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Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No1901/2006, as amended

Ixiaro

Japanese encephalitis vaccine, (inactivated, adsorbed)

Procedure No: EMEA/H/C/000963

P46 038

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

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I. ASSESSMENT

Recommendation

Based on the review of the data on safety and immunogenicity, the Rapporteur considers that the data of the interim report of study IC51-325, long-term immunity and safety follow up of infants from 2 months to 18 years of age in a paediatric population in a JEV-endemic country for prevention of JEV infection should not be added to the SmPC and PIL of the product till all results of the ongoing booster study are available.

Introduction

This report concerns assessment of the interim report of safety and immunogenicity study CSR IC51-325:

"Long-term Immunity and Safety With or Without a Booster Dose Following Primary Vaccination With the Japanese Encephalitis Vaccine IC51 (IXIARO) in a Pediatric Population in a JEV-endemic Country"

which is submitted in the frame of **Article 46** of Regulation (EC) No 1901/2006 for **Ixiaro.**

The MAH states that the clinical study interim report IC51-325 is submitted as Post Approval Measure resulting from the Typ II variation EMEA/H/C/0963/II/0039G.

IXIARO is licensed in the EU since 31th of March 2009. The clinical development program to support licensure of IXIARO in adults consisted of 9 studies in which approx. 4,700 subjects were enrolled and vaccinated. Currently Ixiaro is indicated for active immunization against Japanese encephalitis in children and adults from 2 months onwards.

In accordance with the approved Paediatric Investigation Plan (PIP) EMEA-000559-PIP01-09-M03 the MAH has performed three clinical studies evaluating IXIARO in children.

In study IC51-221 immunogenicity and safety of different dosages of IXIARO (2 doses of either 0.5 ml or 0.25 ml given on Day 0 and Day 28) has been compared to the locally licensed comparator vaccine JenceVac (a mouse-brain derived, inactivated JE vaccine manufactured by Korean Green Cross) on Days 0, 7 and 28 in a total of 60 children ≥ 1 to < 3 years of age. The results of study IC51-221 were discussed during the PIP agreement. Based on those data the PDCO agreed that no further dose finding was needed in children <3 years of age.

Study IC51-322 was designed to assess the systemic and local safety profile and immunogenicity of IXIARO administered in 2 doses in a 28-day interval in a paediatric population (>2 months to 18 years) from non-endemic regions. It was planned to recruit 100 subjects, however due to slow recruitment, an interim report is provided including data from 60 subjects.

Study IC51-323 was designed to assess the systemic and local safety profile of IXIARO administered in 2 doses in a 28-day interval in a paediatric population (>2 months to 18 years) from endemic regions. In a subset of subjects immunogenicity of IXIARO was analysed. The study also assessed a potential 'half dose' or 3µg given in 0.25ml in children ≥3 years to < 12 years. Active comparators used were Prevenar and Havrix.

Study IC51-325 is the follow-up study of IC51-323 to investigate the long-term immunity and safety with or without a Booster does following a primary vaccination with IXIARO. The study involves children and adolescents aged ≥ 9 months to < 17 years and 7 months (at the time of enrolment into

Study IC51-323 representing ages ≥ 2 months to < 17 years at the primary immunization) who had completed the Study IC51-323 and had received 2 vaccinations of IXIARO according to the protocol. 300 children and adolescents are enrolled, who are randomized 1:1 to either receive a Booster dose intramuscular 12 months after the first vaccination or not.

Assessment

➢ **Methods**

- Study Objectives:

The primary objective of this study is:
To assess the immune response (geometric mean titers [GMTs] and seroconversion rates [SCRs]) 28 days after one single booster vaccination with the purified inactivated JE vaccine IC51 administered at 12 months after the primary immunization in a pediatric population from JEV-endemic regions.

The secondary objectives are:
- To assess persistence of immunity (GMTs and rate of subjects with PRNT50 titers of ≥ 1:10) following primary vaccination with IC51 in a pediatric population from JEV-endemic regions (without booster).
- To assess persistence of immunity (GMTs and rate of subjects with PRNT50 titers of ≥ 1:10) following a booster vaccination with IC51 in a pediatric population from JEV-endemic regions.
- To assess the long-term safety profile of IC51 and the safety profile of a booster dose in a pediatric population from JEV-endemic regions.
- To assess age-dependent differences in the persistence of the immunity, immune response to a booster and the safety profile of IC51.

- Primary endpoint:
- Seroconversion rates as defined by percentage of subjects with PRNT50 (i.e., a serum dilution giving 50% reduction in plaques in a plaque reduction neutralization test) titers of ≥ 1:10 at 1 month after the booster dose.

- Secondary endpoints:
- Rate of subjects achieving a ≥ 4- fold increase in JEV neutralizing antibody titers at 1 month after the booster dose.
- Geometric mean titers for JEV neutralizing antibodies measured using a validated plaque reduction neutralization test (PRNT) at 1 month after the booster dose.
- Geometric mean titers and rate of subjects with a PRNT50 titer of ≥ 1:10 at Month 12 (and for future analyses at Months 24 and 36) after first IC51 vaccination in IC51- 323 with and without the booster dose.
- Rate of subjects with serious adverse events (SAEs) following immunization and medically attended AEs up to Month 12 (and for future analyses to Months 24 and 36) after the first IC51 vaccination in IC51- 323 with and without the booster dose.
- Severity, duration and relationship to vaccinations.
- Rate of subjects with unsolicited AEs up to Month 12 (and for future analyses to Months 24 and 36) after the first IC51 vaccination in IC51- 323 with and without the booster dose. Severity, duration and relationship to vaccinations.
- Rate of subjects with SAEs and medically attended AEs within 1 month following the booster dose. Severity, duration and relationship to vaccinations.
- Rate of subjects with unsolicited AEs within 1 month following the booster dose.
- Severity, duration and relationship to vaccinations.
- Rate of subjects with solicited AEs for up to 7 days following the booster dose.
- Severity and duration.

- Study design

  - Description of overall study design and plan

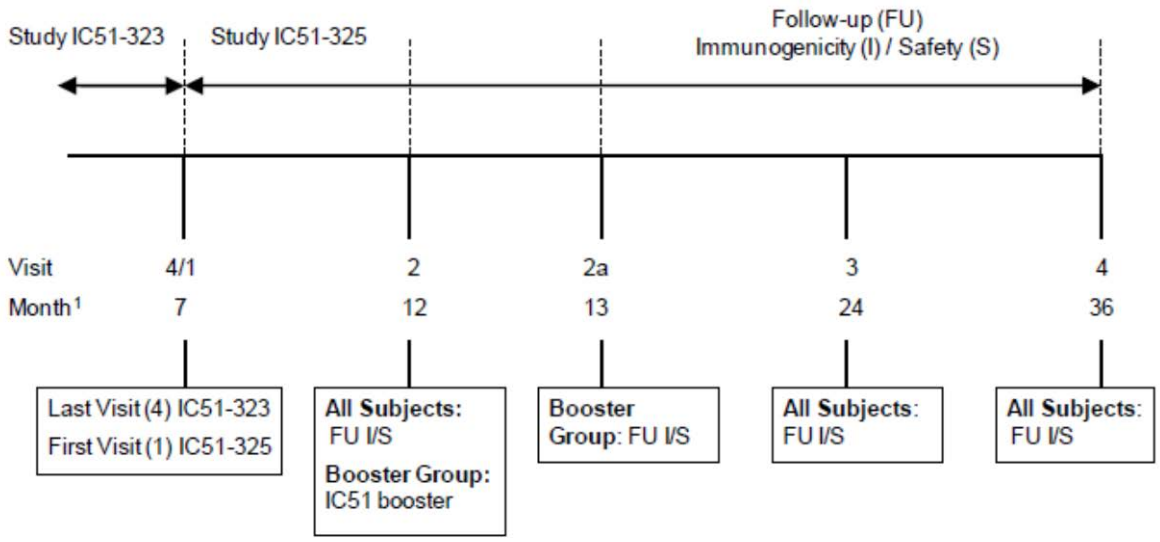
This study is to support a booster recommendation for pediatric use of a novel vaccine against JEV infection.

This is a continuing open-label, randomized Phase 3 study involving children aged ≥ 9 months to < 17 years and 7 months (at enrolment) who were vaccinated with IC51 (2 vaccinations) in Study IC51-323. That study was an open-label, randomized (3:1) clinical trial in which children received either IC51 or a comparator vaccine (HAVRIX 720 or Prevnar, depending on age). Those subjects who were randomized to IC51, either received IC51 0.5 mL (≥ 12 years) or 0.25 mL (< 3 years) depending on their age; the study also contained a dose-finding phase for the age group ≥ 3 to < 12 years. Study IC51-323 enrolled a total of 1.411 children to receive IC51. Immunogenicity was studied in a subset of 496 thereof.

In this follow-up study, 300 children from Study IC51-323, stratified by age, were planned to be randomized (1:1) into 2 groups. Where possible, the preferred option was to conduct the last visit of the previous study (Visit 4) and the first visit of this study (Visit 1) on the same day. If this was not possible, a separate visit was conducted for selection of the study population.
One group (Non-booster Group) was to be followed up yearly for 36 months after the first IC51 vaccination was administered in Study IC51-323 to evaluate the long-term immunity and safety. The second group (Booster Group) was to receive a booster dose of IC51 at 12 months after the first IC51 vaccination in Study IC51-323. Subjects were to be followed up 1 month after the booster and yearly for a further 24 months to evaluate the booster response, long-term immunity and the safety profile of a booster dose.

A schematic of the study design is presented in Figure 1.

Figure 1: Study design



[1] Visit time points refer to the time of first IC51 dose in Study IC51-323.

One group (Non-booster Group) was to be followed up yearly for 36 months after the first IC51 vaccination was administered in Study IC51-323 to evaluate the long-term immunity and safety. The second group (Booster Group) was to receive a booster dose of IC51 at 12 months after the first IC51 vaccination in Study IC51-323. Subjects were to be followed up 1 month after the booster and yearly for a further 24 months to evaluate the booster response, long-term immunity and the safety profile of a booster dose.

An interim analysis was conducted on safety and immunogenicity data in Study IC51-325 up to and including Visit 2a, i.e., Visit 2 (Month 12) data from subjects in the Non-booster Group and Visit 2a (Month 13; 1 month after the booster dose) data from subjects in the Booster Group. This clinical study report documents the results of that interim analysis. A further 2 analyses are planned on data from Visit 3 (Month 24) and Visit 4 (Month 36).

This study was designed according to the EMA Note for Guidance on Clinical Evaluation of New Vaccines and based on feedback by the FDA and the agreed Pediatric Investigation Plan with the EMA.

For subjects in the Booster Group, the booster was administered once at 12 months after the first dose of the primary immunization with IC51 in Study IC51-323. The IC51 dose administered for boosting depended on the age of the subject at the visit at which the booster dose was given. Subjects aged ≥ 14 months to < 3 years at Visit 2 were to receive a 0.25 mL dose and subjects aged ≥ 3 to < 18 years were to receive a dose of 0.5 mL.
For adults, the rate of subjects with PRNT50 ≥ 1:10 varies between approximately 60% and 80% at 12 months after the first dose of IC51. Based on these data, the EMA has approved that booster doses of IC51 should be administered within the second year after the primary series, and at 12 months in subjects who are at continuous risk of contracting JE.

Subjects were stratified by age as follows:
Subjects in the Booster Group aged ≥ 14 months to < 3 years (at Visit 2 of this study):
- IC51 0.25 mL, single booster dose intramuscularly, 12 months after first IC51 vaccination.

Subjects in the Booster Group aged ≥ 3 to < 18 years (at Visit 2 of this study):
- IC51 0.5 mL, single booster dose intramuscularly, 12 months after first IC51 vaccination.

Batch number: JEV10C48B

Study duration per subject was estimated to be 30 months (overall, including the parent study [IC51-323], duration was estimated to be 37 months).

For subjects in the Booster Group, the IC51 booster dose was to be given at Visit 2 (12 months [± 1 month] after the first dose of IC51 in Study IC51-323). Subjects (or parent/guardian) were to be issued with diaries to record solicited and unsolicited adverse events (AEs) on 7 consecutive days (Day 0 to Day 6) after the booster injection.
Immunogenicity and safety data were to be collected throughout the study from all subjects.

Assessor's comments:
This study was designed to investigate the neccessity and time-frame of a booster-dose of Ixiaro after primary immunisation in the pediatric population. The immunogenicity results of study IC51-325 must be interpreted with some caution. In this study the immunogenicity of Ixiaro has been investigated in children and adolescents from the Philippines where natural exposure to JEV and other flaviviruses is very common. Baseline seropositivity for JEV and DENV was found in a high proportion of subjects in the parent study IC51-323. Consequently, natural boosting by JEV exposure in some individuals can also not be excluded.

- Study population / sample size

300 healthy children were eligible for enrollment if they were 9 months to 18 years of age, received 2 recommended doses in the parent study IC51-323, with their parent(s) / legal representative providing signed consent form and able to understand the protocol requirements and to fill in the diary card. Female subjects with either no childbearing potential or a negative pregnancy test will be enrolled.

Subjects meeting at least one of the following criteria were ineligible for inclusion:
1. Vaccination against JE virus (except within Study IC51-323 and Study IC51-325), yellow fever, West Nile virus and dengue fever at any time prior to, or planned during, the study.
2. History of or clinical manifestation of any Flavivirus disease during Study IC51-323 or Study IC51-325.
3. Participation in another study with an investigational drug during Study IC51-323 or Study IC51-325.
4. Planned active or passive immunization within 2 weeks before and 1 week after the IC51 booster.
(Participation in the trial was not to lead to omission or unlicensed schedules of immunizations that are part of the national immunization program. Instead, participation of a child in Study IC51-325 needed to be timed in a way that allowed receiving these vaccines outside of the time window around IC51 vaccination. In general, active immunization other than vaccines administered at the appropriate age as part of national immunization programs or indicated through travel were to be avoided during the entire study.)

5. History of or development of any immunodeficiency including post-organ-transplantation after inclusion into Study IC51-323 or Study IC51-325.
6. History of or development of an autoimmune disease during Study IC51-323 or Study IC51-325.
7. Administration of chronic (defined as more than 14 days) immunosuppressants or other immune-modifying medications started during Study IC51-323 or Study IC51-325.
(For corticosteroids, this meant prednisone or equivalent at ≥ 0.05 mg/kg/day; topical and inhaled steroids were allowed.)
8. Acute febrile infection at Visit 2 (only for the Booster Group).
(An acute febrile infection at Visit 2 was not to lead to exclusion from further participation in the study; however, Visit 2 and the administration of the IC51 booster dose was to be postponed until recovery.)
9. Pregnancy (positive pregnancy test at Visit 1 and Visit 2), lactation or unreliable contraception in female subjects after onset of menarche.
10. Hypersensitivity reactions to IC51 or AEs in Study IC51-323 requiring withdrawal from further vaccination or anaphylaxis, or severe cases of atopy requiring emergency treatment or hospital admission during Study IC51-323 or Study IC51-325.
11. History of urticaria after hymenoptera envenomation, drugs, physical or other provocations or of idiopathic cause during Study IC51-323 or Study IC51-325.
12. Known infection with human immunodeficiency virus (HIV), hepatitis B virus (measurement of hepatitis B surface antigen titers) or hepatitis C virus.
13. Illicit drug use and/or current drug or alcohol addiction.
14. Inability or unwillingness by the legal representative(s) and/or the subject (where applicable) to provide informed consent/assent and to abide by the requirements of the study.
15. Persons who had been committed to an institution (by a court or by an authority).

Between 08-December-2010 (first subject first visit) and 11-Nov-2011, a total of **300 subjects** were enrolled at 3 centers in the Philippines and data are summarized till Visit 2 or Visit 2 a.

- Randomization procedure

An interactive voice response system (IVRS)/interactive web response system (IWRS) was used to allocate subjects to the treatment groups (i.e., Booster or Non-booster Group).
Investigators were to use the IVRS/IWRS to enroll and randomize subjects.

- Blinding

For this open-label study, measures to maintain blinding are not applicable for this study.

- Treatments

Subjects in the Booster Group were administered a single booster injection, the dose of which depended on their age at the booster administration visit (i.e., Visit 2, Month 12):
- IC51 3 µg/0.25 mL, intramuscularly, for subjects aged < 3 years;
- IC51 6 µg/0.5 mL, intramuscularly, for subjects aged ≥ 3 years.

To determine JEV neutralizing antibody titers and SCRs, blood samples were to be collected from all subjects at all visits (at Visit 1 only if not already performed as part of Visit 4 in Study IC51-323).

- Outcomes/Safety Criteria

For subjects in the Booster Group, the IC51 booster dose was to be given at Visit 2 (12 months [± 1 month] after the first dose of IC51 in Study IC51-323). Subjects (or parent/guardian) were to be issued with diaries to record solicited and unsolicited adverse events (AEs) on 7 consecutive days (Day 0 to Day 6) after the booster injection.
Immunogenicity and safety data were to be collected throughout the study from all subjects.

Solicited AEs were:
- Local symptoms: injection site pain (i.e., pain without touching), itching, tenderness (i.e., pain upon touching), hardening, swelling, redness.
- Systemic symptoms: headache, muscle pain, flu-like symptoms, excessive fatigue, rash, fever (measured), nausea, vomiting, diarrhea, irritability, loss of appetite.

Inspection of Injection Site by Investigator

At Visit 2, approximately 1 hour after the booster dose and at Visit 2a, the injection site was to be inspected by the investigator, and presence, size and severity of local reactions were assessed and recorded.

Recording Solicited Adverse Events in the Diary
One hour after the booster dose was administered, the investigator and the subject/subject's legal representative were to complete the first day of the subject diary together. The subject/subject's legal representative was to be trained by the investigator on how to complete the diary for the following 6 days, including the recording of any symptoms, the measuring of the size of the affected area with a ruler, where appropriate, and taking the body temperature with an infrared thermometer in the subject's ear.
Any symptoms that were ongoing after Day 6, and the date of the last day of symptoms, were also to be recorded.
Subjects were to complete the diary themselves unless they were unable to read and write or understand the diary process, in which case the subject's legal representative was to complete the diary. The presence/absence and size/severity of local and systemic symptoms were to be recorded once a day, at approximately the same time. The subject/subject's legal representative was to record the severity of a symptom by ticking the appropriate description from a list, to help remember the event. This list was not identical to the grading scale used by the investigator to assess severity. The information provided by the subject's diary was to form the basis of the investigator's severity assessment when the diary was reviewed with the subject/subject's legal representative at Visit 2a (or Early Termination Visit if applicable).

Unsolicited Adverse Events
An AE was defined as any untoward medical occurrence in a subject administered an investigational product, whether or not related to the treatment (i.e., vaccine).
Any symptoms or medical events not solicited were unsolicited AEs and were to be graded for intensity/severity and causality by the investigator.
Laboratory values falling outside the reference range were to be assessed by the investigator and, if clinically relevant, reported as an AE.

Medically Attended Adverse Events
All AEs where the subject was seeking medical care (i.e., doctor's office, emergency service or hospital) were to be considered medically attended AEs. An AE was not considered medically attended if the subject was using non-prescribed drugs.

The investigator had to immediately report all SAEs.

- Statistical and analytical plans
-

Analysis Populations
Safety Population: All safety analyses were based on the Safety Population, defined as subjects who entered into the study and were randomized.
Intent-to-treat (ITT) Population: The ITT Population was the primary analysis population for the immunogenicity analyses and was defined as all subjects randomized.
Per–Protocol (PP) Population: Immunogenicity analyses were repeated for the PP Population and excluded any randomized subjects who met certain criteria.

- Protocol amendments

There were no changes in the conduct of the study and no amendments to the protocol.

- **Results**

  - Recruitment/number analyzed

Of the 300 subjects enrolled in the study, 5 subjects were excluded from the ITT population due to major protocol violations. Table 1 shows the enrolled subjects.

All subjects were Asian in origin. Age was a factor in determining a subject's dose group in the Booster Group and so differences between dose groups in weight, height and body mass index were expected.

Proportions of male and female subjects were similar in the IC51 0.25 mL dose group but there were more males (59.7%) than females (40.3%) in the IC51 0.5 mL dose group. More details on age of subjects are provided in the immunogenicity analysis.

Table 1: Analysis population, all enrolled subjects

	Booster N=150 n (%)	Non-booster N=150 n (%)	Total N=300 n (%)
Safety Population	150 (100.0)	150 (100.0)	300 (100.0)
Intent-to-treat Population	150 (100.0)	150 (100.0)	300 (100.0)
Per-protocol Population	146 (97.3)	149 (99.3)	295 (98.3)

Major Protocol violations: incorrect dose, twice no vaccination received, once subject did not show up, Visit 2 a out of timeframe.

Assessor's comments:
Overall the study was well conducted. Safety results were available for all of the 300 randomized subjects. The dropout rate (1.6%) is low for the time of the interim analysis. 6 minor protocol violations were listed. Two subjects reported a medical history of dengue prior to first vaccination in the parent study, one subject had visit 2 out of timeframe, one subject used prohibited medication of Prednisone and two subjects received the second dose of Ixiaro out of the timeframe in the parent study IC51-323.

- Preliminary safety analysis

In the safety results, 'Month 12' and 'Month 13' refer to data collected at Visit 2 and Visit 2a, respectively; the time points are not a strict cut-off of 12 or 13 months after the initial vaccination in Study IC51-323.

Of the 150 subjects in the Booster Group, 148 subjects received the booster dose at Visit 2 (12 months). Mean time from first vaccination in Study IC51-323 to Visit 1 of this study (Month 7) and mean time from Visit 2 (Month 12) when the booster was administered to Visit 2a (Month 13) are summarized in Table 2.

Table 3: **Mean Time from First Vaccination in Study IC51-323 to Visit 1 of Study IC51-325 and Mean Time from Visit 2 to Visit 2a, Booster Group**

	IC51 0.25 mL N=81 n (%)	IC51 0.5 mL N=67 n (%)	Total N=150 n (%)
Time from first vaccination in Study IC51-323 to Visit 1 (Month 7) in IC51-325 (days)			
n	81	67	150
Mean (SD)	258.8 (50.64)	262.6 (43.52)	259.9 (47.43)
Median	287.0	285.0	287.0
Min, Max	194, 315	196, 323	194, 323
Time from Visit 2 (Month 12) to Visit 2a (Month 13) (days)			
n	81	67	148
Mean (SD)	29.3 (9.79)	28.1 (7.15)	28.7 (8.69)
Median	31.0	30.0	30.5
Min, Max	7, 52	7, 49	7, 52

Assessor's comments:
Two subjects in the Booster group withdrew from study prior vaccination. The mean time of approximately 9 months from the first vaccination in the parent study IC51-323 to Visit 1 of the current study was comparable for the two dose groups (258.8 days in 0.25 mL dose group vs. 262.6 days in the 0.5 mL dose group). The time-period from Visit 2 at month 12 (Booster-vaccination) to

Visit 2a at month 13 (blood draw for antibody determination) was 28.7 days with a standard deviation of 8.69. For both dose groups the time-periods were comparable.

Long-term Safety analysis prior to Booster vaccination

All AEs reported as not recovered/not resolved at Month 7 (i.e., Visit 4 in Study IC51-323/Visit 1 in this study) and all new AEs reported in the Booster and Non-booster Groups up to Visit 2 (Month 12) were included in the analysis of AEs and are summarized in Table 3 and by age group in Table 4. The same 4 age groups used for analysis and randomization in the parent study, i.e., ≥ 2 months to < 1 year; ≥ 1 year to < 3 years; ≥ 3 years to < 12 years; and ≥ 12 years to < 17 years of age *at primary immunization*/Visit 1 in Study IC51-323, were used for the analysis of unsolicited AEs from Visit 1 of this study (Month 7) to Visit 2 (Month 12).

Table 3: **Summary of Adverse Events from Visit 1 (Month 7) up to Visit 2 (Month 12), Safety Population**

	Booster N=150 n (%) [95% CI]	Non-booster N=150 n (%) [95% CI]	Total N=300 n (%) [95% CI]
Number of subjects with at least one:			
Unsolicited AE	57 (38.0) [30.2, 46.3]	64 (42.7) [34.6, 51.0]	121 (40.3) [34.7, 46.1]
Unsolicited AE that was:			
Probably related	0	0	0
Possibly related	0	0	0
Unsolicited AE with severity grade of:			
Grade 1	52 (34.7) [27.1, 42.9]	55 (36.7) [29.0, 44.9]	107 (35.7) [30.2, 41.4]
Grade 2	4 (2.7) [0.7, 6.7]	7 (4.7) [1.9, 9.4]	11 (3.7) [1.8, 6.5]
Grade 3	1 (0.7) [0.0, 3.7]	2 (1.3) [0.2, 4.7]	3 (1.0) [0.2, 2.9]
Grade 4	0	0	0
SAE	0	1 (0.7) [0.0, 3.7]	1 (0.3) [0.0, 1.8]
Related SAE	0	0	0
Serious or medically attended AE	16 (10.7) [6.2, 16.7]	30 (20.0) [13.9, 27.3]	46 (15.3) [11.4, 19.9]
Medically attended AE	16 (10.7) [6.2, 16.7]	30 (20.0) [13.9, 27.3]	46 (15.3) [11.4, 19.9]
Related medically attended AE	0	0	0
Unsolicited AE of special interest	5 (3.3) [1.1, 7.6]	4 (2.7) [0.7, 6.7]	9 (3.0) [1.4, 5.6]
Related unsolicited AE of special interest	0	0	0
AE that led to discontinuation	0	0	0
AE that led to death	0	0	0

Assessor's comment:
The safety profile of both groups was comparable. 40.3 % of study subjects reported unsolicited adverse events that started at beginning of the current trial until Visit 2 (month 12) or were still unresolved from the parent Study IC51-323. The majority of AEs were rated with Grade 1 and 3.7 % rated their reported AEs as Grade 2. Only 1 % of subjects rated their observed AEs as Grade 3. None of the AEs was rated as Grade 4. One unrelated SAE(a subject with concussion secondary to a fall) was reported. 46 subjects (15.3%) reported medically attended AEs, which were infections and infestations. No related medically AE was observed until Visit 2 in the clinical trial. No deaths ocurred in the study so far.

The next Table 4 shows a summary of all adverse events from Visit 1 up to Visit 2 stratified by age groups.

Table 4: **Summary of All Adverse Events from Visit 1 (Month 7) up to Visit 2 (Month 12) by Age Group, Safety Population**

	≥ 2 Months to < 1 Year (at Visit 1 in IC51-323) N=30 n (%) [95% CI]	≥ 1 to < 3 Years (at Visit 1 in IC51-323) N=187 n (%) [95% CI]	≥ 3 to < 12 Years (at Visit 1 in IC51-323) N=27 n (%) [95% CI]	≥ 12 to < 17 Years (at Visit 1 in IC51-323) N=56 n (%) [95% CI]
Number of subjects with at least one:				
Unsolicited AE	15 (50.0) [31.3, 68.7]	84 (44.9) [37.7, 52.3]	7 (25.9) [11.1, 46.3]	15 (26.8) [15.8, 40.3]
Unsolicited AE that was:				
Probably related	0	0	0	0
Possibly related	0	0	0	0
Unsolicited AE with severity grade of:				
Grade 1	15 (50.0) [31.3, 68.7]	72 (38.5) [31.5, 45.9]	7 (25.9) [11.1, 46.3]	13 (23.2) [13.0, 36.4]
Grade 2	0	9 (4.8) [2.2, 8.9]	0	2 (3.6) [0.4, 12.3]
Grade 3	0	3 (1.6) [0.3, 4.6]	0	0
Grade 4	0	0	0	0
SAE	0	1 (0.5) [0.0, 2.9]	0	0
Related SAE	0	0	0	0
Serious or medically attended AE	7 (23.3) [9.9, 42.3]	35 (18.7) [13.4, 25.1]	1 (3.7) [0.1, 19.0]	3 (5.4) [1.1, 14.9]
Medically attended AE	7 (23.3) [9.9, 42.3]	35 (18.7) [13.4, 25.1]	1 (3.7) [0.1, 19.0]	3 (5.4) [1.1, 14.9]
Related medically attended AE	0	0	0	0
Unsolicited AE of special interest	1 (3.3) [0.1, 17.2]	7 (3.7) [1.5, 7.6]	0	1 (1.8) [0.0, 9.6]
Related unsolicited AE of special interest	0	0	0	0
AE that led to discontinuation	0	0	0	0
AE that led to death	0	0	0	0

Assessor's comments:
Overall the rate of systemic as well as local solicited AEs was very low in all age groups which were investigated in the ongoing study.
There is a clear trend that the incidence of unsolicited AEs was highest in the younger age group (50 %) and much lower in subjects ≥ 3 years to < 12 years (25.9 %) and in subjects ≥ 12 years to < 17 years (26.8 %). The same trend was observed for infections and infestations (medically attended AEs). None of the reported AEs in any age group was considered by the investigators to be related to the study vaccine.

Booster Dose Safety

All AEs reported in the Booster Group from after the booster dose at Visit 2 (Month 12) up until Visit 2a (Month 13) were included in the analysis of AEs and are summarized in Table 5.
For the purpose of comparing with the safety data at primary immunization, AEs starting between Visit 2 and Visit 2a for the Booster Group were tabulated stratified by age *at booster immunization*/Visit 2, as follows: ≥ 9 months to 3 years; ≥ 3 to 12 years; ≥ 12 to 18 years.

Table 5: **Summary of Adverse Events after the Booster Dose up to Visit 2a (Month 13), Booster Group Only, Safety Population**

	IC51 0.25 mL N=81 n (%) [95% CI]	IC51 0.5 mL N=67 n (%) [95% CI]	Total N= 150 n (%) [95% CI]
Number of subjects with at least one:			
Solicited or unsolicited AE	24 (29.6) [20.0, 40.8]	25 (37.3) [25.8, 50.0]	49 (32.7) [25.2, 40.8]
Solicited AE	12 (14.8) [7.9, 24.4]	17 (25.4) [15.5, 37.5]	29 (19.3) [13.3, 26.6]
Unsolicited AE	17 (21.0) [12.7, 31.5]	14 (20.9) [11.9, 32.6]	31 (20.7) [14.5, 28.0]
Unsolicited AE that was:			
Probably related	0	0	0
Possibly related	1 (1.2) [0.0, 6.7]	1 (1.5) [0.0, 8.0]	2 (1.3) [0.2, 4.7]
Solicited or unsolicited AE with severity grade of:			
Grade 1	17 (21.0) [12.7, 31.5]	21 (31.3) [20.6, 43.8]	38 (25.3) [18.6, 33.1]
Grade 2	5 (6.2) [2.0, 13.8]	3 (4.5) [0.9, 12.5]	8 (5.3) [2.3, 10.2]
Grade 3	2 (2.5) [0.3, 8.6]	1 (1.5) [0.0, 8.0]	3 (2.0) [0.4, 5.7]
Grade 4	0	0	0
SAE	1 (1.2) [0.0, 6.7]	1 (1.5) [0.0, 8.0]	2 (1.3) [0.2, 4.7]
Related SAE	1 (1.2) [0.0, 6.7]	0	1 (0.7) [0.0, 3.7]
Serious or medically attended AE	10 (12.3) [6.1, 21.5]	3 (4.5) [0.9, 12.5]	13 (8.7) [4.7, 14.4]
Medically attended AE	10 (12.3) [6.1, 21.5]	3 (4.5) [0.9, 12.5]	13 (8.7) [4.7, 14.4]
Related medically attended AE	1 (1.2) [0.0, 6.7]	0	1 (0.7) [0.0, 3.7]
Unsolicited AE of special interest	0	1 (1.5) [0.0, 8.0]	1 (0.7) [0.0, 3.7]
Related unsolicited AE of special interest	0	1 (1.5) [0.0, 8.0]	1 (0.7) [0.0, 3.7]
AE that led to discontinuation	0	0	0
AE that led to death	0	0	0

Overall, 32.7% of study subjects who received a booster dose of IC51 reported any solicited or unsolicited AE between Visit 2 (Month 12) and Visit 2a (Month 13); 29.6% with the 0.25 mL booster and 37.3% with the 0.5 mL booster dose. Solicited AE were reported by a total of 19.3% of subjects after the booster, and unsolicited AE by a total of 20.7% of subjects; in two subjects (1.3%), unsolicited AEs were possibly related to vaccination.

One SAE (abscess; Subject 23101256; booster dose of IC51 0.25 mL) reported between booster dose administration and Visit 2a (Month 13) was considered related to the study vaccine by the investigator, but not by the sponsor; this SAE was also the only medically attended AE that was considered related to the study vaccine. Overall, 2 subjects (1.3%) were reported with SAEs and a small number of subjects overall (13 subjects, 8.7%) were reported with medically attended AEs (Table 5):

- In the ≥ 9 months to < 3 years age group, no SAE was reported. A total of 9 subjects (11.3%) had medically attended AEs.
- In the ≥ 3 years to < 12 years age group, 1 subject (2.6%) had an SAE and 3 subjects (7.7%) had medically attended AEs. The SAE of abscess, which was also a medically attended AE, was considered related to study vaccine by the investigator, but not by the sponsor.
- In the ≥ 12 years to < 18 years age group, 1 subject (3.4%) had an SAE of dengue fever and 1 subject (3.4%) had a medically attended AE.

The majority of medically attended AEs up to Visit 2a (Month 13) were infections and infestations and the most frequently reported medically attended AE was upper respiratory tract infection. The only

medically attended AE considered related to the study vaccine by the investigator was an SAE of abscess.

Assessor's comment:
Again the safety profile of Ixiaro observed was comparable. Overall the rate of medically attended AEs observed in the time-period after the booster dose at Visit 2 until Visit 2a was 8.8 % of all subjects (13 of 148 subjects). The percentage of medically attended AEs was lower after the Booster in comparison to the primary vaccination. Unfortunately for this interim analysis these data were only presented in line listings. The MAH should provide a summary of all medically attended AEs per age stratum in the final report of this study. Two SAEs were recorded within the time frame of one month: one subject suffered from an abscess rated as related by the investigator but not by the sponsor and one subject suffered from dengue fever (unrelated). As the abscess was not located at the vaccination site the assessor concurs with the sponsor's judgement of non-relatedness.

Solicited Adverse Events

Solicited AEs experienced by subjects aged ≥ 9 months to < 3 years within 7 days after the booster dose are summarized by maximum severity in Table 6.

Table 6: **Solicited Adverse Events Experienced by Subjects Aged ≥ 9 Months to < 3 Years within 7 Days after the Booster Dose by Maximum Severity, Safety Population**

≥ 9 Months to < 3 Year at booster	IC51 0.25 mL N=80				
Severity Grade[a]	1 %	2 %	3 %	All % (n/N)	[95% CI]
Any Local AE	2.5	1.3	1.3	5.0 (4/80)	[1.4, 12.3]
Pain (without touching)	0	0	0	0 (0/55)	[0.0, 4.5]
Itching	0	0	0	0 (0/55)	[0.0, 4.5]
Tenderness (upon touching)	1.3	0	0	1.3 (1/80)	[0.0, 6.8]
Hardening	0	0	0	0 (0/80)	[0.0, 4.5]
Swelling	1.3	1.3	1.3	3.8 (3/80)	[0.8, 10.6]
Redness	0	0	1.3	1.3 (1/80)	[0.0, 6.8]
Any Systemic AE	8.8	1.3	0	10.0 (8/80)	[4.4, 18.8]
Irritability	1.3	1.3	0	2.5 (2/80)	[0.3, 8.7]
Nausea	0	0	0	0 (0/56)	[0.0, 4.5]
Vomiting	0	0	0	0 (0/80)	[0.0, 4.5]
Diarrhea	0	0	0	0 (0/80)	[0.0, 4.5]
Flu-like symptoms	0	0	0	0 (0/56)	[0.0, 4.5]
Excessive fatigue	0	0	0	0 (0/80)	[0.0, 4.5]
Muscle pain	0	0	0	0 (0/55)	[0.0, 4.5]
Rash	1.3	0	0	1.3 (1/80)	[0.0, 6.8]
Headache	0	0	0	0 (0/55)	[0.0, 4.5]
Loss of appetite	2.5	0	0	2.5 (2/80)	[0.3, 8.7]
Fever	6.3	0	0	6.3 (5/80)	[2.1, 14.0]

Assessor's comment:
The profile of solicited reactions is comparable to that seen for most other vaccines. Overall a low percentage of subjects in the age group ≥ 9 months to < 3 years reported solicited adverse events. 5 % of subjects reported any local AE and 10 % reported any systemic AE. The most frequently reported local AEs were injection site swelling (3.8 %) and the most frequently reported solicited systemic AEs were fever (6.3 %) as well as loss of appetite and irritability (each 2.5 %). The majority of AEs were graded as mild with the exception of one subject, who graded the swelling with Grade 3. Two events were rated with Grade 2: one subject reported swelling and another subject reported irritability.

The solicited adverse events experienced by subjects aged ≥ 3 years to < 12 years within 7 days after the booster dose are summarized by maximum severity in Table 7.

Table 7: **Solicited Adverse Events Experienced by Subjects Aged ≥ 3 to < 12 Years within 7 Days after the Booster Dose by Maximum Severity, Safety Population**

≥ 3 to < 12 Years at booster	IC51 0.25 mL N=1					IC51 0.5 mL N=38				
Severity Grade[a]	1 %	2 %	3 %	All % (n/N)	[95% CI]	1 %	2 %	3 %	All % (n/N)	[95% CI]
Any Local AE	0	0	0	0 (0/1)	[0.0, 97.5]	10.5	0	0	10.5 (4/38)	[2.9, 24.8]
Pain (without touching)	0	0	0	0 (0/1)	[0.0, 97.5]	5.7	0	0	5.7 (2/35)	[0.6, 17.7]
Itching	0	0	0	0 (0/1)	[0.0, 97.5]	0	0	0	0 (0/35)	[0.0, 9.3]
Tenderness (upon touching)	0	0	0	0 (0/1)	[0.0, 97.5]	2.6	0	0	2.6 (1/38)	[0.1, 13.8]
Hardening	0	0	0	0 (0/1)	[0.0, 97.5]	2.6	0	0	2.6 (1/38)	[0.1, 13.8]
Swelling	0	0	0	0 (0/1)	[0.0, 97.5]	2.6	0	0	2.6 (1/38)	[0.1, 13.8]
Redness	0	0	0	0 (0/1)	[0.0, 97.5]	0	0	0	0 (0/38)	[0.0, 9.3]
Any Systemic AE	0	0	100.0[b]	100.0 (1/1)	[0.0, 97.5]	13.2	2.6	0	15.8 (6/38)	[6.0, 31.3]
Irritability	0	0	0	0 (0/1)	[0.0, 97.5]	0	0	0	0 (0/38)	[0.0, 9.3]
Nausea	0	0	0	0 (0/1)	[0.0, 97.5]	0	0	0	0 (0/34)	[0.0, 9.3]
Vomiting	0	0	0	0 (0/1)	[0.0, 97.5]	0	0	0	0 (0/38)	[0.0, 9.3]
Diarrhea	0	0	0	0 (0/1)	[0.0, 97.5]	0	0	0	0 (0/38)	[0.0, 9.3]
Flu-like symptoms	0	0	100.0	100.0 (1/1)	[0.0, 97.5]	0	0	0	0 (0/34)	[0.0, 9.3]
Excessive fatigue	0	0	100.0	100.0 (1/1)	[0.0, 97.5]	0	0	0	0 (0/38)	[0.0, 9.3]
Muscle pain	0	0	0	0 (0/1)	[0.0, 97.5]	2.9	0	0	2.9 (1/34)	[0.1, 13.8]
Rash	0	0	0	0 (0/1)	[0.0, 97.5]	2.6	0	0	2.6 (1/38)	[0.1, 13.8]
Headache	0	0	0	0 (0/1)	[0.0, 97.5]	2.9	0	0	2.9 (1/34)	[0.1, 13.8]
Loss of appetite	0	0	100.0	100.0 (1/1)	[0.0, 97.5]	5.3	0	0	5.3 (2/38)	[0.6, 17.7]
Fever	100.0	0	0	100.0 (1/1)	[0.0, 97.5]	7.9	2.6	0	10.5 (4/38)	[2.9, 24.8]

Assessor's comment:
There was one application of a wrong dosage: Per protocol all subjects aged ≥ 3 years to < 12 years should have received a Booster dose of 0.5 mL of Ixiaro, but 1 subject incorrectly received 0.25 mL of Ixiaro, which is shown on the left site of the Table 7. The subject who received the incorrect dose experienced no local solicited AE but flu-like symptoms, excessive fatigue and loss of appetite all classified Grade 3 and fever classified Grade 1.
10.5% of 38 subjects who received the correct Booster dose of 0.5 mL experienced local solicited AEs which were all classified Grade 1. The most frequently reported systemic solicited AEs were fever (10.5 %) and loss of appetite (5.3 %). All systemic events were classified Grade 1, but one event of fever was classified Grade 2. Apparently there is no dose dependent frequency of solicited adverse events. As expected a lower frequency of solicited local and systemic events was reported in the age group ≥ 9 months to < 3 years (15 %) compared to subjects aged ≥ 3 years to < 12 years (26.3 %).

Solicited AEs experienced by subjects aged ≥ 12 years to < 18 years within 7 days after the booster dose are summarized by maximum severity in Table 8.

Table 8: **Solicited Adverse Events Experienced by Subjects Aged ≥ 12 to < 18 Years within 7 Days after the Booster Dose by Maximum Severity, Safety Population**

≥ 12 to < 18 Years at booster	IC51 0.5 mL N=29				
Severity Grade*	1 %	2 %	3 %	All % (n/N)	[95% CI]
Any Local AE	13.8	0	0	13.8 (4/29)	[3.9, 31.7]
Pain (without touching)	13.8	0	0	13.8 (4/29)	[3.9, 31.7]
Itching	0	0	0	0 (0/29)	[0.0, 11.9]
Tenderness (upon touching)	6.9	0	0	6.9 (2/29)	[0.8, 22.8]
Hardening	0	0	0	0 (0/29)	[0.0, 11.9]
Swelling	0	0	0	0 (0/29)	[0.0, 11.9]
Redness	0	0	0	0 (0/29)	[0.0, 11.9]
Any Systemic AE	17.2	3.4	0	20.7 (6/29)	[8.0, 39.7]
Irritability	0	0	0	0 (0/29)	[0.0, 11.9]
Nausea	0	0	0	0 (0/29)	[0.0, 11.9]
Vomiting	0	3.4	0	3.4 (1/29)	[0.1, 17.8]
Diarrhea	0	3.4	0	3.4 (1/29)	[0.1, 17.8]
Flu-like symptoms	0	0	0	0 (0/29)	[0.0, 11.9]
Excessive fatigue	0	0	0	0 (0/29)	[0.0, 11.9]
Muscle pain	3.4	0	0	3.4 (1/29)	[0.1, 17.8]
Rash	0	0	0	0 (0/29)	[0.0, 11.9]
Headache	6.9	0	0	6.9 (2/29)	[0.8, 22.8]
Loss of appetite	3.4	0	0	3.4 (1/29)	[0.1, 17.8]
Fever	6.9	0	0	6.9 (2/29)	[0.8, 22.8]

Assessor's comments:
The profile of solicited reactions is comparable to that seen with most other vaccines. In the ≥ 12 years to < 18 years age group, 13.8% of subjects (4 of 29 subjects) had at least 1 solicited local AE and 20.7 % at least 1 solicited systemic AE within 7 days after the booster dose of 0.5 mL of Ixiaro. Pain and tenderness were mostly classified Grade 1 and fever as well as headache (each 6.9 % as systemic AEs Grade 1). 1 event of vomiting and 1 event of diarrhea were classified Grade 2. No Grade 3 events were reported.

Unsolicited Adverse Events

Unsolicited AEs experienced by subjects aged ≥ 9 months to < 3 years after the booster dose to Visit 2a (Month 13) are summarized in Table 9.

Table 9: **Unsolicited Adverse Events after the Booster Dose to Visit 2a (Month 13), Subjects Aged ≥ 9 Months to < 3 Years, Safety Population**

≥ 9 Months to < 3 Years at booster	IC51 0.25 mL N=80 n (%) [95% CI]
Number of subjects with at least one AE:	16 (20.0) [11.9, 30.4]
Infections and infestations	14 (17.5) [9.9, 27.6]
Bronchitis	3 (3.8) [0.8, 10.6]
Nasopharyngitis	3 (3.8) [0.8, 10.6]
Upper respiratory tract infection	3 (3.8) [0.8, 10.6]
Rhinitis	2 (2.5) [0.3, 8.7]
Gastroenteritis viral	1 (1.3) [0.0, 6.8]
Herpangina	1 (1.3) [0.0, 6.8]
Impetigo	1 (1.3) [0.0, 6.8]
Otitis media	1 (1.3) [0.0, 6.8]
Pharyngotonsillitis	1 (1.3) [0.0, 6.8]
General disorders and administration site conditions:	2 (2.5) [0.3, 8.7]
Pyrexia	2 (2.5) [0.3, 8.7]

Unsolicited AEs experienced by subjects aged ≥ 3 years to < 12 years after the booster dose to Visit 2a (Month 13) are summarized in Table 10.

Table 10: **Unsolicited Adverse Events after the Booster Dose to Visit 2a (Month 13), Subjects Aged ≥ 3 Years to < 12 Years, Safety Population**

≥ 3 Years to < 12 Years at booster	IC51 0.25 mL N=1 n (%) [95% CI]	IC51 0.5 mL N=38 n (%) [95% CI]	Total N=39 n (%) [95% CI]
Number of subjects with at least one AE:	1 (100.0)[a] [2.5, 100.0]	9 (23.7) [11.4, 40.2]	10 (25.6) [13.0, 42.1]
Infections and infestations	1 (100.0) [2.5, 100.0]	7 (18.4) [7.7, 34.3]	8 (20.5) [9.3, 36.5]
Nasopharyngitis	0 (0.0) [0.0, 97.5]	2 (5.3) [0.6, 17.7]	2 (5.1) [0.6, 17.3]
Upper respiratory tract infection	0 (0.0) [0.0, 97.5]	2 (5.3) [0.6, 17.7]	2 (5.1) [0.6, 17.3]
Abscess	1 (100.0) [2.5, 100.0]	0 (0.0) [0.0, 9.3]	1 (2.6) [0.1, 13.5]
Infection parasitic	0 (0.0) [0.0, 97.5]	1 (2.6) [0.1, 13.8]	1 (2.6) [0.1, 13.5]
Rhinitis	0 (0.0) [0.0, 97.5]	1 (2.6) [0.1, 13.8]	1 (2.6) [0.1, 13.5]
Viral infection	0 (0.0) [0.0, 97.5]	1 (2.6) [0.1, 13.8]	1 (2.6) [0.1, 13.5]
Gastrointestinal disorders:	0 (0.0) [0.0, 97.5]	2 (5.3) [0.6, 17.7]	2 (5.1) [0.6, 17.3]
Abdominal pain	0 (0.0) [0.0, 97.5]	2 (5.3) [0.6, 17.7]	2 (5.1) [0.6, 17.3]
General disorders and administration site conditions	0 (0.0) [0.0, 97.5]	1 (2.6) [0.1, 13.8]	1 (2.6) [0.1, 13.5]
Pyrexia	0 (0.0) [0.0, 97.5]	1 (2.6) [0.1, 13.8]	1 (2.6) [0.1, 13.5]
Skin and subcutaneous tissue disorders	0 (0.0) [0.0, 97.5]	1 (2.6) [0.1, 13.8]	1 (2.6) [0.1, 13.5]
Pruritus	0 (0.0) [0.0, 97.5]	1 (2.6) [0.1, 13.8]	1 (2.6) [0.1, 13.5]

Unsolicited AEs experienced by subjects aged ≥ 12 years to < 18 years after the booster dose to Visit 2a (Month 13) are summarized in Table 11.

Table 11: **Unsolicited Adverse Events after the Booster Dose to Visit 2a (Month 13), Subjects Aged ≥ 12 Years to < 18 Years, Safety Population**

≥ 12 Years to < 18 Years at booster	IC51 0.5 mL N=29 n (%) [95% CI]
Number of subjects with at least one AE:	5 (17.2) [5.8, 35.8]
Infections and infestations	4 (13.8) [3.9, 31.7]
Asymptomatic bacteriuria	1 (3.4) [0.1, 17.8]
Carbuncle	1 (3.4) [0.1, 17.8]
Dengue fever	1 (3.4) [0.1, 17.8]
Gastroenteritis	1 (3.4) [0.1, 17.8]
Hordeolum	1 (3.4) [0.1, 17.8]
Wound infection	1 (3.4) [0.1, 17.8]
Investigations	1 (3.4) [0.1, 17.8]
Blood bilirubin increased	1 (3.4) [0.1, 17.8]
Respiratory, thoracic and mediastinal disorders	1 (3.4) [0.1, 17.8]
Cough	1 (3.4) [0.1, 17.8]

Assessor's comment
With regards to the frequency of reported unsolicited AE no age dependency was seen as for the solicited AEs. Overall the unsolicited AEs after the booster dose were reported by 20.7 % of subjects. The majority of subjects reported infections and infestations which mostly consisted of upper respiratory tract infections and nasopharyngitis. The reported frequencies of unsolicited AEs are comparable to the frequencies reported for the 5 months period between Visit 1 and Visit 2 before the booster dose was given. There is one AE (pruritus) considered related to the study vaccine in the age group ≥ 3 years to < 12 years. This event of pruritus falls under the predefined "cases of special interest" (i.e. allergies) after the booster dose. No neurological AEs of special interest were reported until Visit 2a.

Evaluation of laboratory parameter

Hematology

Four subjects had clinically significant hematology values at Visit 2a (Month 13) and 1 subject at Visit 2 (Month 12):

- Increased platelet count, 1 subject (IC51 0.25 mL group) at Visit 2a (Month 13);
- Decreased platelet count and increased hematocrit, 1 subject (IC51 0.5 mL group) at Visit 2a (Month 13);
- Increased white blood cell count, 1 subject (IC51 0.25 mL group) at Visit 2a (Month 13);
- Increased red blood cell count, 1 subject (IC51 0.25 mL group) at Visit 2a (Month 13);
- Decreased white blood cell count, 1 subject (IC51 0.5 mL group) at Visit 2 (Month 12).

Biochemistry
Three subjects had clinically significant biochemistry values at Visit 1 (Month 7), 1 subject at Visit 2 (Month 12) and 1 subject at Visit 2 (Month 12) and Visit 2a (Month 13):

- Increased AST and ALT, 2 subjects at Visit 1 (Month 7); these 2 subjects also had unsolicited AEs reported of increased AST and increased ALT;
- Increased alkaline phosphatase and increased ALT and AST, 1 subject at Visit 1 (Month 7); this subject also had an unsolicited AE reported of hepatic enzyme increased;
- Decreased creatinine, 1 subject at Visit 2 (Month 12);
- Increased bilirubin (Visit 2 [Month 12]) and increased AST (Visit 2a [Month 13]), 1 subject (IC51 0.5 mL group); this subject also had an unsolicited AE reported of elevated total bilirubin.

Urinalysis
Three subjects had clinically significant urinalysis

- Presence of protein and red blood cells in the urine, 1 subject at Visit 1 (Month 7); this subject also had an unsolicited AEs reported of proteinuria and red blood cells urine;
- Presence of white blood cells in the urine, 1 subject at Visit 2 (Month 12);
- Presence of protein in the urine, 1 subject (IC51 0.5 mL group) at Visit 2a (Month 13).

Assessor's comments
No marked changes were noted neither for the time period before the booster dose nor after the booster dose.

SAEs
Before the administration of the Booster dose one SAE of concussion was reported of severe intensitiy, which was considered as unrelated by the investigator. One subject was admitted to hospital after he received the booster dose and was diagnosed with dengue hemorrhagic fever.The SAE of dengue was considered not related. Another SAE of abscess was reported, which was considered as related by the investigator. Two independent DSMB members, who concluded that they would hardly see any relationship, unless the abscess developed at the site of the vaccine administration, which was not the case.

Assessor's comment:
All three reported SAEs were considered as unrelated and all three SAEs are considered resolved. No deaths were reported.

Assessor's discussion on safety:
Ixiaro given as a Booster dose 12 months after primary vaccination was demonstrated to be safe and well-tolerated in all pediatric age groups in this study. Overall the safety and reactogenicity profile of Ixiaro seen after a Booster dose resulted in a lower AE rate compared to previous experience with this vaccine in a pediatric population after primary vaccination. No death was reported. All three reported SAEs were considered as unrelated and resolved. No new safety signals occurred.

- Preliminary immonogenicity analysis

All immunogenicity analyses were carried out using the ITT Population and were repeated using the PP Population as a supportive analysis.
The immunogenicity of IC51 was assessed for the Booster Group at 13 months (Visit 2a) after the primary immunization, which was approximately 1 month after a single booster dose was administered at Visit 2, and for the Non-booster Group immunogenicity was assessed at 12 months after the primary immunization. The immunogenicity endpoints were SCR rates, fold increase rates and GMTs. The

analyses were repeated with stratifications by age group and pre-existing JEV and DENV status (see Table 12 for baseline status).

Table 12: **Pre-existing JEV and DENV Serological Data in Study IC51-323, Overall and by Age Group, Safety Population**

	IC51 0.25 mL N=81 n (%)	IC51 0.5 mL N=67 n (%)	Booster N=150 n (%)	Non-booster N=150 n (%)	Total N=300 n (%)
Entire study population					
Pre-existing JEV immunity					
Seropositive	1 (1.2)	17 (25.4)	19 (12.7)	15 (10.0)	34 (11.3)
Seronegative	80 (98.8)	50 (74.6)	131 (87.3)	134 (89.3)	265 (88.3)
Not assessable	0	0	0	1 (0.7)	1 (0.3)
Pre-existing DENV antibodies					
Positive	7 (8.6)	33 (49.3)	41 (27.3)	44 (29.3)	85 (28.3)
Negative	72 (88.9)	34 (50.7)	107 (71.3)	101 (67.3)	208 (69.3)
Not assessable	1 (1.2)	0	1 (0.7)	3 (2.0)	4 (1.3)
Missing	1 (1.2)	0	1 (0.7)	2 (1.3)	3 (1.0)
Age group 2 mth to <1 year [a]	**N=15**	-	**N=15**	**N=15**	**N=30**
Pre-existing JEV immunity					
Seropositive	0		0	1 (6.7)	1 (3.3)
Seronegative	15 (100.0)	-	15 (100.0)	14 (93.3)	29 (96.7)
Not assessable	0		0	0	0
Pre-existing DENV antibodies					
Positive	2 (13.3)		2 (13.3)	1 (6.7)	3 (10.0)
Negative	12 (80.0)	-	12 (80.0)	13 (86.7)	25 (83.3)
Not assessable	0		0	1 (6.7)	1 (3.3)
Missing	1 (6.7)		1 (6.7)	0	1 (3.3)
Age group 1 to <3 years [a]	**N=66**	**N=28**	**N=95**	**N=92**	**N=187**
Pre-existing JEV immunity					
Seropositive	1 (1.5)	2 (7.1)	3 (3.2)	0	3 (1.6)
Seronegative	65 (98.5)	26 (92.9)	92 (96.8)	91 (98.9)	183 (97.9)
Not assessable	0	0	0	1 (1.1)	1 (0.5)
Pre-existing DENV antibodies					
Positive	5 (7.6)	5 (17.9)	10 (10.5)	8 (8.7)	18 (9.6)
Negative	60 (90.9)	23 (82.1)	84 (88.4)	80 (87.0)	164 (87.7)
Not assessable	1 (1.5)	0	1 (1.1)	2 (2.2)	3 (1.6)
Missing	0	0	0	2 (2.2)	2 (1.1)
Age group 3 to <12 years [a]		**N=11**	**N=11**	**N=16**	**N=27**
Pre-existing JEV immunity					
Seropositive		0	0	4 (25.0)	4 (14.8)
Seronegative	-	11 (100.0)	11 (100.0)	12 (75.0)	23 (85.2)
Not assessable		0	0	0	0
Pre-existing DENV antibodies					
Positive		6 (54.5)	6 (54.5)	10 (62.5)	16 (59.3)
Negative	-	5 (45.5)	5 (45.5)	6 (37.5)	11 (40.7)
Not assessable		0	0	0	0
Missing		0	0	0	0
Age group 12 to <17 years [a]		**N=28**	**N=29**	**N=27**	**N=56**
Pre-existing JEV immunity					
Seropositive		15 (53.6)	16 (55.2)	10 (37.0)	26 (46.4)
Seronegative	-	13 (46.4)	13 (44.8)	17 (63.0)	30 (53.6)
Not assessable		0	0	0	0
Pre-existing DENV antibodies					
Positive		22 (78.6)	23 (79.3)	25 (92.6)	48 (85.7)
Negative	-	6 (21.4)	6 (20.7)	2 (7.4)	8 (14.3)
Not assessable		0	0	0	0
Missing		0	0	0	0

A small number of subjects (34 of 300 subjects [11.3%]) in the Safety Population had a pre-existing JEV antibody PRNT50 titer of 1:10 or greater and were considered seropositive at baseline of Study IC51-323: 19 subjects (12.7%) in the Booster Group (0.25 mL, 1 [1.2%]; 0.5 mL, 17 [25.4%]) and 15 subjects (10.0%) in the Non-booster Group.

Baseline DENV antibodies were present in 85 of 300 subjects (28.3%): 41 subjects (27.3%) in the Booster Group (0.25 mL, 7 [8.6%]; 0.5 mL, 33 [49.3%]) and 44 subjects (29.3%) in the Non-booster Group.

In the immunogenicity results, 'Month 12' and 'Month 13' refer to data collected at Visit 2 and Visit 2a, respectively; the time points are not a strict cut-off of 12 or 13 months after the initial vaccination in Study IC51-323. The mean time between Visit 2 and Visit 2a was 28.7 days, with a minimum of 7 days and a maximum of 52 days. To determine if time between Visit 2 and Visit 2a had an influence, GMTs were also summarized at Visit 2a for the Booster Group, by dose, stratified by the number of days between the Visit 2 (Month 12) and Visit 2a (Month 13) visits (7 to 15 days; 16 to 21 days; 22 to 35 days; 36 to 52 days).

The majority of subjects (107 of 150 subjects) had immunogenicity samples taken between 22 and 35 days (i.e., Visit 2a) after the booster dose, which was administered at Visit 2. The seroconverion rates (primary endpoint), fold increase rates and geometric mean titers are summarized in Table 13 before and after the Booster dose.

Table 13: **Seroconversion, Fold Increase Rates and Raw Geometric Mean Titers, After Primary Immunization and Booster of IXIARO by Dose Group, Intent-to-treat Population**

	IC51 0.25 mL N=81	**IC51 0.5 mL N=67**
Visit 1 (Day 0) in Study IC51-323, Pre-Primary Series	**N=81**	**N=67**
Seroconversion		
n (%)	1 (1.2)	17 (25.4)
95% CI	0.2; 6.7	16.5; 36.9
Geometric mean titers, value		
Geometric mean (SD)	5.04 (1.080)	8.45 (2.758)
95% CI for geometric mean	4.96; 5.13	6.60; 10.83
Median (Min, Max)	5.00 (5.0, 10.0)	5.00 (5.0, 328.0)
Visit 3 (Day 56) Visit 3 in Study IC51-323, Post-Primary Series	**N=13[a]**	**N=34[a]**
Seroconversion		
n (%)	13 (100.0)	34 (100.0)
95% CI	77.2; 100.0	89.8; 100.0
Geometric mean titers, value		
Geometric mean (SD)	442.36 (1.686)	192.91 (2.984)
95% CI for geometric mean	322.67; 606.44	131.72; 282.51
Median (Min, Max)	523.00 (186.0, 913.0)	164.16 (43.0, 2936.0)
Visit 1 (Month 7)	**N=81**	**N=67**
Seroconversion		
n (%)	75 (92.6)	57 (85.1)
95% CI	84.8; 96.6	74.7; 91.7
Geometric mean titers, value		
Geometric mean (SD)	64.08 (3.341)	40.44 (3.509)
95% CI for geometric mean	49.08; 83.67	29.77; 54.92
Median (Min, Max)	72.00 (5.0, 3882.0)	42.00 (5.0, 1430.0)

continued

	IC51 0.25 mL N=81	IC51 0.5 mL N=67
Visit 2 (Month 12), Pre-Booster	**N=81**	**N=67**
Seroconversion		
n (%)	79 (97.5)	60 (89.6)
95% CI	91.4; 99.3	80.0; 94.8
Geometric mean titers, value		
Geometric mean (SD)	67.27 (2.703)	40.40 (3.158)
95% CI for geometric mean	53.99; 83.81	30.52; 53.49
Median (Min, Max)	70.00 (5.0, 776.0)	32.00 (5.0, 764.0)
Visit 2a (Month 13), Post-Booster	**N=81**	**N=67**
Seroconversion		
n (%)	81 (100.0)	67 (100.0)
95% CI	95.5; 100.0	94.6; 100.0
Four-fold increase in titers		
n (%)	74 (91.4)	62 (92.5)
95% CI	83.2; 95.8	83.7; 96.8
Ten-fold increase in titers		
n (%)	70 (86.4)	52 (77.6)
95% CI	77.3; 92.2	66.3; 85.9
Geometric mean titers, value		
Geometric mean (SD)	2910.84 (3.303)	1365.87 (3.778)
95% CI for geometric mean	2235.06; 3790.96	987.62; 1888.98
Median (Min, Max)	3128.00 (129.0, 41226.0)	1363.00 (90.0, 32280.0)

Vaccination with a booster of IC51, comprising a dose of either 0.25 mL or 0.5 mL given approximately 12 months after the initial vaccination, produced a pronounced immune response at Visit 2a (Month 13) in all subjects in the ITT Population (Table 13):

- Prior to the booster, seroconversion (defined as a PRNT50 titer ≥ 1:10) was still evident in 97.5% of subjects (95% CI: 91.4 to 99.3) in the group of subjects who later received the IC51 0.25 mL booster and in 89.6% of subjects (95% CI: 80.0 to 94.8) in the IC51 0.5 mL booster group;
- After the booster, seroconversion occurred in all subjects in both the IC51 0.25 mL booster group (100.0% of subjects [95% CI: 95.5 to 100.0]) and the IC51 0.5 mL booster group (100.0% of subjects [95% CI: 94.6 to 100.0]);
- Four-fold or higher increases in post-booster titers over the pre-booster titers were observed in 91.9% of subjects (95% CI: 86.4 to 95.3) overall (in the IC51 0.25 mL booster group, 91.4% of subjects [95% CI: 83.2 to 95.8] and in the IC51 0.5 mL booster group, 92.5% of subjects [95% CI: 83.7 to 96.8]);
- Ten-fold or higher increases in post-booster versus pre-booster titers were observed in 82.4% of subjects (95% CI: 75.5 to 87.7) overall (in the IC51 0.25 mL booster group, 86.4% of subjects [95% CI: 77.3 to 92.2] and in the IC51 0.5 mL booster group, 77.6% of subjects [95% CI: 66.3 to 85.9]);
- Geometric mean titers rose substantially after the booster dose in both the IC51 0.25 mL booster group (from 67.27 pre-booster to 2910.84 [95% CI: 2235.06 to 3790.96]) and the IC51 0.5 mL booster group (from 40.40 pre-booster to 1365.87 [95% CI: 987.62 to 1888.98]).

Assessor's comments:
Participants who were primarily vaccinated with two doses of the lower dose increment (0.25 mL) showed higher seroconversion rates (97.5 %) pre Booster- dose compared to participants who received two doses of the higher dose increment (0.5 mL) (89.6 %). The same trend was observed for the increase of titre after the Booster-dose. The Ten-fold increases in post-booster versus pre-booster titers were observed in 86.4 % of subjects, who received a 0.25 mL dose versus 77.6 % in subjects, who received a 0.5 mL dose. GMT increased approximately two times higher (2910.84) in the 0.25 mL group compared to the 0.5 mL group (1365.87). Seroconversion rate was 100 % in both dose groups.

As the time between Visit 2 (booster administration) and Visit 2a (serological sampling) was variable with a mean of 28.7 days, a minimum of 7 days and a maximum of 52 days, GMTs were also

summarized at Visit 2a for the Booster Group, by dose, stratified by the number of days between the Visit 2 (Month 12) and Visit 2a (Month 13) visits (7 to 15 days; 16 to 21 days; 22 to 35 days; 36 to 52 days) shown in Table 14.

Table 14: **Geometric Mean Titers after the IXIARO Booster by Number of Days Between Booster Administration (Visit 2) and Serology (Visit 2a), Intent-to-treat Population**

	IC51 0.25 mL N=81	IC51 0.5 mL N=67	Booster Group N=150
7 to 15 days			
GMT at Visit 2a			
n	7	2	9
Geometric mean	2086.62	766.97	1670.52
(SD)	(3.941)	(7.706)	(4.298)
95% CI	587.01; 7417.25	0.00; 71264355959.50	544.57; 5124.47
16 to 21 days			
GMT at Visit 2a			
n	10	7	17
Geometric mean	3256.89	1193.36	2154.08
(SD)	(2.207)	(4.876)	(3.477)
95% CI	1848.72; 5737.66	275.69; 5165.73	1134.95; 4088.33
22 to 35 days			
GMT at Visit 2a			
n	53	54	107
Geometric mean	3304.47	1402.71	2144.35
(SD)	(3.128)	(3.665)	(3.636)
95% CI	2413.25; 4524.82	984.02; 1999.56	1674.31; 2746.35
36 to 52 days			
GMT at Visit 2a			
n	11	4	15
Geometric mean	1763.08	1611.76	1721.39
(SD)	(4.881)	(4.629)	(4.557)
95% CI	607.75; 5114.74	140.74; 18457.40	743.25; 3986.83

Geometric mean titers were pronounced after the booster dose regardless of the time elapsed between the booster dose and the serology sampling date:

- In the IC51 0.25 mL group, GMT in subjects with serology samples taken after 7 to 15 days was 2086.62 [95% CI: 587.01 to 7417.25]; after 16 to 21 days it was 3256.89 [95% CI: 1848.72 to 5737.66]; after 22 to 35 days it was 3304.47 [95% CI: 2413.25 to 4524.82]; and after 36 to 52 days it was 1763.08 [95% CI: 607.75 to 5114.74].
- In the IC51 0.5 mL group, GMT in subjects with serology samples taken after 7 to 15 days was 766.97 [95% CI: 0.00 to 71264355959.50]; after 16 to 21 days it was 1193.36 [95% CI: 275.69 to 5165.73]; after 22 to 35 days it was 1402.71 [95% CI: 984.02 to 1999.56]; and after 36 to 52 days it was 1611.76 [95% CI: 140.74 to 18457.40].

Assessor's comments:
Due to the limited number of subjects in the different time-frames (7 to 15 days, 16 to 21 day and 36 to 52 days) the results of GMTs should be interpreted with caution. Nevertheless a clear trend of increasing GMTs was observed with increasing time after the Booster dose until Day 35. After Day 35 a trend of decreasing GMTs was seen.

Age dependency on Boosterability
A summary of SCR, fold increase rates and GMTs by age group is presented in Table 15 for the ITT Population.

Table 15: **Seroconversion, Fold Increase Rates and Raw Geometric Mean Titers After Primary Immunization and Booster of IXIARO by Age Group (as at Primary Immunization), Stratified by Dose Group, Intent-to-treat Population**

	IC51 0.25 mL		IC51 0.5 mL		
	2 months to < 1 year	1 year to < 3 years	1 year to < 3 years	3 years to < 12 years	12 years to < 17 years
Visit 1 (Day 0) in Study IC51-323, Pre-Primary Series	**N=15**	**N=66**	**N=28**	**N=11**	**N=28**
Seroconversion					
n (%)	0	1 (1.5)	2 (7.1)	0	15 (53.6)
95% CI	0.0; 20.4	0.3; 8.1	2.0; 22.6	0.0; 25.9	35.8; 70.5
GMTs					
Geometric mean	5.00	5.05	5.93	5.00	14.82
(SD)	(1.000)	(1.089)	(1.925)	(1.000)	(3.427)
95% CI	5.00; 5.00	4.95; 5.16	4.60; 7.64	5.00; 5.00	9.19; 23.90
Visit 3 (Day 56) in Study IC51-323, Post-Primary Series	**N=2[a]**	**N=11[a]**	**N=4[a]**	**N=11**	**N=19[a]**
Seroconversion					
n (%)	2 (100.0)	11 (100.0)	4 (100.0)	11 (100.0)	19 (100.0)
95% CI	34.2; 100.0	74.1; 100.0	51.0; 100.0	74.1; 100.0	83.2; 100.0
GMTs					
Geometric mean	691.01	407.90	295.26	188.32	178.85
(SD)	(1.483)	(1.672)	(2.143)	(2.597)	(3.462)
95% CI	20.06; 23808.97	288.73; 576.25	87.82; 992.73	99.18; 357.57	98.30; 325.42
Visit 1 (Month 7)	**N=15**	**N=66**	**N=28**	**N=11**	**N=28**
Seroconversion					
n (%)	15 (100.0)	60 (90.9)	19 (67.9)	10 (90.9)	28 (100.0)
95% CI	79.6; 100.0	81.6; 95.8	49.3; 82.1	62.3; 98.4	87.9; 100.0
GMTs					
Geometric mean	79.40	61.03	25.35	34.71	68.47
(SD)	(2.411)	(3.559)	(3.812)	(2.666)	2.965
95% CI	48.77; 129.26	44.67; 83.39	15.09; 42.60	17.96; 67.08	44.92; 104.37
Visit 2 (Month 12), Pre-Booster	**N=15**	**N=66**	**N=28**	**N=11**	**N=28**
Seroconversion					
n (%)	15 (100.0)	64 (97.0)	22 (78.6)	10 (90.9)	28 (100.0)
95% CI	79.6; 100.0	89.6; 99.2	60.5; 89.8	62.3; 98.4	87.9; 100.0
GMTs					
Geometric mean	62.22	68.48	32.21	26.22	60.06
(SD)	(2.106)	(2.848)	(3.458)	(2.555)	(2.820)
95% CI	41.18; 93.99	52.94; 88.57	19.91; 52.12	13.96; 49.24	40.18; 89.78

continued

	IC51 0.25 mL		IC51 0.5 mL		
	2 months to < 1 year	1 year to < 3 years	1 year to < 3 years	3 years to < 12 years	12 years to < 17 years
Visit 2a (Month 13), Post-Booster	**N=15**	**N=66**	**N=28**	**N=11**	**N=28**
Seroconversion					
n (%)	15 (100.0)	66 (100.0)	28 (100.0)	11 (100.0)	28 (100.0)
95% CI	79.6; 100.0	94.5; 100.0	87.9; 100.0	74.1; 100.0	87.9; 100.0
Four-fold increase in titers					
n (%)	15 (100.0)	59 (89.4)	27 (96.4)	11 (100.0)	24 (85.7)
95% CI	79.6; 100.0	79.7; 94.8	82.3; 99.4	74.1; 100.0	68.5; 94.3
Ten-fold increase in titers					
n (%)	15 (100.0)	55 (83.3)	25 (89.3)	10 (90.9)	17 (60.7)
95% CI	79.6; 100.0	72.6; 90.4	72.8; 96.3	62.3; 98.4	42.4; 76.4
GMTs					
N	4075.93	2696.43	2029.32	1483.94	889.87
Geometric mean	(2.596)	(3.443)	(3.764)	(3.243)	(3.675)
(SD)	2403.23;	1989.71;	1213.80;	673.18;	537.18;
95% CI	6912.87	3654.18	3392.76	3271.15	1474.11

Assessor's comments:
Seroconversion rates observed pre-Booster differed only slightly in the different age and dose groups (78.6 % aged 1 to 3 years 0.5 mL to 100 % in most age groups). One month after the Booster-dose all subjects showed 100 % seroconversion. With regards to Ten-fold increase in titers the magnitude of the immune response in the older age group was generally lower compared to the younger age groups. There is however a significant difference in the antibody levels observed following vaccination with Booster doses of either 0.25mL or 0.5mL vaccine. Children receiving the half dose had higher GMTs after the Booster dose at month 13 (4075.93 < 1 year and 2696.93 < 3years) compared to children receiving the full vaccine dose (2029.32, 1 year to < 3 years; 1483.94, 3 years to < 12 years and 889.87, 12 years to < 17 years). Children in all age groups were boosterable one year after the first administration of Ixiaro, but resulted in different antibody levels depending on the dose (0.25 mL or 0.5 mL) of the booster and the age of the vaccinee.

Just for information:
Results from booster vaccinations in adult subjects indicate that the immune response is boosterable in subjects with low or no detectable antibody levels up to 24 month following the primary vaccination series.

After the Booster Dose: Influence of Pre-booster JEV Antibody Status
Seroconversion rates and GMTs by pre-booster JEV status, stratified by dose group, are summarized in Table 16.

Table 16: **Seroconversion and Raw Geometric Mean Titers by Dose Group, Stratified by Pre-booster JEV Immunity, Intent-to-treat Population**

	IC51 0.25 mL N=81		IC51 0.5 mL N=67	
	Seropositive pre-vaccination	**Seronegative pre-vaccination**	**Seropositive pre-vaccination**	**Seronegative pre-vaccination**
Visit 2 (Month 12), Pre-Booster	**N=79**	**N=2**	**N=60**	**N=7**
Seroconversion				
n (%)	79 (100.0)	0	60 (100.0)	0
95% CI	95.4; 100.0		94.0; 100.0	
GMTs				
Geometric mean (SD)	71.85 (2.496)	5.00 (1.000)	51.56 (2.583)	5.00 (1.000)
95% CI	58.54; 88.18	5.00; 5.00	40.35; 65.88	5.00; 5.00
Visit 2a (Month 13), Post-Booster	**N=79**	**N=2**	**N=60**	**N=7**
Seroconversion				
n (%)	79 (100.0)	2 (100.0)	60 (100.0)	7 (100.0)
95% CI	95.4; 100.0	34.2; 100.0	94.0; 100.0	64.6; 100.0
GMTs				
Geometric mean (SD)	3106.10 (3.104)	224.01 (2.183)	1483.72 (3.904)	671.93 (2.087)
95% CI	2410.01; 4003.23	0.20; 248709.35	1043.64; 2109.39	340.31; 1326.71
GMT ratio	13.87		2.21	
95% CI for GMT ratio	2.77; 69.30		0.77; 6.31	

Assessor's comment:
Table 16 shows determination of JEV antibody levels of the Booster group at month 12 (seropositive or seronegative subjects).
These results should again be interpreted with caution due to the very low number of subjects being seronegative prior to the Booster. All seronegative subjects seroconverted after the Booster with a much lower antibody response 224.01 (0.25 mL dose group); 671.93 (0.5 mL dose group) compared to the seropositive subjects 3106.10 (0.25 mL dose group); 1483.72 (0.5 mL dose group).

Immunogenicity without the Booster

A summary of SCR and GMTs from all time points before and since the primary immunization with IXIARO in Study IC51-323 by treatment group, is presented in Table 17 for the ITT Population.

Table 17: **Seroconversion and Raw Geometric Mean Titers after Primary Immunization with IXIARO, by Treatment Group, Intent-to-treat Population**

	Booster N=150	Non-booster N=150	Total N=300
Visit 1 (Day 0) of Study IC51-323, Pre-Primary Series	**N=150**	**N=149**	**N=299**
Seroconversion			
n (%)	19 (12.7)	15 (10.1)	34 (11.4)
95% CI	8.3; 18.9	6.2; 15.9	8.3; 15.5
Geometric mean titers, value			
Geometric mean (SD)	6.47 (2.129)	6.17 (2.264)	6.32 (2.194)
95% CI for geometric mean	5.73; 7.31	5.41; 7.05	5.78; 6.91
Median (Min, Max)	5.00 (5.0, 328.0)	5.00 (5.0, 2878.0)	5.00 (5.0, 2878.0)
Visit 3 (Day 56) of Study IC51-323, Post-Primary Series	**N=49[a]**	**N=49[a]**	**N=98[a]**
Seroconversion			
n (%)	49 (100.0)	49 (100.0)	98 (100.0)
95% CI	92.7; 100.0	92.7; 100.0	96.2; 100.0
Geometric mean titers, value			
Geometric mean (SD)	240.74 (2.782)	178.40 (3.013)	207.24 (2.912)
95% CI for geometric mean	179.43; 322.99	129.96; 244.88	167.26; 256.77
Median (Min, Max)	209.00 (43.0, 2936.0)	160.00 (20.0, 1326.0)	192.00 (20.0, 2936.0)
Visit 1 (Month 7)	**N=150**	**N=150**	**N=300**
Seroconversion			
n (%)	134 (89.3)	129 (86.0)	263 (87.7)
95% CI	83.4; 93.3	79.5; 90.7	83.5; 90.9
Geometric mean titers, value			
Geometric mean (SD)	51.96 (3.455)	41.85 (3.343)	46.63 (3.408)
95% CI for geometric mean	42.54; 63.47	34.45; 50.85	40.57; 53.61
Median (Min, Max)	56.00 (5.0, 3882.0)	49.99 (5.0, 4650.0)	53.50 (5.0, 4650.0)
Visit 2 (Month 12), Pre-Booster	**N=148**	**N=149**	**N=297**
Seroconversion			
n (%)	139 (93.9)	134 (89.9)	273 (91.9)
95% CI	88.8; 96.8	84.1; 93.8	88.3; 94.5
Geometric mean titers, value			
Geometric mean (SD)	53.41 (2.986)	45.53 (3.146)	49.30 (3.069)
95% CI for geometric mean	44.71; 63.79	37.82; 54.82	43.37; 56.04
Median (Min, Max)	55.00 (5.0, 776.0)	48.00 (5.0, 4385.0)	51.00 (5.0, 4385.0)

Up to Visit 2 (Month 12), the booster and non-booster group did not differ in treatments; hence the antibody persistence data could be pooled for the total population for Month 12, resulting in a higher sample size.

As already observed in Study IC51-323, the antibody levels declined considerably between Day 56 and Month 7 (Visit 4 in Study IC51-323/Visit 1 in Study IC51-325):

seroconversion from 100.0% to 87.7% of the total subjects and the GMT from 207.24 to 46.63. At Visit 2 (Month 12), the immune response persisted and remained consistent with the level of response seen at Visit 1 (Month 7) (Table 17; ITT Population):

- Seroconversion rates overall were slightly lower at Visit 1 (Month 7; 87.7% of subjects [95% CI: 83.5 to 90.9]) than at Visit 2 (Month 12) (91.9% of subjects [95% CI: 88.3 to 94.5]);
- Geometric mean titers overall were approximately the same at Visit 1 (Month 7; 46.63 [95% CI: 40.57 to 53.61]) and Visit 2 (Month 12) (49.30 [95% CI: 43.37 to 56.04]).

Results for the time points before the booster were similar for the Booster Group and the Non-booster Group.

Age-dependent Differences
A summary of SCR and GMTs stratified by age group is presented in Table 18 for the ITT Population.

Table 18: **Seroconversion and Raw Geometric Mean Titers after Primary Immunization with IXIARO, Stratified by Age Group (as at Primary Immunization), Intent-to-treat Population**

	≥ 2 months to < 1 year	≥ 1 year to < 3 years	≥ 3 years to < 12 years	≥ 12 years to < 17 years
Visit 1 (Day 0) of IC51-323, Pre-Primary Series	**N=30**	**N=186**	**N=27**	**N=56**
Seroconversion				
n (%)	1 (3.3)	3 (1.6)	4 (14.8)	26 (46.4)
95% CI	0.6; 16.7	0.6; 4.6	5.9; 32.5	34.0; 59.3
GMTs				
Geometric mean (SD)	5.30 (1.378)	5.15 (1.300)	6.04 (1.640)	14.05 (4.312)
95% CI	4.70; 5.98	4.96; 5.35	4.96; 7.34	9.50; 20.78
Visit 3 (Day 56) of IC51-323, Post-Primary Series	**N=2[a]**	**N=33[a]**	**N=27**	**N=36[a]**
Seroconversion				
n (%)	2 (100.0)	33 (100.0)	27 (100.0)	36 (100.0)
95% CI	34.2; 100.0	89.6; 100.0	87.5; 100.0	90.4; 100.0
GMTs				
Geometric mean (SD)	691.01 (1.483)	244.85 (2.407)	232.12 (3.106)	152.78 (3.112)
95% CI	20.06; 23808.97	179.33; 334.30	148.26; 363.41	104.06; 224.33
Visit 1 (Month 7)	**N=30**	**N=187**	**N=27**	**N=56**
Seroconversion				
n (%)	30 (100.0)	156 (83.4)	23 (85.2)	54 (96.4)
95% CI	88.6; 100.0	77.4; 88.1	67.5; 94.1	87.9; 99.0
GMTs				
Geometric mean (SD)	71.21 (2.228)	42.01 (3.578)	39.46 (3.456)	57.09 (3.294)
95% CI	52.80; 96.05	34.95; 50.50	24.16; 64.44	41.49; 78.56
Visit 2 (Month 12), Pre-Booster	**N=30**	**N=185**	**N=27**	**N=55**
Seroconversion				
n (%)	30 (100.0)	169 (91.4)	23 (85.2)	51 (92.7)
95% CI	88.6; 100.0	86.4; 94.6	67.5; 94.1	82.7; 97.1
GMTs				
Geometric mean (SD)	66.49 (2.108)	49.45 (3.045)	32.15 (3.172)	51.13 (3.521)
95% CI	50.33; 87.84	42.08; 58.12	20.37; 50.76	36.38; 71.86

Assessor's comments:
As already observed in the Booster groups the GMTs declined in all age groups considerably between Day 56 and month 7. A slight GMT decline was observed between month 7 and month 12 in all age-groups. The immune response persisted in all age groups until 12 months after the first vaccination of Ixiaro. In both middle age groups the antibody persistence was generally lower compared to the youngest and oldest age groups. Overall the results of antibody persistence in all age groups were comparable between the Booster-group and Non-Booster-group till month 12 after the first vaccination.

Influence of Pre-existing JEV Antibodies

Table 11.5 Seroconversion and Raw Geometric Mean Titers by Dose Group, Stratified by Pre-booster JEV Immunity, Intent-to-treat Population

	IC51 0.25 mL N=81		IC51 0.5 mL N=67	
	Seropositive pre-vaccination	**Seronegative pre-vaccination**	**Seropositive pre-vaccination**	**Seronegative pre-vaccination**
Visit 2 (Month 12), Pre-Booster	**N=79**	**N=2**	**N=60**	**N=7**
Seroconversion				
n (%)	79 (100.0)	0	60 (100.0)	0
95% CI	95.4; 100.0		94.0; 100.0	
GMTs				
Geometric mean (SD)	71.85 (2.496)	5.00 (1.000)	51.56 (2.583)	5.00 (1.000)
95% CI	58.54; 88.18	5.00; 5.00	40.35; 65.88	5.00; 5.00
Visit 2a (Month 13), Post-Booster	**N=79**	**N=2**	**N=60**	**N=7**
Seroconversion				
n (%)	79 (100.0)	2 (100.0)	60 (100.0)	7 (100.0)
95% CI	95.4; 100.0	34.2; 100.0	94.0; 100.0	64.6; 100.0
GMTs				
Geometric mean (SD)	3106.10 (3.104)	224.01 (2.183)	1483.72 (3.904)	671.93 (2.087)
95% CI	2410.01; 4003.23	0.20; 248709.35	1043.64; 2109.39	340.31; 1326.71
GMT ratio	13.87		2.21	
95% CI for GMT ratio	2.77; 69.30		0.77; 6.31	

Abbreviations: CI, confidence interval; GMTs, geometric mean titers; JEV, Japanese encephalitis virus; N, number of subjects with data; n, number of subjects; $PRNT_{50}$, serum dilution giving 50% reduction in plaques in a plaque reduction neutralization test, SD, standard deviation.

NOTE 1: Seroconversion was defined as a $PRNT_{50}$ titer $\geq$ 1:10. Geometric mean titers and 95% CIs were calculated by taking the anti-logs of the means and 95% CI of the log transformed titers at each visit. The 95% CIs for percentages were calculated according to the methods of Altman. Percentages are based on the number of subjects in the Intent-to-treat Population with pre-vaccination JEV status defined and non-missing titers at Visit 0 and current visit (N).

NOTE 2: Seropositive pre-vaccination is defined as subjects seropositive pre-booster vaccination for the Booster Group and pre-IC51-323 vaccination (Primary Series) for the Non-Booster Group. Seronegative pre-vaccination is defined in the same way.

NOTE 3: Treatment and dose groups are based on the group randomized to, and dose received in, the IC51-325 study.

NOTE 4: The minimum dilution factor was 10, values of < 10 have been replaced with 5 in this table.

Source: Section 14, Table 14.2.1.3 and Table 14.2.2.5.

Assessor's discussion on immunogenicity

12 months after the primary vaccination series with Ixiaro all age groups showed sustained antibody persistence. GMTs remained slightly higher in the younger age groups who received either 0.25 mL compared to the older age groups who received 0.5 mL. All subjects in the Booster group were boosterable and achieved protective titers of antibodies one month after vaccination with either 0.25 mL or 0.5 mL of Ixiaro. Most subjects had at least a 4-fold titer increase one month after the booster dose in all pediatric age groups. Antibody titers declined considerably between day 56 and month 7 and stayed more or less stable until month 12 after the primary vaccination series. Higher GMTs were observed in younger children who were aged less than 1 year at priming compared to the older pediatric age groups.

II. RAPPORTEUR'S OVERALL CONCLUSION AND FURTHER ACTION IF REQUIRED

The ongoing study was well conducted, with all randomized participants being vaccinated in the booster group and analyzed for safety and immunogenicity outcomes. The dropout rate was low.

The vaccine proved to be safe and well tolerated by subjects aged 9 months to 18 years for the booster dose with either 0.25 mL or 0.5 mL depending on the age of the subjects . Analysis of frequency of AEs was performed according to 3 age Strata (≥ 9 months to < 3 years old subjects received 0.25 mL as a Booster dose whereas subjects aged ≥ 3 years to < 12 years received 0.5 mL).
A lower frequency of solicited local and systemic events was reported in the youngest age group (15 %) compared to subjects aged ≥ 3 years to < 12 years (26.3 %). The highest frequency (34.5 %) of solicited local and systemic events was reported from the adolescents aged ≥ 12 years to < 18 years.
Contrary to that the frequency of reported unsolicited AE showed no age dependency for the solicited AEs. Overall the unsolicited AEs after the booster dose were reported by 20.3 % of subjects. The majority of subjects reported infections and infestations, which were frequently reported being upper respiratory tract infections and nasopharyngitis. Overall the rate of adverse events was lower after the given Booster-dose compared to the primary vaccinations.
All three reported SAEs were considered as unrelated and all three SAEs are considered resolved. No deaths were reported. No new safety signals were seen.

Antibody persistence up to 12 month after the first vaccination was still high with lower antibody titers in the middle aged children compared to the youngest and oldest age groups.
The immune response to the booster dose given 12 months after the first vaccination of Ixiaro showed high antibody titers and seroconversion rate of 100 % in all age groups and subjects of both dose groups. Ten-fold increases in post-booster versus pre-booster titers were observed in 86.4 % of subjects who received a 0.25 mL dose versus 77.6 % in subjects who received a 0.5 mL dose. GMTs were two fold higher (2910.84) in the 0.25 mL group compared to the 0.5 mL group (1365.87) [Table 13]. The magnitude of the immune responses in the older age group was generally lower compared to the younger age groups.

Nevertheless this study was designed to investigate the neccessity and time-frame of a booster-dose of Ixiaro after primary immunisation in the pediatric population. The immunogenicity results of study IC51-325 must be interpreted with caution. In this study the immunogenicity of Ixiaro has been investigated in children and adolescents from the Philippines, where natural exposure to JEV and other flaviviruses is very common. Baseline seropositivity for JEV and DENV was found in a high proportion of subjects in the parent study IC51-323 and a natural boosting by JEV infection in some individuals can also not be excluded and might have biased the results.

Ixiaro is approved in the EU for children older than 2 months as a traveller's vaccine. Natural boosting of JEV usually does not occur in Europe.

The design of this Booster study IC51-325 is in compliance with the latest version of the paediatric investigation plan (PIP).

Overall these data of safety and immunogenicity of a booster dose of Ixiaro generated in a pediatric population should be implemented in the SmPC and PIL after all results of the ongoing study will be available.

☒ PAM is fulfilled -