.3	3.1
Solicited AE	58.0	59.4
Unsolicited AE	72.5	65.6
Probably related	3.8	0
Possibly related	3.8	3.1
Solicited or unsolicited AE by severity grade		
Grade 1	51.9	64.1
Grade 2	26.7	17.2
Grade 3	4.6	6.3
Grade 4	0.8	0

Adapted from BLA 125280/125.6, 5.3.5.1.3 – Clinical Study Report IC51-323, Table 12.1

Table 15. Overview of Safety Data through Day 56 for Participants 1 to <18 Years of Age in Study IC51-323

Rate (%) of participants reporting ≥1:	IXIARO 0.25 mL (N=740)	IXIARO 0.5 mL (N=540)	IXIARO total (N=1280)	HAVRIX720 (N=394)
Death	0	0	0	0
SAE	0.8	0	0.5	1.0
Related SAE	0	0	0	0
Medically attended AE	24.1	5.2	16.1	14.2
Related medically attended AE	1.5	0.2	0.9	1.0
Solicited AE	45.8	33.9	40.8	29.4
Unsolicited AE	58.9	29.4	46.5	46.4
Probably related	1.2	0.2	0.8	1.3
Possibly related	4.6	1.1	3.1	2.5
Solicited or unsolicited AEs by severity grade				
Grade 1				
Grade 2	51.1	40.9	46.8	49.7
Grade 3	13.8	6.5	10.7	6.6
Grade 4	6.5	1.5	4.4	3.3
	0.8	0	0.2	0

Adapted from BLA 125280/125.6, 5.3.5.1.3 – Clinical Study Report IC51-323, Table 12.2

Analyses of safety data through the end of the study (Month 7) were most notable for 2 additional SAEs among IXIARO recipients 2 months to <1 year of age and 15 additional SAEs, including one death, for IXIARO recipients 1 to <18 years of age. Only one nonfatal SAE was assessed as related to IXIARO, and a similar rate of additional SAEs

was observed among recipients of Prevnar and HAVRIX720. Rates of medically attended AEs and unsolicited AEs were modestly increased for all treatment groups through Month 7 compared to Day 56, but only a select few of these events were assessed as related to study treatment.

Overall there was only 1 death and very few SAEs throughout the entire study. These events will be discussed in detail in sections 6.1.12.3 and 6.1.12.4 below. Since all SAEs were medically attended, the rates of medically attended AEs reflect the study's primary safety endpoint of SAEs and medically attended AEs through Day 56. The majority of medically attended AEs were infections and infestations (most commonly upper respiratory tract infection, see summary of unsolicited AEs below). Rates of medically attended AEs and unsolicited AEs assessed as related to study treatment were generally low (1-5%) across treatment groups. The majority of AEs associated with IXIARO in each age subgroup were mild, and severe AEs accounted for only 1.5% of all AEs associated with IXIARO 0.5 mL and 7% of all AEs associated with IXIARO 0.25 mL.

There were no statistically significant differences in rates of medically attended AEs between IXIARO 0.25 mL and Prevnar for participants 2 months to <1 year of age or between IXIARO both treatment arms and HAVRIX720 for participants 1 to <18 years of age. Similarly, there were no statistically significant differences in overall rates of solicited and unsolicited AEs or in rates of unsolicited AEs stratified by severity grade between IXIARO and the active comparator for either age subgroup. Among participants 1 to <18 years of age, there were statistically significant differences in rates of medically attended AEs and unsolicited AEs between recipients of IXIARO 0.25 mL and recipients of IXIARO 0.5 mL (and similarly between recipients of IXIARO 0.25 mL and recipients of HAVRIX720), reflecting an expected higher rate of symptoms prompting medical attention among the youngest subgroup (1 to <3 years of age). No statistically significant differences were observed when the analysis was limited to AEs assessed as related to study treatment.

Among participants <1 year of age, there were no differences in rates of unsolicited AEs or medically attended AEs between recipients of IXIARO and recipients of Prevnar.

Reviewer comment: Assessments of causality as indicated in the above analyses are those of individual blinded investigators. Upon evaluation of the data, this reviewer found the investigators' assessments to be reasonable.

Local and systemic solicited AEs collected by diary card for 7 days after each study vaccination are summarized by age subgroup in Tables 16-19 below. Safety data was not assessed for participants 1 year of age or older following administration of the second HAVRIX720 at Month 7.

Table 16. Solicited Adverse Reactions in Participants 2 Months to <1 Year of Age in Study IC51-323

Rate (%) of participants reporting:	IXIARO Dose 1 (N=131)	Prevnar Dose 1 (N=64)	IXIARO Dose 2 (N=131)	Prevnar Dose 2 (N=64)
Injection Site Reactions				
Tenderness	3.1	12.7	0.8	3.3
Hardening	0.0	7.9	0.0	1.6
Swelling	1.5	6.3	1.5	1.6
Redness	17.6	25.4	5.3	16.4
Systemic Reactions				
Irritability	15.3	12.7	8.4	8.2
Vomiting	7.6	6.3	3.8	1.6
Diarrhea	11.5	6.3	8.4	4.9
Excessive fatigue	3.1	7.9	1.5	3.3
Rash	8.4	9.5	3.8	4.9
Loss of appetite	5.3	9.5	5.3	6.6
Fever (≥37.7˚C)	23.7	25.4	14.5	23.3

Source: BLA 125280/125.6, 5.3.5.1.3 – Clinical Study Report IC51-323, Section 14, Tables 14.3.4.1 and 14.3.4.2

Table 17. Solicited Adverse Reactions in Participants 1 to <3 Years of Age in Study IC51-323

Rate (%) of participants reporting:	IXIARO Dose 1 (N=640)	HAVRIX720 Dose 1 (N=213)	IXIARO Dose 2 (N=637)
Injection Site Reactions			
Pain*	3.6 (6/165)	7.4 (4/54)	3.6 (6/166)
Itching*	0.6 (1/180)	0 (0/63)	0 (0/184)
Tenderness	3.1	5.6	1.4
Hardening	0.9	0.5	0.3
Swelling	2.0	3.3	1.7
Redness	6.1	7.5	2.5
Systemic Reactions			
Irritability	7.7	5.6	2.7
Nausea*	2.2 (5/228)	1.3 (1/78)	0.9 (2/229)
Vomiting	4.2	5.6	2.8
Diarrhea	7.0	5.2	4.6
Flu-like symptoms*	7.7 (13/169)	13.3 (8/60)	4.0 (7/176)
Excessive fatigue	2.5	0.9	1.1
Muscle pain*	2.3 (3/130)	0 (0/42)	0.7 (1/136)
Rash	4.2	2.3	1.3
Headache*	1.5 (2/135)	4.4 (2/45)	1.4 (2/143)
Loss of appetite	5.6	4.2	2.5
Fever (≥37.7°C)	20.2	15.5	12.7

Source: BLA 125280/125.6, 5.3.5.1.3 – Clinical Study Report IC51-323, Section 14, Tables 14.3.4.1 and 14.3.4.2

*Where the number of participants with available data for a particular symptom differs from the number of participants with available diary card data, the proportion (n/N) is provided; n is the number of participants who reported that symptom, and N is the number of participants with available data for that symptom.

Table 18. Solicited Adverse Reactions in Participants 3 to <12 Years of Age in Study IC51-323

Rate (%) of participants reporting:	IXIARO Dose 1 (N=291-300)	HAVRIX720 Dose 1 (N=99-101)	IXIARO Dose 2 (N=293-300)
Injection Site Reactions			
Pain	5.5	3.0	1.7
Itching	1.4	0	0
Tenderness	4.3	1.0	2.0
Hardening	1.3	0	0
Swelling	2.0	3.0	2.0
Redness	3.0	1.0	0.7
Systemic Reactions			
Irritability	0	1.0	0.3
Nausea	0.3	0	0.3
Vomiting	1.7	1.0	0.7
Diarrhea	0.7	.0	1.0
Flu-like symptoms	1.4	2.0	0.3
Excessive fatigue	1.0	1.0	0.7
Muscle pain	2.4	3.0	0.3
Rash	1.0	0	0.0
Headache	3.8	4.0	1.4
Loss of appetite	1.0	2.0	1.0
Fever (≥37.7°C)	10.7	8.9	4.7

Source: BLA 125280/125.6, 5.3.5.1.3 – Clinical Study Report IC51-323, Section 14, Tables 14.3.4.1 and 14.3.4.2
*Number of accessible diary cards for a particular symptom differs from the number of accessible diary cards overall.

Reviewer comment: Not shown are solicited AEs following IXIARO 0.25 mL among 100 participants 3 to <12 years of age enrolled into the initial dose-finding run-in phase. Generally the rates of solicited AEs for these participants were similar to those following IXIARO 0.5 mL with the exception of a higher rate of fever (15%) following the first dose of IXIARO 0.25 mL.

Table 19. Solicited Adverse Reactions in Participants 12 to <18 Years of Age in Study IC51-323

Rate (%) of participants reporting:	IXIARO Dose 1 (N=240)	HAVRIX720 Dose 1 (N=80)	IXIARO Dose 2 (N=238)
Injection Site Reactions			
Pain	15.0	12.5	6.7
Itching	0.8	0	0.4
Tenderness	10.0	13.8	4.6
Hardening	1.3	0	0.4
Swelling	0.4	1.3	0.8
Redness	0.8	6.3	3.8
Systemic Reactions			
Irritability	2.1	1.3	0
Nausea	2.1	1.3	0
Vomiting	1.3	0	0
Diarrhea	0.4	2.5	0
Flu-like symptoms	3.3	7.5	1.3
Excessive fatigue	2.5	1.3	0.4
Muscle pain	2.9	5.0	1.3
Rash	0.8	1.3	0
Headache	4.6	5.0	3.4
Loss of appetite	2.1	2.5	0.4
Fever (≥37.7°C)	3.8	6.3	5.0

Source: BLA 125280/125.6, 5.3.5.1.3 – Clinical Study Report IC51-323, Section 14, Tables 14.3.4.1 and 14.3.4.2

Most solicited AEs were mild to moderate and resolved within several days. Severe injection site reactions occurred among 2.8% of all participants following either dose of IXIARO, with a maximum age group stratified rate of 3.8% among participants 1 to <3 years of age and a minimum rate of 0% among participants 2 months to <1 year of age and participants 12 to <18 years of age. Severe systemic solicited AEs occurred among 0.3% of all participants after either dose of IXIARO, with a maximum age group stratified rate of 1.5% among participants 2 months to <1 year of age and a minimum rate of 0% among participants 1 to <3 years of age.

Reviewer comment: The overall rates of solicited AEs following IXIARO were similar to those following the active comparators, both within age subgroups or for the age-combined study population. There were no instances where a higher solicited AE rate for IXIARO was statistically significant. Rates of solicited AEs following IXIARO were generally lower following the second dose compared to the first dose. Rates of solicited systemic AEs were generally higher in the youngest age subgroups, whereas rates of injection site reactions were highest for the oldest age subgroup (with the exception of redness, which was most frequent in the youngest age subgroup).

The most common solicited AEs following IXIARO were injection site reactions, fever, fatigue, myalgias, and flu-like symptoms. The majority of these AEs were mild in severity, with moderate to severe rates of <1% for most solicited AEs, including injection site reactions. The major exception to this observation was fever, which is summarized

for the first study vaccination in detail in Table 20 below, with stratification by age subgroup and maximum severity.

Reviewer comment: Since fever was pre-specified for this study as an otic temperature ≥ 37.7˚C, the summary presented in Table 20 includes a post-hoc analysis of fever rates using a fever definition of ≥ 38.0˚C, which is a more commonly used definition for studies of U.S. licensed vaccines. The analysis in Table 20 focuses exclusively on the first study vaccination, since solicited fever rates following the second IXIARO vaccination were generally much lower than those following the first vaccination. Additionally, there is no solicited fever data available following the second comparator vaccination at Month 7 for participants aged ≥ 6 months.

Table 20. Rates of Solicited Fever in the 7 Days Following IXIARO and Active Comparators (First Dose, by Age Subgroup and Maximum Severity)

Rate (%) of participants reporting:	Any fever ≥37.7˚C	Any fever ≥38.0˚C	Grade 2 (38.7-39.3˚C)	Grade 3 (39.4-40.5˚C)	Grade 4 (>40.5˚C)
Age <1 year					
IXIARO	23.7	15.3	6.1	0	0
Prevnar	25.4	12.7	1.6	1.6	0
Age 1 to <3 years					
IXIARO	20.2	11.9	3.0	1.6	0
HAVRIX720	15.5	11.3	1.4	1.9	0
Age 3 to <12 years					
IXIARO	10.7	6.7	2.0	1.0	0
HAVRIX720	8.9	5.9	2.0	0	0
Age 12 to <18 years					
IXIARO	3.8	0.8	0.4	0	0
HAVRIX720	6.3	5.0	1.3	1.3	0

Source: BLA 125280/125.10, 5.3.5.1.3 – Post-Hoc Analyses for Study IC51-323

Similar to most other solicited systemic AEs, rates of fever were inversely correlated with age subgroup. Fever rates were evenly distributed across all 7 days of data collection, with no identifiable peak day. Fever rates across all age subgroups decreased substantially when the slightly more restrictive (and more commonly accepted) definition of ≥ 38.0˚C was applied. There were no notable differences in solicited fever rates between IXIARO and active comparators, except for somewhat higher rates of Grade 2 fevers following IXIARO in the youngest 2 age subgroups (age <3 years). Additional post-hoc analyses revealed no clear pattern of increased solicited fever rates associated with baseline JEV or DENV serostatus or with vaccine lot.

There were a total of 12 febrile convulsions throughout the entire study period: 8 among recipients of IXIARO (1.3% of recipients 1 to <3 years of age), 3 among recipients of HAVRIX720 (1.4% of recipients 1 to <3 years of age), and 1 in a recipient of Prevnar (rate 1.6%). Only one of these febrile convulsions occurred within 7 days following study vaccination: a 22 month-old female who had a febrile convulsion concomitant with an upper respiratory tract infection and a urinary tract infection 2 days after her second dose of IXIARO. None of the febrile convulsions were assessed as related to study treatment.

Reviewer comment: Nine of the 12 febrile convulsions were assessed as SAEs, and those associated with IXIARO are discussed further below. Febrile convulsions occurred at similar rates for IXIARO compared to HAVRIX720 and Prevnar, and the reviewer agrees with a negative assessment of causality since most occurred > 7 days following vaccination, and a reasonable alternate causality was provided for the single febrile convulsion that occurred within 7 days following vaccination.

The most common unsolicited AEs through Day 56 are summarized by frequency and organ system class in Table 21 for participants 2 months to <1 year of age and in Table 22 for participants 1 to <18 years of age.

Table 21. Most Common (> 1%) Unsolicited AEs through Day 56 for Participants 2 Months to <1 Year of Age in Study IC51-323

Rate (%) of participants reporting:	IXIARO (N=131)	Prevnar (N=64)
Infections and infestations		
Upper respiratory infection	38.2	37.5
Gastroenteritis	8.4	1.6
Impetigo	5.3	3.1
Nasopharyngitis	4.6	4.7
Rhinitis	3.8	4.7
Viral infection	4.6	3.1
Furuncle	3.8	3.1
Viral rash	3.1	1.6
Bronchitis	3.1	0
Pneumonia	2.3	1.6
Otitis media acute	1.5	1.6
Roseola	1.5	1.6
Bullous impetigo	1.5	0
Gastroenteritis viral	1.5	0
Oral candidiasis	1.5	0
General disorders		
Pyrexia	14.5	9.4
Respiratory disorders		
Cough	3.8	4.7
Gastrointestinal disorders		
Diarrhea	2.3	1.6
Eye disorders		
Conjunctivitis	2.3	4.7
Investigations		
ALT increased	1.5	1.6
AST increased	1.5	1.6
Vascular disorders		
Hematoma	1.5	1.6

Adapted from BLA 125280/125.6, 5.3.5.1.3 – Clinical Study Report IC51-323, Table 12.6

The majority of unsolicited AEs among participants 2 months to <1 year of age were mild in severity. There were no Grade 4 unsolicited AEs, and 3.1% of participants in each treatment group reported a Grade 3 unsolicited AE. There were no statistically significant differences between treatment groups in rates of particular unsolicited AEs or

in rates of unsolicited AEs grouped by organ system class, although there was a trend toward increased rates of gastroenteritis, viral gastroenteritis, and diarrhea among recipients of IXIARO (none of which were assessed as treatment related).

Unsolicited AEs assessed as treatment related occurred overall in 7.6% of IXIARO recipients and 3.1% of Prevnar recipients (difference not statistically significant) but were generally uncommon for any particular diagnosis or symptom. The most common (> 1% of participants) unsolicited AEs assessed as related to IXIARO were ALT and AST elevations, pyrexia, and cough (1.5% each).

Reviewer comment: There is no clear biologically plausible reason to suspect that IXIARO would cause gastroenteritis or viral gastroenteritis, and no such association was observed in adult studies of IXIARO.

Table 22. Most Common (> 1%) Unsolicited AEs through Day 56 for Participants 1 to <18 Years of Age in Study IC51-323

Rate (%) of participants reporting:	IXIARO 0.25 mL (N=740)	IXIARO 0.5 mL (N=540)	IXIARO total (N=1280)	HAVRIX720 (N=394)
Infections and infestations				
Upper respiratory infection	23.1	9.1	17.2	16.8
Nasopharyngitis	7.0	1.5	4.7	4.8
Gastroenteritis	4.9	0.4	3.0	3.0
Rhinitis	4.2	0.2	2.5	2.5
Impetigo	2.3	0.6	1.6	2.3
Bronchitis	2.4	0.2	1.5	2.3
Viral infection	2.2	0.9	1.6	1.3
Furuncle	1.9	0.6	1.3	1.3
Mumps	0.5	1.3	0.9	0.5
General disorders				
Pyrexia	10.8	3.9	7.9	7.1
Gastrointestinal disorders				
Diarrhea	3.1	0.2	1.9	1.3
Toothache	0.1	1.5	0.7	0.5
Respiratory disorders				
Cough	4.6	1.1	3.1	2.5
Eye disorders				
Conjunctivitis	2.0	1.1	1.6	1.8
Nervous system disorders				
Headache	0	1.5	0.6	0.3

Adapted from BLA 125280/125.6, 5.3.5.1.3 – Clinical Study Report IC51-323, Table 12.10.

The majority of unsolicited AEs among participants 1 to <18 years of age were mild in severity. One unsolicited AE was Grade 4 in severity: bronchopneumonia in a recipient of IXIARO 0.25 mL. This Grade 4 AE was also classified as a SAE (discussed below) but was not assessed as treatment related. Grade 3 unsolicited AEs occurred in 2.3% of participants in each treatment group. There were no statistically significant differences between IXIARO and HAVRIX720 in rates of particular unsolicited AEs or in rates of unsolicited AEs grouped by organ system class, although similar to rates of medically attended AEs, rates of unsolicited AEs were generally higher among the younger recipients of IXIARO 0.25 mL compared to the older recipients of IXIARO 0.5 mL.

Unsolicited AEs assessed as treatment related occurred overall in 3.9% of IXIARO recipients and 3.8% of HAVRIX720 recipients and were generally uncommon for any particular diagnosis or symptom. The most common (> 1% of participants) unsolicited AE assessed as related to IXIARO was pyrexia (1.6%).

6.1.12.3 Deaths

One death occurred during the study. A 12 year-old male randomized to IXIARO was admitted to the hospital with afebrile seizure and altered mental status 4 months after his second study vaccination. An admission physical exam was remarkable for Glasgow Coma Scale of 7 and occasional pulmonary rales. A computed tomography scan of the head was unremarkable, and laboratory evaluations were significant for peripheral leukocytosis and hyperglycemia, but hematology and serum chemistry evaluations were otherwise unremarkable. He later developed fever to 41˚C and disseminated intravascular coagulopathy and died 1 day later despite empiric therapy with penicillin G, chloramphenicol, paracetamol, diazepam, and phenobarbital. The presumed cause of death was bacterial meningitis and pneumonia, but no cerebrospinal fluid sample or chest radiograph was obtained to confirm the diagnoses.

Reviewer comment: Other potential etiologies include viral encephalitis or meningoencephalitis (with systemic involvement), intoxication, or late-presenting inborn error of metabolism, although the laboratory evaluations in this case are insufficient to corroborate or exclude any of these possibilities. The reviewer agrees with the investigator's assessment of causality given the long latency period between vaccine exposure and illness. Encephalitis and other serious neurologic reactions have occurred following vaccination with mouse brain-derived JEV vaccines (e.g., JE-VAX) but have typically occurred with a much shorter latency period and have not previously been described in adults following vaccination with IXIARO.

6.1.12.4 Nonfatal Serious Adverse Events

Rates of SAEs were 1.6% following IXIARO, 2.5% following HAVRIX720, and 1.6% following Prevnar. One nonfatal SAE was assessed as related to IXIARO and is discussed in detail here.

A 5 year-old male randomized to IXIARO developed cough and rhinorrhea followed by fever and non-pruritic rash on the face and trunk 83 days after his second study vaccination. The cough and rhinorrhea resolved, but the fever and rash persisted and five days later the participant developed periungual desquamation and fissuring of the lips. After 12 days of fever up to 40˚C and worsening perioral fissuring the participant was hospitalized and a diagnosis of Kawasaki disease (KD) was made, supported by cervical adenopathy, thrombocytosis, and dilated coronary arteries and pericardial

effusion on echocardiogram. Treatment with ampicillin, aspirin and intravenous immunoglobulin resulted in defervescence, and the participant was discharged home after 7 days to continue outpatient therapy with aspirin. The investigator assessed this Grade 4 SAE as possibly related to study treatment, but the sponsor's assessment was not related.

Reviewer comment: The pathogenesis of KD is poorly understood and has features consistent with both an infectious process and an auto-immune vasculitis. KD has been described following childhood vaccinations, but a systematic review of such cases in the U.S. did not indicate an increased risk above baseline rates associated with vaccinations. While the investigator for this case assessed the causality as possibly related to IXIARO, the reviewer agrees with the sponsor's assessment based on the long latency period, absence of a clear biologic mechanism, and absence of a clear causal relationship between KD and vaccines in general. Furthermore, KD typically occurs in children 5 years of age and younger and affects children of Asian ethnicity most commonly.

The remaining nonfatal SAEs following IXIARO were assessed as unrelated to study treatment, and none resulted in discontinuation from the study. These SAEs are summarized briefly below:

- A 3 month-old female randomized to IXIARO was hospitalized with Grade 3 pneumonia 42 days after her second study vaccination. She was treated with antibiotics and recovered.
- An 11 month-old male randomized to IXIARO was hospitalized with Grade 4 pneumonia 37 days after his second study vaccination. He was treated with antibiotics and recovered.
- A 1 year-old male randomized to IXIARO was hospitalized with Grade 3 pneumonia 75 days after his second study vaccination. He was treated with antibiotics and recovered.
- A 1 year-old female randomized to IXIARO was hospitalized with Grade 4 bronchopneumonia 25 days after her second study vaccination. She was treated with antibiotics and recovered.
- A 1 year-old female randomized to IXIARO was hospitalized with Grade 3 bronchopneumonia 47 days after her second study vaccination. She was treated with antibiotics and recovered.
- A 1 year-old male randomized to IXIARO was hospitalized with Grade 1 scalp hematoma associated with a closed head injury and Grade 1 gastroenteritis with fever 12 days after his first study vaccination. He was discharged one day later following a full recovery.
- A 1 year-old female randomized to IXIARO experienced a Grade 3 febrile convulsion preceded by upper respiratory tract infection 39 days after her second study vaccination.
- A 1 year-old male randomized to IXIARO experienced a Grade 3 febrile convulsion preceded by upper respiratory tract infection 56 days after his second study vaccination.
- A 1 year-old female randomized to IXIARO experienced a Grade 3 febrile convulsion associated with urinary tract infection and upper respiratory tract infection 2 days after her second study vaccination.
- A 1 year-old male randomized to IXIARO was hospitalized with Grade 3 Dengue fever (diagnosed by clinical criteria, including rash, leucopenia, and

thrombocytopenia) 28 days after his first study vaccination. He was treated with supportive therapy and was discharged 5 days later.

- A 2 year-old female randomized to IXIARO was hospitalized with Grade 2 gastroenteritis and urinary tract infection 5 months after her second study vaccination. She was treated with antibiotics and discharged after 2 days.
- A 2 year-old female randomized to IXIARO experienced a Grade 2 febrile convulsion associated with urinary tract infection 22 days after her first study vaccination.
- A 2 year-old male randomized to IXIARO was hospitalized with Grade 3 cellulitis of the buttocks 12 days after his second study vaccination. He was treated with antibiotics and discharged after 3 days.
- A 2 year-old male randomized to IXIARO experienced a Grade 3 febrile convulsion preceded by upper respiratory tract infection 28 days after his second study vaccination.
- A 4 year-old male randomized to IXIARO was struck by a motorcycle 49 days after his second study vaccination and sustained Grade 1 injuries.
- A 4 year-old female randomized to IXIARO was diagnosed with acute Hepatitis A infection (Grade 1) 43 days after her second study vaccination.
- A 6 year-old male randomized to IXIARO was hospitalized with a Grade 3 urinary tract infection 3 months after his second study vaccination. He was treated with antibiotics and recovered.
- A 7 year-old male randomized to IXIARO was diagnosed with Grade 1 strabismus and infantile esotropia 2 months after his second study vaccination.
- A 12 year-old male randomized to IXIARO was hospitalized with Grade 3 Dengue fever, tonsillopharyngitis, and upper respiratory infection 3 months after his second study vaccination. He was treated with antibiotics and recovered.
- A 14 year-old female randomized to IXIARO became pregnant 5 months after her second study vaccination and delivered a stillbirth female at her home at 43 weeks gestation without any prenatal care.
- A 14 year-old female randomized to IXIARO was hospitalized with Grade 3 Typhoid fever 4 months after her second study vaccination. She was treated with antibiotics and recovered.

Reviewer comment: The vast majority of nonfatal SAEs were infections of clear bacterial or viral etiology. SAEs were most frequent among participants 1 to <3 years of age, reflecting the high background incidence of such infections in this age subgroup compared to older children. The reviewer agrees with the investigators' assessments of non-causality for all of these SAEs.

6.1.12.5 Adverse Events of Special Interest (AESI)

Adverse events of special interest included neurological disorders and hypersensitivity reactions, based on prior experience with JE-VAX. No potential neurological AEs of special interest were reported during the study.

Reviewer comment: The MedDRA terms used for analysis of neurological disorders included: leukocencephalomyelitis, Guillain-Barre Syndrome, neuritis, parasthesia, dysasthesia, hyperesthesia, hypoesthesia, neuralgia, encephalitis, meningitis, and convulsion. The SAEs related to presumed bacterial meningitis (coded as disseminated intravascular coagulation) and febrile convulsions (assessed as unrelated to IXIARO, as discussed above) were not counted as potential neurological AEs of special interest.

The rates of potential hypersensitivity reactions among children in this study were similar between treatment groups and similar to those observed among adults vaccinated with IXIARO. Among participants 2 months to <1 year of age, the rates of potential hypersensitivity reactions through Day 56 were 4.6% for IXIARO 0.25 mL and 6.3% for Prevnar. Among participants 1 to <18 years of age, the rates of potential hypersensitivity reactions through Day 56 were 4.3% for IXIARO 0.25 mL, 2.0% for IXIARO 0.5 mL, and 3.3% for HAVRIX720. The most frequently reported AE of special interest in both age subgroups was conjunctivitis. Two episodes of rash were assessed by the investigator as related to IXIARO, and the remainder of potential hypersensitivity reactions following IXIARO was assessed as unrelated to study treatment.

Reviewer Comment: The hypersensitivity reactions linked to JE-VAX are thought to be caused by the gelatin used in production of the vaccine. Although IXIARO does not contain any gelatin as an excipient, monitoring for hypersensitivity reactions continues to be an important component of vaccine development and post-marketing surveillance. The MedDRA terms used for analysis of hypersensitivity events included: anaphylactic reaction, rash, dermatitis, optic neuritis, erythema, pruritus, urticaria, hypersensitivity, flushing, conjunctivitis, dyspnea, hypotension, circulatory collapse, wheezing, eye pruritus, swollen joint, angioedema, asthma, bronchial hyperactivity, and allergic cough.

6.1.12.6 Clinical Test Results

There were no reported AEs associated with vital signs, and few participants experienced clinically insignificant changes in hematology and serum chemistry parameters (none of which represented medically attended AEs).

6.1.12.7 Dropouts and/or Discontinuations

The rate of discontinuations was very low and likely did not substantially impact the safety evaluations in this study. Only two participants discontinued participation due to an AE:

- A 10 year-old male experienced Grade 2 solicited headache starting 1 day after his first dose of IXIARO 0.25 mL, in association with Grade 1-2 injection site reaction, Grade 1 fever, irritability and excessive fatigue, and Grade 2 muscle pain, loss of appetite, and sinusitis. The headache persisted for 12 days and was assessed as probably related to study treatment.
- A 1 year-old female experienced Grade 2 vomiting 2 days after her first dose of IXIARO 0.25 mL, in association with Grade 1 irritability, diarrhea, fever, and rash and Grade 2 excessive fatigue and loss of appetite. The vomiting resolved after 2 days and was assessed as possibly related to study treatment.

6.1.13 Reviewer's Comments and Conclusions

This was a randomized, active-controlled, open-label study to assess the safety and immunogenicity of IXIARO in infants, children, and adolescents 2 months to <18 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.

In terms of safety, there were no significant differences in rates of medically attended (mostly unsolicited) adverse events and serious adverse events through 56 days following the first dose of IXIARO compared to Prevnar (for infants 2 months to < 1 year of age) or HAVRIX720 (for children and adolescents 1 to < 18 years of age). This

observation extended through a longer 7 month follow-up period and was consistent across age subgroups. Symptoms of local and systemic reactogenicity were generally mild and occurred at rates similar to those observed with the U.S.-licensed active comparator vaccines. Rates of febrile convulsions within 7 months following the first vaccination were similar for all treatment groups (~1.6% for IXIARO and both comparators), and none of the febrile convulsions were plausibly related to study vaccination.

In terms of immunogenicity (as a predictor of vaccine effectiveness), 85% of subjects were seronegative for JEV at baseline ($PRNT_{50}$ titer <1:10). Depending on age subgroup, 99-100% of participants who received an age-appropriate dose and who were randomized to the immunogenicity subgroup had a $PRNT_{50}$ titer of ≥1:10 at Day 56, and 85-100% of these participants had a $PRNT_{50}$ titer of ≥1:10 at Month 7. The $PRNT_{50}$ GMTs at 28 days following completion of the IXIARO primary immunization series were similar to or greater than those observed in previous studies with adults, while the $PRNT_{50}$ GMTs at 6 months following completion of the IXIARO primary immunization series were similar to or slightly lower than those observed previously in adults at 5 months after completion of the primary series. There were no clinically significant differences in immunogenicity measures in children when results were stratified by baseline JEV or DENV serostatus.

In conclusion, this study supports the use of IXIARO in infants, children, and adolescents 2 months to <18 years of age who are at risk of exposure to JEV.

6.2 Trial #2: IC51-322

Title: Immunogenicity and Safety of the Japanese Encephalitis Vaccine IC51 (IXIARO) in a Pediatric Population in Non-endemic Countries. (NCT NCT01047839)

6.2.1 Objectives (Primary, Secondary, etc)

IC51-322 was a Phase 3 study to assess the safety and immunogenicity of IXIARO in infants, children, and adolescents 2 months to <18 years of age living in regions non-endemic for JEV.

The primary objective was to assess immunogenicity of IXIARO by JEV $PRNT_{50}$ geometric mean titer and proportion of participants with $PRNT_{50}$ titer ≥1:10 at 56 days following the first vaccination. The secondary objectives were:

- To assess safety of IXIARO in a pediatric population from regions where JEV is not endemic
- To assess age-dependent differences in the immunogenicity and safety profile of IXIARO.

6.2.2 Design Overview

IC51-322 was an open-label, uncontrolled multicenter study conducted at 8 sites in the United States, Germany, Austria, Romania, Denmark, Sweden, and Australia. The study began in February 2010 with an enrollment target of 100 participants. Study participants were followed for 7 months from the first vaccination.

Reviewer comment:

This study was conducted as a pediatric post-marketing requirement intended to evaluate the safety and immunogenicity of IXIARO in a non-endemic pediatric population

and to evaluate the vaccine effectiveness of IXIARO in this population by comparing neutralizing antibody responses to those in adults and in the larger study population residing in an endemic region (study IC51-323). Both the U.S. Food and Drug Administration and the European Medicines Agency provided input into the design of the study. Due to slower than expected recruitment into this study at the time that the final report for study IC51-323 was ready for regulatory submission (coincident with the expiration of remaining doses of JE-VAX, the only JEV vaccine licensed for pediatric use in the U.S.), CBER recommended that the applicant submit an analysis of data available from this study at the time when study IC51-323 was completed.

6.2.3 Population

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

Inclusion criteria:

- Age 2 months to <18 years at the time of first vaccination.
- Written informed consent by the participant's legal representative(s) and written informed assent, if applicable.
- Post-menarchal females were required to have a negative pregnancy test prior to enrollment and be willing to practice a reliable method of contraception.
- Planned travel to an area where JEV is endemic after completion of the vaccination schedule (must avoid exposure to JEV until 1 week after the second dose of IXIARO, plan to return from travel before the Month 7 visit, and be available for scheduled clinic visits).

Exclusion criteria:

- Clinical manifestation or history of any flavivirus disease.
- Prior vaccination against Japanese encephalitis, yellow fever, West Nile virus, or dengue virus.
- Active or passive immunization within 1 week before and 1 week after each IXIARO vaccination.
- Use of any other investigational drug or vaccine in addition to IXIARO from 30 days prior to the first vaccination through the end of the study period.
- Immunodeficiency, including post-organ transplantation or a family history of congenital or hereditary immunodeficiency.
- History of autoimmune disease.
- Receipt of ≥ 14 days of immunosuppressant or immune-modifying drug therapy (including corticosteroids at prednisone dose equivalent of ≥ 0.05 mg/kg/day) within 4 weeks prior to the first IXIARO vaccination.
- Pregnancy, lactation, or unreliable contraception in post-menarchal females.
- Acute febrile infection at a visit where IXIARO vaccination is scheduled.
- History of hypersensitivity reaction to vaccines or investigational vaccine components, or history of urticaria.
- Known infection with HIV, hepatitis B virus, or hepatitis C virus.
- Illicit drug use, history of drug or alcohol addiction, or current drug or alcohol addiction.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Study treatment was intramuscular vaccination with IXIARO in 2 doses given 28 days apart, using the same age-dependent dosage used for study IC51-323 (0.25 mL for participants 2 months to <3 years of age and 0.5 mL for participants 3 to <18 years of age). Three commercial batches were used for this study: JEV08K16A, JEV09K35A and JEV10H62A.

Reviewer comment: The dosage selection for participants 3 to <12 years of age was informed by the immunogenicity results for this age subgroup form the run-in dose-ranging phase of study IC51-323.

6.2.5 Directions for Use

The vaccination procedures for study IC51-322 were the same as described for IC51-323.

6.2.7 Surveillance/Monitoring

The safety monitoring for study IC51-322 followed the same schedule as for IC51-323, with the exception of monitoring specific to active comparator vaccinations on Day 56 and Month 7, as there were no active comparator treatment groups in IC51-322. An independent DSMB reviewed safety and immunogenicity data for the first 40 participants and recommended proceeding with the remainder of study.

6.2.8 Endpoints and Criteria for Study Success

The primary study endpoints for the interim analysis were related to immunogenicity and were JEV neutralizing antibody GMTs and proportion of participants with JEV neutralizing antibody titer ≥1:10 at Day 56 (28 days following completion of the IXIARO primary immunization series). Neutralizing antibody titers were measured by $PRNT_{50}$ assay. There were no pre-specified criteria for study success.

Secondary endpoints for the interim analysis related to immunogenicity included:

- $PRNT_{50}$ GMT and proportion of participants with $PRNT_{50}$ titer ≥1:10 at Month 7 (6 months following completion of the IXIARO primary immunization series).
- $PRNT_{50}$ GMT and proportion of participants with $PRNT_{50}$ titer ≥1:10 at Day 56 and Month 7, stratified by dose, age group, travel to JEV endemic areas, travel to JEV endemic areas before Day 56, and travel to JEV endemic areas after Day 56.

Reviewer comment: The endpoints for this study were appropriate to assess the safety profile and immunogenicity of IXIARO in the study population. The original analysis plan included an analysis of neutralizing antibody response stratified by prior vaccination for tick-borne encephalitis, but this analysis was not conducted because only 3 participants had a history of this vaccination.

Secondary endpoints for the interim analysis related to safety included rates of participants who experienced:

- SAEs and medically attended AEs through Day 56 and Month 7.
- Solicited AEs over 7 consecutive days following each study vaccination.
- Unsolicited AEs in through Day 56 and Month 7.

Reviewer comment: Solicited AEs collected by diary card were the same as for study IC51-323.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The Statistical Analysis Plan included descriptive analyses only without formal hypothesis testing. The study sample size was calculated to provide immunogenicity data for 80 participants, assuming a 10% loss to follow-up and an additional 10% loss of evaluable data due to major protocol violations.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

All analysis populations (Per Protocol, Intent to Treat, and Safety) were defined using the same criteria as for study IC51-323.

6.2.10.1.1 Demographics

Table 23 summarizes the demographic data for the participants enrolled in study IC51-322.

Table 23. Demographic Information for Study IC51-322

Randomized to treatment assignment	**IXIARO 0.25 mL (N=5)**	**IXIARO 0.5 mL (N=55)**	**Total (N=60)**
Mean age in years (SD)	1.5 (0.8)	13.5 (4.3)	12.5 (5.3)
2 to <12 months	1	0	1
1 to <3 years	4	0	4
3 to <12 years	0	14	14
12 to <18 years	0	41	41
Gender – male (%)	2 (40.0%)	24 (43.6%)	26 (43.3%)
Ethnicity			
Asian (%)	2 (40.0%)	6 (10.9%)	8 (13.3%)
Caucasian (%)	2 (40.0%)	48 (87.3%)	50 (83.3%)
African American or African heritage (%)	1 (20%)	1 (1.8%)	2 (3.3%)
Geographic region			
North America			26 (43.3%)
Europe			28 (46.7%)
Australia			6 (10%)

Adapted from BLA 125280/125, 5.3.5.2.3 – Clinical Study Report IC51-322, Table 10.3

Reviewer comment: Caucasians and Asians were overrepresented compared to the U.S. population, while Africans/African Americans and Hispanics were underrepresented. Only 5 participants were <3 years old (only one <1 year old), which likely predicts the relative uptake of IXIARO in non-endemic travelers in these age subgroups.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Nineteen participants (31.7%) reported a medical history, including 8 with history of infections and infestations and 6 with a history of respiratory disorders. No participants had baseline positive JEV serostatus by PRNT50 assay.

6.2.10.1.3 Participant Disposition

Table 24 summarizes the disposition of participants in study IC51-322 at the time of the interim analysis.

Table 24. Disposition of Participants in Study IC51-322

Randomized to treatment assignment	**IXIARO 0.25 mL (N=5)**	**IXIARO 0.5 mL (N=55)**	**IXIARO total (N=60)**
Vaccinated at least once	5	55	60
Completed study	3 (60.0%)	19 (34.5%)	22 (36.7%)
Completed Visit 3 (Day 56)	5 (100%)	48 (87.3%)	53 (88.3%)
Ongoing awaiting Visit 3	0 (0%)	6 (10.9%)	6 (10.0%)
Premature discontinuation	0 (0%)	1 (1.8%)	1 (1.7%)
Consent withdrawn	0	1	1
Protocol violation/deviation[1]	4 (80.0%)	32 (65.3%)	36 (66.7%)
Major violation/deviation	2 (40.0%)	27 (55.1%)	29 (53.7%)
Minor violation/deviation	3 (60.0%)	12 (24.5%)	15 (27.8%)

Adapted from BLA 125280/125, 5.3.5.2.3 – Clinical Study Report IC51-322, Tables 10.1 and 10.2

[1]Some participants committed both major and minor protocol violations or deviations but are counted only once in this row.

The most frequently reported major protocol deviations (N=21) were due to vaccine storage temperature excursions. An additional 7 participants received prohibited concomitant vaccinations or medications.

Reviewer comment: The high rate of major protocol violations significantly limited the number of immunogenicity data points usable for the Per Protocol (PP) analysis set, but these data are included in the Intent to Treat (ITT) analysis set.

6.2.11 Efficacy Analyses

Clinical efficacy was not assessed in this study. As discussed previously, evaluation of IXIARO vaccine effectiveness was based on JEV-neutralizing antibody responses, which provide reasonable evidence of protection against clinical disease.

6.2.11.1 Analyses of Primary Endpoint(s)

The primary immunogenicity endpoints for study IC51-322 were $PRNT_{50}$ GMT and proportion of participants with $PRNT_{50}$ titer ≥1:10 at Day 56. The results of the primary immunogenicity analyses for the ITT population are summarized in Table 25.

Table 25. $PRNT_{50}$ Geometric Mean Titers and Proportion of Participants with $PRNT_{50}$ titer ≥1:10 at Day 56 (Intent to Treat Population), Study IC51-322

Age Subgroup	2 months to <3 years	3 to <18 years
Treatment (N)	IXIARO 0.25 mL (N=5)	IXIARO 0.5 mL (N=49)
$PRNT_{50}$ GMT [95% CI]	216.2 [106.0, 441.0]	332.1 [251.2, 439.0]
% $PRNT_{50}$ ≥1:10 [95% CI]	100% [56.6, 100.0]	100% [92.3, 100]

Adapted from BLA 125280/125.6, 5.3.5.2.3 – Clinical Study Report IC51-322, Table 11.3

All participants in both age subgroups had $PRNT_{50}$ titers ≥1:10 at Day 56. The Day 56 $PRNT_{50}$ GMT for the 3 to <18 year-old subgroup was skewed high by a single participant with a $PRNT_{50}$ titer of 7380. Nonetheless, the $PRNT_{50}$ GMTs for each age subgroup were not significantly different from those observed in study IC51-323, although the confidence intervals for GMTs were wide due to the small sample size. $PRNT_{50}$ GMTs were slightly higher for the Per Protocol population (total N=25), though the differences were not statistically significant. Post-hoc analyses stratifying immunogenicity results by gender did not reveal any statistically significant differences in $PRNT_{50}$ GMTs at Day 56, although confidence intervals were too wide to draw meaningful conclusions.

Reviewer comment: Despite the statistical limitations imposed by sample size on comparisons between immunogenicity data from this study and data from IC51-323, IXIARO clearly elicited robust neutralizing antibody responses among all participants in IC51-322 for whom immunogenicity data was available.

6.2.11.2 Analyses of Secondary Endpoints

Results of immunogenicity analyses at Month 7 are summarized for the ITT population in Table 26.

Table 26. JEV $PRNT_{50}$ Geometric Mean Titers and Seroprotection Rates at Month 7 (Intent to Treat Population), Study IC51-322

Age Subgroup	2 months to <3 years	3 to <18 years
Treatment (N)	IXIARO 0.25 mL (N=2)	IXIARO 0.5 mL (N=16)
$PRNT_{50}$ GMT [95% CI]	48.0 [20.0, 115.0]	84.0 [56.3, 125.4]
% $PRNT_{50}$ ≥1:10 [95% CI]	100% [34.2, 100.0]	100% [80.6, 100.0]

Adapted from BLA 125280/125.6, 5.3.5.2.3 – Clinical Study Report IC51-322, Table 11.3

All participants in both age subgroups had $PRNT_{50}$ titers ≥1:10 at Month 7. $PRNT_{50}$ GMTs for each age subgroup were not significantly different from those observed in study IC51-323, although the confidence intervals for GMTs were wide due to the small sample size. $PRNT_{50}$ GMTs were slightly higher for the Per Protocol population (total N=11), though the differences were not statistically significant. Pre-specified secondary analyses stratifying immunogenicity results by age subgroup and travel to JEV-endemic areas did not reveal any statistically significant differences in $PRNT_{50}$ GMTs at Day 56 or Month 7, although confidence intervals were too wide to draw meaningful conclusions.

Reviewer comment: Despite the statistical limitations imposed by sample size, $PRNT_{50}$ titers ≥1:10 clearly persisted for at least 6 months after completion of the primary series among those participants in study IC51-322 for whom immunogenicity data was available. Similar to the situation with study IC51-323, the Month 7 GMTs raise the question of whether a booster dose might be warranted earlier than 1 year after completion of the primary series for infants and young children (2 months to <3 years of age) who are at continued risk for exposure to JEV. This question will be addressed for non-endemic travelers by the long-term continuation phase of IC51-322 (study IC51-324, where $PRNT_{50}$ titers will be measured at 12 months following completion of the primary immunization series).

6.2.11.3 Subpopulation Analyses

In addition to the pre-specified secondary endpoint subpopulation analyses, a post-hoc analysis stratifying immunogenicity results by gender did not reveal any statistically significant differences in $PRNT_{50}$ GMTs at Day 56 or Month 7, although confidence intervals were too wide to draw meaningful conclusions.

6.2.11.4 Dropouts and/or Discontinuations

There was only one study discontinuation, which occurred in the1 to <18 year-old age subgroup (enrolled N=55) and likely did not significantly affect the immunogenicity analyses.

6.2.12 Safety Analyses

6.2.12.1 Methods

The Safety population used for safety analyses included all participants who received at least 1 study vaccination and who had safety data available in the follow-up period of interest. Safety data collection methods were the same as for study IC51-323.

Reviewer comment: At the time of the interim analysis (60 participants enrolled), the Safety population included 53 participants (88.3% of enrollees) who had completed follow-up through Day 56 and 22 participants (36.7% of enrollees) who had completed follow-up through Month 7. Data for solicited AEs in the 7 days post-vaccination was available for 60 participants (100%) following the first study vaccination and for 52 participants (92.9%) following the second study vaccination.

6.2.12.2 Overview of Adverse Events

An overview of safety data through day 56 is presented in Table 27. There were no deaths during the entire study and no SAEs through Day 56.

Table 27. Overview of Safety Data through Day 56 in Study IC51-322

Rate (%) of participants reporting at least one:	**IXIARO 0.25 mL (N=5)**	**IXIARO 0.5 mL (N=55)**
Death	0	0
SAE	0	0
Related SAE	0	0
Medically attended AE	20.0	3.6
Related medically attended AE	0	0
Solicited AE	40.0	63.6
Unsolicited AE	60.0	16.4
Probably related	0	0
Possibly related	20.0	1.8
Solicited or unsolicited AE by severity grade		
Grade 1	60.0	60.0
Grade 2	0	5.5
Grade 3	0	1.8
Grade 4	0	0

Adapted from BLA 125280/125.6, 5.3.5.2.3 – Clinical Study Report IC51-322, Table 12.1

Safety data through Month 7 included few additional unsolicited AEs, 2 SAEs (both medically attended, discussed in detail below) and 1 additional medically attended AE (assessed as unrelated to study treatment). A majority of all AEs through Month 7 were mild in severity, with severe AEs reported for only 2 participants. All severe AEs (Grade 4 diabetes mellitus and Grade 3 abdominal pain, vomiting, and dehydration) occurred subsequent to Day 56 and were assessed as unrelated to study vaccination.

Reviewer comment: Assessments of causality as indicated in the above analyses are those of individual blinded investigators. Upon evaluation of the data, this reviewer found the investigators' assessments to be reasonable.

Solicited AEs following either IXIARO vaccination among participants 2 months to <3 years of age included injection site hardening, injection site redness, and diarrhea each occurring in 2 of 5 participants. No fevers occurred in the 7 days following vaccinations among participants aged <3 years.

Reviewer comment: The absence of solicited fevers among participants 2 months to <3 years of age differs from the rates of 15-20% observed in study IC51-323. This difference is most likely due to sampling error (only 5 participants in this age subgroup for study IC51-322) but other factors such as differences ethnicity and background rates of coincident bacterial and viral infections could be considered as potential explanations.

Solicited AEs following IXIARO 0.5 mL in participants 3 to <18 years of age are summarized in Table 28.

Table 28. Solicited Adverse Reactions Following IXIARO Among Children and Adolescents 3 to <18 Years of Age in Study IC51-322

Rate (%) of participants reporting:	Dose 1 (N=55)	Dose 2 (N=49)
Injection Site Reactions		
Pain	18.2	16.3
Itching	3.6	2.0
Tenderness	30.9	24.5
Hardening	0	2.0
Swelling	0	0
Redness	5.5	0
Systemic Reactions		
Irritability	0	6.1
Nausea	1.8	2.0
Vomiting	0	2.0
Diarrhea	1.8	0
Flu-like symptoms	0	0
Excessive fatigue	12.7	0
Muscle pain	27.3	2.0
Rash	1.8	2.0
Headache	1.8	4.1
Loss of appetite	1.8	0
Fever (≥37.7°C)	5.5	2.0

Adapted from BLA 125280/125.6, 5.3.5.2.3 – Clinical Study Report IC51-322, Section 14, Tables 14.3.4.1 and 14.3.4.2

Similar to study IC51-323, solicited AEs in study IC51-322 were less frequent following the second vaccination compared to the first vaccination. The rates of solicited fevers were most similar to those observed among participants 12 to <18 years of age in study IC51-323, which is consistent with the age distribution of participants enrolled into study IC51-322 (mostly 12 to <18 years old). All solicited injection site reactions following either IXIARO vaccination were mild, while the overall severity of solicited systemic reactions was mild in 40.0% of participants, moderate in 1.7% of participants, and severe in 1.7% of participants. Solicited AEs typically resolved within several days.

The most common unsolicited AEs reported through Day 56 were general disorders (4 participants, rate 6.7%) and respiratory disorders (3 participants, rate 5.0%). Unsolicited AEs in other organ system classes were reported by only 1-2 participants. Only two participants experienced unsolicited AEs assessed as related to study vaccination: mild cough and oropharyngeal pain 2 days after the first vaccination with IXIARO and mild erythematous rash and pruritis 8 days after the first vaccination with IXIARO (potential hypersensitivity-related AE of special interest, as discussed below).

6.2.12.4 Nonfatal Serious Adverse Events

Two nonfatal SAEs were reported subsequent to Day 56. One SAE was a diagnosis of new onset type 1 diabetes mellitus in a 15 year-old Caucasian female 3.5 months after her second dose of IXIARO and assessed as unrelated to study vaccination. The other SAE involved a 15 year-old Caucasian female who was hospitalized with mild paresthesia and tremor and attacks of dizziness 4.5 months after her second dose of IXIARO. Inpatient evaluation included normal electrocardiogram and cranial and spinal

MRI. The participant was diagnosed with tingling paresthesia secondary to hyperventilation, rotatory vertigo, and suspected dissociative disorder and was discharged from the hospital after 7 days having recovered from her symptoms. The investigator's assessment of causality was possibly related to study vaccination for dizziness and unrelated to study vaccination for paresthesia and tremor. However, the sponsor's assessment of causality for the dizziness was unrelated to study vaccination given the long interval between vaccination and onset of the AE.

Reviewer comment: The reviewer agrees with the sponsor's assessment of causality. The medical evaluation of this participant did not reveal any organic cause of her symptoms and did not result in diagnosis of any neurological, psychiatric, or cardiac disease or disorder.

6.2.12.5 Adverse Events of Special Interest (AESI)

Neurological and hypersensitivity-related AEs of special interest were assessed similarly as for study IC51-323. The SAE involving paresthesia described above was the only potential neurological AE of special interest reported during the study. Four participants (rate 6.7%) experienced potential hypersensitivity-related AEs of special interest:

- Two participants experienced AEs of asthma that were assessed as unrelated to study vaccination.
- One participant experienced contact dermatitis 12 days after the first vaccination and was assessed as unlikely related to study vaccination.
- One participant experienced erythematosus rash and pruritus 8 days after the first vaccination. This AE resolved after 2 days and was assessed as possibly related to study vaccination.

Reviewer comment: The observed rate of potential hypersensitivity-related AEs of special interest in study IC51-322 is similar to that observed in the larger study population of IC51-323, with a potential causal relationship to IXIARO assessed for only one episode of pruritis and rash.

6.2.12.6 Clinical Test Results

Clinical laboratory evaluations were not included in this interim analysis.

Reviewer comment: Given the paucity of clinically significant laboratory abnormalities observed in study IC51-323 and in adult studies with IXIARO, clinical laboratory information is unlikely to be of critical importance to the review and interpretation of this study.

6.2.12.7 Dropouts and/or Discontinuations

There were no discontinuations due to AEs. The impact of study discontinuations (1 participant who withdrew consent) on the analyses of study data is likely minimal.

6.2.13 Reviewer's Comments and Conclusions

This was an open-label, uncontrolled study to assess the safety and immunogenicity of IXIARO in infants, children, and adolescents 2 months to <18 years of age preparing to travel to regions endemic for JEV. The study has not yet completed its target enrollment due to slower than expected recruitment. However, CBER advised the sponsor to submit an interim analysis of IC51-322 along with the final report for the larger pediatric

study conducted in the Philippines (IC51-323) to facilitate availability of a licensed pediatric JEV vaccine in the U.S.

In terms of safety, there were very few SAEs and medically attended AEs, none of which were likely related to IXIARO. Local and systemic reactogenicity was generally mild, and rates of solicited and unsolicited AEs in this study were similar to those observed in study IC51-323 with the exception of fewer solicited fevers among participants 2 months to <3 years of age.

In terms of immunogenicity, 100% of subjects with available immunogenicity data had a neutralizing antibody titer of ≥1:10 as measured by $PRNT_{50}$ at Day 56 and Month 7. $PRNT_{50}$ GMTs were generally similar to those observed in study IC51-323 and to those observed in prior studies in adults.

In summary, the safety and immunogenicity data from study IC51-322 support the use of IXIARO in children residing in non-endemic areas who are at risk of exposure to JEV as a result of to travel to endemic areas.

6.3 Trial #3: IC51-221

Title: A Single Centre Open Label Phase II Clinical Study to Evaluate the Immunogenicity and Safety of Inactivated Japanese Encephalitis Vaccine in 60 Healthy Indian Participants in the Age Group of 1 To <3 Years – A Dose Response Study.

6.3.1 Objectives (Primary, Secondary, etc)

IC51-211 was a Phase 2 study to evaluate the safety and immunogenicity of IXIARO in children 1 to <3 years of age and to determine the most appropriate dose of IXIARO for this age subgroup.

The primary objective was to evaluate the immune response to 0.25 mL (3 mcg) and 0.5 mL (6 mcg) doses of IXIARO administered in a 2-dose schedule 28 days apart. The secondary objectives were:

- To evaluate the safety and reactogenicity of 0.25 mL and 0.5 mL doses of IXIARO.
- To evaluate the immune response of IXIARO in comparison with JenceVac.

Reviewer comment: JenceVac is not licensed in the U.S.

6.3.2 Design Overview

IC51-221 was an open-label, randomized, controlled dose-ranging study conducted in Bangalore, India. The study began in July 2007 and concluded in October 2007. Study participants were followed for 56 days from the first vaccination.

Reviewer comment: This pediatric dose-ranging study was conducted prior to initial U.S. licensure of IXIARO.

6.3.3 Population

Healthy male and female children 1 to <3 years of age were enrolled at a single clinical site in Bangalore, India, which is a region where JEV is not endemic.

Inclusion criteria:

- Age 1 to <3 years at the time of the first vaccination.
- Free of significant health problems as established by medical history and clinical laboratory screening tests.

Exclusion criteria

- History of clinical manifestation of any flavivirus infection.
- Prior vaccination against Japanese encephalitis, yellow fever, West Nile virus, or dengue virus.
- Use of any investigational drug or vaccine other than IXIARO or use of any registered vaccine from 30 days prior to the first vaccination through the end of the study period.
- Any history of immunodeficiency or family history of congenital or hereditary immunodeficiency.
- History of autoimmune disease.
- Receipt of ≥ 14 days of immunosuppressant or immune-modifying drug therapy within 6 months prior to the first IXIARO vaccination.
- Any acute infection within 4 weeks prior to enrollment.
- History of hypersensitivity reaction to vaccines or investigational vaccine components (in particular protamine sulfate or thimerosal), or history of urticaria.
- Confirmed or suspected infection with HIV, hepatitis B virus, or hepatitis C virus.
- Diabetes mellitus requiring insulin therapy, severe cardiopulmonary disorders, or history of malignancy.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Study participants were randomized in a 2:2:1 ratio to receive IXIARO 0.25 mL, IXIARO 0.5 mL, or JenceVac as summarized in Table 29.

Table 29. Study IC51-221 Treatment Assignments

Study Day	IXIARO 0.25 mL (N=24)	IXIARO 0.5 mL (N=24)	JenceVac 0.5 mL (N=12)
Day 0	X	X	X
Day 7			X
Day 28	X	X	X

IXIARO was available as described for Study IC51-323. A single investigational batch (ICB05/502) was used for this study.

JenceVac is a mouse brain-derived purified inactivated Japanese encephalitis vaccine manufactured by Shantha Biotechnics (India) from the ----(b)(4)---- strain of JEV and is not licensed in the U.S. Each 0.5 mL dose of JenceVac contained ---------(b)(4)----------. Commercial batch 0034032 was used for this study and supplied as 5 mL multi-dose vials, which were used only once each (single 0.5 mL dose).

6.3.5 Directions for Use

IXIARO was administered intramuscularly as described above for study IC51-323. JenceVac was administered subcutaneously as indicated.

6.3.7 Surveillance/Monitoring

Table 30 summarizes the surveillance and monitoring for study IC51-221.

Table 30. Surveillance and Monitoring for Study IC51-221

Visit	1	2	3	4	5
Study Day (± range)	**Day -10 (-10 to -1)**	**Day 0 (± 4 d)**	**Day 7 (± 4 d)**	**Day 28 (± 4 d)**	**Day 56 (± 4 d)**
Eligibility criteria	X	X	X[1]	X	
Medical history	X				
Physical exam/vital signs	X	X	X	X	X
Hematology/biochemistry	X			X	X
Urinalysis	X			X	X
Concomitant medications	X	X	X	X	X
Immediate adverse events (60 min after vaccination)		X	X[1]	X	X
Assessment of previous injection site			X	X	X
Dispense diary		X	X[1]	X	
Collect and review diary			X	X[1]	X
Adverse event collection		X	X	X	X

Adapted from BLA 125280/125, 5.3.5.1.3 – Clinical Study Report IC51-221, Table 9.6.2
[1]Participants assigned to JenceVac only.

All scheduled follow-up occurred at the clinical study site. For 7 days following each study vaccination, the study participants' parents or guardians used diary cards to record daily axillary temperatures, solicited and unsolicited adverse events (AEs), and concomitant medications. Safety data collected from diary cards and interviews at each follow-up clinic visit was captured using a paper case report form (CRF).

An independent data safety monitoring board (DSMB) reviewed safety data after 35% of participants completed the Day 7 follow-up visit and thereafter conducted regular monthly reviews of safety data until the last vaccination of the last enrolled participant.

6.3.8 Endpoints and Criteria for Study Success

There were no formal criteria for study success. The primary endpoint was proportion of participants with $PRNT_{50}$ titer ≥1:10 at day 56. Secondary endpoints related to immunogenicity included proportion of participants with $PRNT_{50}$ titer ≥1:10 at Day 28 and $PRNT_{50}$ GMT at Day 28 and Day 56. Secondary endpoints related to safety included proportions of participants experiencing any adverse event, local and systemic solicited adverse events, and changes in clinical laboratory parameters.

Reviewer comment: The endpoints for this study were appropriate to assess the preliminary safety and immunogenicity of IXIARO in children 1 to <3 years of age and to compare the safety and immunogenicity of the two investigational IXIARO doses to each other and to the JenceVac comparator vaccine.

6.3.9 Statistical Considerations & Statistical Analysis Plan

The Statistical Analysis Plan included descriptive analyses only without formal hypothesis testing.

6.3.10 Study Population and Disposition

6.3.10.1Populations Enrolled/Analyzed

All analysis populations (Per Protocol, Intent to Treat, and Safety) were defined using the same criteria as for studies IC51-323 and IC51-322.

6.3.10.1.1 Demographics

Table 31 summarizes the demographic data for the participants enrolled in study IC51-221.

Table 31. Demographic Information for Study IC51-221

Randomized to treatment assignment	**IXIARO 0.25 mL (N=24)**	**IXIARO 0.5 mL (N=24)**	**JenceVac (N=12)**
Mean age in years (SD)	1.7 (0.5)	2.1 (0.6)	2.2 (0.8)
Gender – male (%)	14 (58.3%)	14 (58.3%)	9 (75.0%)
Ethnicity – Indian (%)	24 (100%)	24 (100%)	24 (100%)

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

One participant in each IXIARO treatment group was seropositive at baseline ($PRNT_{50}$ titer ≥1:10). None of the participants assigned to JenceVac were seropositive at baseline.

6.3.10.1.3 Participant Disposition

All 60 enrolled participants completed the study. Four participants were excluded from the Per Protocol analyses at Day 28 due to unavailability (2 participants) or refusal to provide a serum sample (2 participants).

6.3.11 Efficacy Analyses

Clinical efficacy was not assessed in this study. As discussed previously, evaluation of IXIARO vaccine effectiveness was based on JEV-neutralizing antibody responses, which provide reasonable evidence of protection against clinical disease.

6.3.11.1 Analyses of Primary Endpoint(s)

The primary immunogenicity endpoint was proportion of participants with $PRNT_{50}$ titer ≥1:10 at Day 56, which for the Intent to Treat population was 95.8% (23/24) for IXIARO 0.25 mL, 95.8% (23/24) for IXIARO 0.5 mL, and 91.7% (11/12) for JenceVac. Proportions of participants with $PRNT_{50}$ titer ≥1:10 for the Per Protocol population were not substantially different.

6.3.11.2 Analyses of Secondary Endpoints

Proportions of participants with $PRNT_{50}$ titer ≥1:10 at Day 28 for the Intent to Treat population were 62.5% (15/24) for IXIARO 0.25 mL, 62.5% (15/24) for IXIARO 0.5 mL, and 66.7% (8/12) for JenceVac. Proportions of participants with $PRNT_{50}$ titer ≥1:10 for the Per Protocol population were not substantially different.

Reviewer comment: Proportions of participants with $PRNT_{50}$ titer ≥1:10 were similar to those observed previous studies in adults vaccinated with IXIARO (39.8% at Day 28 and 97.3% at Day 56). The Day 28 data from this study provides evidence of similar immune

response kinetics in young children compared to adults, which was not assessed in studies IC51-323 or IC51-322.

$PRNT_{50}$ GMTs are summarized for the Intent to Treat population in Table 32. $PRNT_{50}$ GMTs for the Per Protocol population were not substantially different.

Table 32. $PRNT_{50}$ Geometric Mean Titers for Study IC51-221, Intent to Treat Population

Study Day	IXIARO 0.25 mL (N=24)	IXIARO 0.5 mL (N=24)	JenceVac (N=12)
Day 0* [95 % CI]	5.3 [4.7, 5.9]	5.2 [4.8, 5.7]	5.0 [4.4, 5.6]
Day 28 [95 % CI]	23.5 [13.0, 42.6]	21.1 [12.1, 36.9]	25.9 [10.2, 66.1]
Day 56 [95 % CI]	208.8 [113.0, 385.9]	216.0 [129.3, 361.1]	238.4 [78.8, 721.2]

*Reciprocal titers <10 were imputed a value of 5.

Reviewer comment: $PRNT_{50}$ GMTs and proportions of participants with $PRNT_{50}$ titer ≥1:10 were equivalent in the 1 to <3 year-old age group for IXIARO 0.25 mL compared to IXIARO 0.5 mL and JenceVac, which informed selection of the 0.25 mL dose for infants and children <3 years old in studies IC51-323 and IC51-322.

6.3.12 Safety Analyses

6.3.12.1 Methods

Safety analyses were conducted on the safety population, consisting of all participants who received were randomized to treatment assignment, received at least 1 study vaccination, and for whom safety data was available.

For 7 days following each study vaccination, diary cards were used to record daily temperatures and solicited AEs. Solicited local AEs were the same as for studies IC51-323 and IC51-323, while solicited systemic AEs were slightly different and included fever, sleep disturbance, unusual crying, unusual drowsiness, loss of appetite, diarrhea, vomiting, and rash. Unsolicited AEs were collected during a 1-hour observation period following each study vaccination and at clinic follow-up visits on Days 7, 28 and 56.

Reviewer comment: The lower bound for Grade 1 fever in this study was 38˚C compared to 37.7˚C for the other pediatric studies.

6.3.12.2 Overview of Adverse Events

Thirteen AEs were reported during the entire study period, affecting 3 participants in the IXIARO 0.25 mL treatment group (rate 12.5%), 5 participants in the IXIARO 0.5 mL treatment group (rate 20.8%), and 4 participants in the JenceVac treatment group (rate 33.3%). There were no deaths, no SAEs, and all AEs were mild in severity (Grade 1).

Among participants in the IXIARO 0.25 mL treatment group, AEs included 2 solicited injection site reactions (Grade 1 tenderness) and 1 unsolicited Grade 1 skin lesion assessed as unrelated to study treatment. Among participants in the IXIARO 0.5 mL treatment group, AEs included 3 solicited injection site reactions (3 Grade 1 tenderness),

1 solicited systemic reaction (Grade 1 fever), and 1 unsolicited skin rash assessed as unrelated to study treatment.

Reviewer comment: There were no substantial differences in rates or severity of AEs between IXIARO 0.25 mL and IXIARO 0.5 mL doses, although the small number of participants and low overall rate of AEs prohibit firm statistical conclusions. The rates of AEs following IXIARO vaccination in this study were lower than those observed among participants 1 to <3 years of age in study IC51-323. These differences may reflect sampling error but may also reflect differences in reporting of symptoms (e.g., due to cultural factors) or differences in background rates of common infections manifesting with fever and gastrointestinal complaints.

6.3.12.6 Clinical Test Results

There were no clinically significant laboratory abnormalities in this study.

6.3.13 Reviewer's Comments and Conclusions

This was an open-label, randomized, controlled study conducted in Bangalore, India, to assess the safety and immunogenicity of 2 doses of IXIARO (0.25 mL and 0.5 mL) in comparison to the licensed Japanese encephalitis vaccine, JenceVac. The design of the study was appropriate, and the quality of the data appears to be adequate.

In terms of immunogenicity, there was no difference in $PRNT_{50}$ geometric mean titers or proportion of participants with $PRNT_{50}$ titer ≥1:10 at Days 28 or 56 between the 2 IXIARO doses, prompting selection of the 0.25 mL dose as the most appropriate to carry forward for further evaluation in infants and children <3 years of age.

In terms of safety, there were few AEs (all mild in severity) following vaccination with either IXIARO dose. Although this study not sufficiently powered to detect uncommon serious adverse reactions, the safety observations indicate low rates of common adverse reactions cause by vaccines (e.g., injection site reactions and systemic complaints such as fever) and suggest a benign safety profile for doses up to 0.5 mL among children 1 to <3 years of age.

In summary, although this study would not be sufficient to support licensure of the 0.5 mL IXIARO dose for children 1 to <3 years of age, it does suggest a favorable risk-benefit profile in this age group if IXIARO were administered at a dose between 0.25 mL and 0.5 mL.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

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. The clinical study data submitted with this BLA supplement were intended to satisfy the PREA post-marketing requirements conferred with initial licensure of IXIARO in 2009, which included a partial waiver for infants younger than 1 year of age and deferred submission of pediatric data for ages 1 to <17.

On 24 April 2013 the results of studies IC51-322 and IC51-323 were presented to the FDA Pediatric Review Committee (PeRC). The PeRC agreed that these studies fully satisfied the PREA PMRs and supported licensure of IXIARO for use in infants, children, and adolescents 2 months to <17 years of age. The previously granted partial waiver is carried forward to infants younger than 2 months of age on the grounds that clinical studies in this age group would be impracticable in non-endemic areas, and that benefit from IXIARO would be limited among infants younger than 2 months of age residing in endemic areas due to protection against JEV disease afforded by maternally derived antibodies.

9.1.4 Immunocompromised Patients

Safety and immunogenicity have not been established in immunocompromised individuals. IXIARO is manufactured from purified inactivated virus, so there is no specific safety concern for use of IXIARO in immunocompromised individuals. Although IXIARO is not contraindicated for immunocompromised individuals, including immunocompromised children, neutralizing antibody responses may be altered compared to healthy individuals, and protective immunity may not be assured.

9.2 Preparation for Administration of the 0.25 mL Dose

To prepare a 0.25 mL dose for administration to an infant or child 2 months to <3 years of age, the healthcare provider attaches a safety needle to the 0.5 mL pre-filled syringe and then pushes the plunger to the red half-dose mark (HDM) printed on the syringe barrel label while the syringe is held upright to expel 0.25 mL of unneeded vaccine. The expelled vaccine and safety needle are disposed in a medical waste container. After attaching a new sterile needle, the 0.25 mL of vaccine remaining in the syringe is administered to the patient. If during the preparation process the plunger is pushed past the HDM (resulting in expulsion of more than 0.25 mL), the syringe must be discarded and the procedure repeated using a new pre-filled syringe.

The extractable volume evaluations conducted during validation of the HDM label affixation process (see Section 5.4) indicate that the mean dose volume remaining in the syringe following completion of the intended preparation procedure is (b)(4), which is ---(b)(4)--- than the intended dose. The upper limit of the extractable volume following the intended preparation procedure during validation testing is -(b)(4)-, which is ---(b)(4)-------- the intended dose. Human factors issues (e.g., failure to actuate the plunger exactly at the HDM) may increase variability in the extractable volume under real-world conditions.

Reviewer comment: The extractable volume evaluations indicate that there is likely little opportunity for adjusting the proposed 0.25 mL preparation process to make the extractable volume consistently closer to the intended dose while ensuring administration of a 0.25 mL dose. Changing the HDM label position by only ----------(b)(4)---------- the mean and maximum extractable volumes to -(b)(4)- and -(b)(4)-, respectively, but also ---(b)(4)--- the minimum extractable volume to -(b)(4)-, which is below the intended dose.

The proposed pre-filled syringe presentation and 0.25 mL dose preparation method is approved for several influenza vaccines in Europe and Canada and will also be the approved presentation and preparation method for the IXIARO 0.25 mL dose in Europe.

Although no precedent for this type of presentation exists among U.S.-licensed vaccines, FDA has approved a single pre-filled syringe presentation for delivery of non-uniform doses of oncology drugs (e.g., granulocyte colony stimulating factors) and antiviral drugs (e.g., peginterferon-alpha-2a). Additional dose variability introduced by human factors issues would likely be no greater than the variability inherent in using a graduated syringe to draw up a specified dose from a vial, which is the approved administration method for several U.S.-licensed vaccines.

9.3 Immune Interference with Concomitant Immunizations

The possibility of immune interference following concomitant immunization with IXIARO and other vaccines has not been assessed in the pediatric population. A study in adults showed no evidence of interference with immune responses to IXIARO and HAVRIX720 when these vaccines were administered concomitantly. Routine vaccinations are more frequent during childhood (especially during the first two years of life) compared to adulthood, so there is potentially greater opportunity for concomitant vaccination with IXIARO and other vaccines among pediatric travelers compared to adult travelers. However, concomitant vaccination may be avoided with adequate travel planning, and in cases where concomitant vaccination is unavoidable the potential for clinical benefit of IXIARO outweighs the uncertain (and unlikely) risk of immune interference.

9.4 Booster Dose

The long-term persistence of JEV-neutralizing antibodies has not been assessed in children vaccinated with IXIARO. Based on the available immunogenicity data through 6 months following completion of the primary immunization series, antibody persistence in children is likely to be similar to that in adults, and children who are at risk for continued exposure or re-exposure to JEV greater than one year after completion of the primary immunization series may benefit from a booster dose. Long-term antibody persistence data is expected from ongoing pediatric studies IC51-324 (extension of IC51-322) and IC51-325 (extension of IC51-323). Although there are no available data to support a pediatric indication for an IXIARO booster dose, safety and immunogenicity of a booster dose is likely to be similar in infants, children, and adolescents compared to adults.

10. CONCLUSIONS

The clinical data submitted with this BLA supplement support the safety and vaccine effectiveness of IXIARO when administered to infants, children, and adolescents 2 months to <17 years of age. Clinical benefit of IXIARO in pediatric age groups was demonstrated by neutralizing antibody responses with a titer of at least1:10 as measured by $PRNT_{50}$ assay at 28 days following completion of the primary immunization series among nearly all recipients of IXIARO 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. The safety concerns identified in these studies are 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.

The IXIARO dosing regimens supported by the pediatric studies are two 0.5 mL doses administered intramuscularly 28 days apart for children and adolescents 3 to <17 years of age (the same as the licensed dosing regimen for individuals 17 years of age and older) and two 0.25 mL doses administered intramuscularly 28 days apart for infants and children 2 months to <3 years of age. The 0.25 mL dose is administered following

expulsion of excess vaccine from the licensed 0.5 mL pre-filled syringe as guided by a half-dose mark printed on a label affixed to the syringe barrel. While this procedure results in a prepared dose that is on average slightly greater than the intended 0.25 mL dose, the safety and vaccine effectiveness of the prepared dose is supported by data from a Phase 2 dose-ranging study with 48 recipients of IXIARO who were 1 to <3 years of age.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

A comparison of the risks and benefits of licensure of IXIARO for use in infants, children, and adolescents 2 months to <18 years of age is presented in Table 33 below and discussed in Section 11.2 following the table.

Table 33: Risk-Benefit Considerations for Pediatric Licensure 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	• There is currently no available U.S. licensed JEV vaccine approved for pediatric use. • There is no available therapy for JEV disease beyond supportive care.	• There is an unmet need for a JEV vaccine for U.S. children who travel to regions where JEV is endemic.
Clinical Benefit	• A JEV-neutralizing antibody titer ≥1:10 is regarded as evidence of protection against clinical disease. • In a clinical trial with 1311 children 2 to <18 years of age living in a region endemic for JEV, 96-100% of participants had a neutralizing antibody titer ≥1:10 at 28 days after completion of the IXIARO primary immunization series (2 doses of 0.25 mL for infants and children 2 months to <3 years, 2 doses of 0.5 mL for children and adolescents 3 to <18 years). 77-100% of participants had a neutralizing antibody titer ≥1:10 at 6 months after completion of the immunization series. Neutralizing antibody GMTs were similar to those observed in prior studies with adults. • In a study with 60 children 2 to <18 years of age living in regions not endemic for JEV, 100% of participants with available immunogenicity data at 28 days and/or 6 months after completion of the IXIARO primary immunization series had a neutralizing antibody titer ≥1:10. Neutralizing antibody GMTs were similar to those observed in the study with children living in a region endemic for JEV and to those observed in prior studies with adults. • The persistence of neutralizing antibody responses in children is not known beyond 6 months after completion of the IXIARO primary immunization series.	• There is substantial likelihood of clinical benefit of IXIARO in children ≥2 months old at risk of JEV infection, based on neutralizing antibody responses following completion of the primary series. • A 0.5 mL 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. • There are no data to support the timing of a booster dose for children who completed the IXIARO primary immunization series and continue to be at risk for JEV exposure.
Risk	• The primary risks of vaccination with IXIARO among children and adolescents 3 to <18 years of age are mild injection site pain and 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 and mild injection site redness, irritability, and diarrhea. • The proposed presentation and preparation method for the 0.25 mL IXIARO dose intended for infants and children 2 months to <3 years of age will result in an administered dose range of ----------(b)(4)----------. Unexplored human factors issues may increase variability of the administered dose range. • Among a 24 Indian children 1 to <3 years of age vaccinated with an IXIARO primary series consisting of two 0.5 mL doses, adverse reactions were no more frequent or severe compared to adverse reactions observed among 24 children of the same age vaccinated an IXIARO primary series consisting of two 0.25 mL doses.	• All the evidence indicates that the risks of vaccination with IXIARO are minor, including the risks associated with a dose of 0.5 mL administered to children 1 to <3 years of age. • The risk-benefit balance of the proposed presentation and preparation method for the 0.25 mL IXIARO dose remains favorable even when the possibility that a (b)(4) dose (--(b)(4)--) may be administered to infants and children 2 months to <3 years of age.
Risk Management	• The applicant has committed to conduct post-marketing studies to assess human factors issues that may affect preparation and administration of the 0.25 mL dose. • There is no safety signal related to hypersensitivity and neurological adverse events of special interest in children vaccinated with IXIARO. Pharmacovigilance activities following licensure of IXIARO for use in children will continue to assess for these adverse events of special interest and for outcomes following exposure to IXIARO during pregnancy.	• Although not expected to be significant, any human factors issues identified by the post-marketing studies may result in re-evaluation of the 0.25 mL IXIARO dose presentation. • Planned 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 IXIARO in infants, children, and adolescents 2 months to <17 years of age who are at risk of infection with JEV. The likelihood of clinical benefit is demonstrated by the high proportion of study participants with a JEV neutralizing antibody titer of ≥1:10 at 28 days after completion of the IXIARO primary immunization series (96-100% across all age subgroups in the three pediatric studies) and at 6 months after completion of the primary immunization series (77-100% across all age subgroups in the three studies). A JEV neutralizing antibody titer of ≥1:10 as measured by PRNT assay is generally regarded as conferring protection against clinical disease.

The most common risks associated with IXIARO in infants and children 2 months to <3 years of age are erythema at the injection site, fever, irritability, and diarrhea. The most common risks associated with IXIARO in children and adolescents 3 to <18 years of age are pain and tenderness at the injection site, muscle pain, and fatigue. These adverse reactions are typically mild, resolve within several days, and are not any more frequent following IXIARO compared to two U.S.-licensed vaccines (HAVRIX720 and Prevnar) used as active comparators in one of the pediatric studies. There are no safety signals in pediatric study participants related to hypersensitivity reactions or neurological adverse events following IXIARO.

The IXIARO doses supported by pediatric studies are 0.5 mL for children and adolescents 3 to <18 years of age and 0.25 mL for infants and children 2 months to <3 years of age. The impact of human factors issues on preparation and administration of the 0.25 mL dose will be assessed by the applicant in post-marketing studies, with the intention that identified issues may be addressed through revisions to the dose preparation instructions or, if necessary, through changes to the presentation. However, there appears to be little risk of increased reactogenicity associated with the range of dose volumes that would likely be administered to infants and children 2 months to <3 years of age following the intended preparation procedure.

Currently there is no available JEV vaccine licensed for pediatric use in the U.S., and there is no available specific therapy for JEV disease, which is fatal in 30% of cases and in nonfatal cases may cause permanent neurologic disability. Consequently, licensure of IXIARO for use in infants, children, and adolescents 2 months to <17 years of age 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, lack of precedent among U.S.-licensed vaccines and thorough assessment of human factors issues for the proposed 0.25 mL dose preparation method, and potential administration of doses ----(b)(4)---- of the intended 0.25 mL dose to infants and children 2 months to <3 years of age.

11.3 Discussion of Regulatory Options

In the opinion of this reviewer, the clinical data support approval of this BLA supplement. Due to issues involving the proposed presentation and preparation method for the 0.25 mL dose, regulatory options for use of IXIARO in infants 2 months to <3 years of age were discussed. Licensure of the 0.5 mL dose for children as young as 1 year of age was explored, but the limited safety data with this dose among children 1 to <3 years of age was determined to be inadequate to support licensure of the 0.5 mL dose for children younger than 3 years of age. Development of a new presentation for the 0.25

mL dose as a prerequisite for licensure of IXIARO for use in children 2 months to <3 years of age was considered, but development of a new presentation was determined not to be a viable option. Another option discussed was to delay licensure of IXIARO for use in children 2 months to <3 years of age until human factors assessments had been completed for the 0.25 mL dose preparation method. However, based on the urgent need for a JEV vaccine licensed for pediatric use and the risk-benefit analysis discussed above, completion of the human factors assessments as a post-marketing commitment was determined to be an acceptable approach with a favorable risk-benefit balance.

11.4 Recommendations on Regulatory Actions

In the opinion of this reviewer, the clinical safety and immunogenicity data submitted in this application support approval of this BLA supplement to license IXIARO for use in infants, children, and adolescents 2 months to <17 years of age.

11.5 Labeling Review and Recommendations

Revisions to the package insert were discussed with the applicant. The main issues were:

- Reformatting for clarity tables presenting pediatric safety and immunogenicity data.
- Exclusion of data describing safety and immunogenicity associated with non-licensed dosing regimens.
- Clarification of preparation instructions for the 0.25 mL dose.
- Revisions for clarity to previously approved text and tables presenting safety and immunogenicity in adults

11.6 Recommendations on Post-marketing Actions

The applicant has committed to conduct post-marketing assessments of human factors issues that may affect preparation and administration of the 0.25 mL dose. These assessments will address the recommendations provided by the consultant from the CDRH Human Factors Team (see Section 5.4.1).