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Priority Review	No
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Supervisory Concurrence	Tsai-Lien Lin, Ph.D., Acting Branch Chief, VEB
Applicant	Valneva Austria GmbH
Established Name	IC51 (IXIARO)
Trade Name	IXIARO®
Pharmacologic Class	Vaccine
Formulation(s), Dose and Route including Adjuvants, etc	IXIARO, Japanese Encephalitis Vaccine, Inactivated, Adsorbed is a sterile suspension for intramuscular injection. Each 0.5 mL dose of vaccine contains 6 antigen units of purified, inactivated JEV and approximately 250 mcg of aluminum hydroxide.
Dosing Regimen	Single booster dose (either 0.25 mL or 0.5 mL) to be administered, 12 months after first IC51 vaccination.
Indication(s) and Intended Population(s)	Japanese Encephalitis Vaccine. Population for pediatric boosting with age ≥14 months to <18 years.

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STATISTICAL REVIEW AND EVALUATION
BLA STN 125280/235

1. EXECUTIVE SUMMARY

1.1 Brief Overview of Studies and Results

The IC51 vaccine (IXIARO®) was licensed in the U.S. in March 2009 for active immunization against Japanese encephalitis virus (JEV) for adults. After licensure, the pediatric development of the vaccine was accomplished, wherein IC51-323 (N=1869) was a phase 3 study in children from 2 months to 18 years of age (pediatric population) in JEV endemic regions. In the current submission, study IC51-325 is an addendum as a follow-up of 300 children who were part of the immunogenicity subset in the parent study IC51-323. Study IC51-325 examined long-term immunogenicity and safety of a single booster dose administered following primary vaccinations with IC51 (Figure 1). The 300 children were randomized into the booster and non-booster groups with equal allocation (1:1).

All of the boosted subjects retained sero-protective titers for two years since booster. In the non-booster group, the seroprotection rate, which was 100% at 1 month post primary-series, reduced to ≈90% at pre-booster time (i.e., 12 months after primary vaccination) and continued at that level with concomitant values of GMT ranging from 45-59 throughout the following 2 years (ref. Table 2).

The long term immunity for 3 years following primary vaccination was evaluated in non-endemic area children as well. Based on a small cohort of 23 children aged 3-18 years in study IC51-324, followed up for 3 years from the last dose of primary series, the seroprotection rates and GMTs, respectively, also reduced to 89.5%-91.3% and 47.8-75.4, between Month 12 and Month 36. Study IC51-324 (designed according to the EMA note for guidance) was a long term follow-up of 23 children receiving IC51 in a previous phase-3 study IC51-322 conducted in the United States, Europe and Australia as non-endemic region.

1.2 Reviewer's Main Conclusions

The study results supported that a booster of IC51 given at 12 months after primary vaccination is immunogenic and well tolerated, with 100% of subjects retaining protective titers after two years since booster. In the non-booster group, the seroprotection rate declined to about 90% pre-booster and continued at that level for another two years. Similar trend was observed from children in the non-endemic region as well.

1.3 Reviewer's Recommendations

From the study, no long term safety concern was discerned, but any final considerations about safety are deferred to medical decision making. Also, given the results of the booster and non-booster groups, recommendation for booster at 12 months post primary series is a clinical decision involving clinical risk and benefit considerations.

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

2.1 Review Strategy

For this BLA resubmission, the reviewer provided statistical review of immunogenicity and safety data.

2.2 BLA Documents That Serve as the Basis for the Statistical Review

This statistical review was based on the following documents:

STN 125280/235 submitted 16 June 2017.

Module 1: Administrative information and labeling.
Module 2: Clinical Overview (Addendum 04).
Module 5: 5.3.5.1. Clinical Study Reports (Final Version 2.0) for IC51-325 (Addendum: Month 36), with datasets and SAS programs.
5.3.5.2. Clinical Study Reports (Final Version 1.0) for IC51-324, with data sets and SAS programs.

3. STUDY IC51-325

3.1 Title

"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. Open-label, Randomized, Phase 3 Study."

3.2 Primary Objective

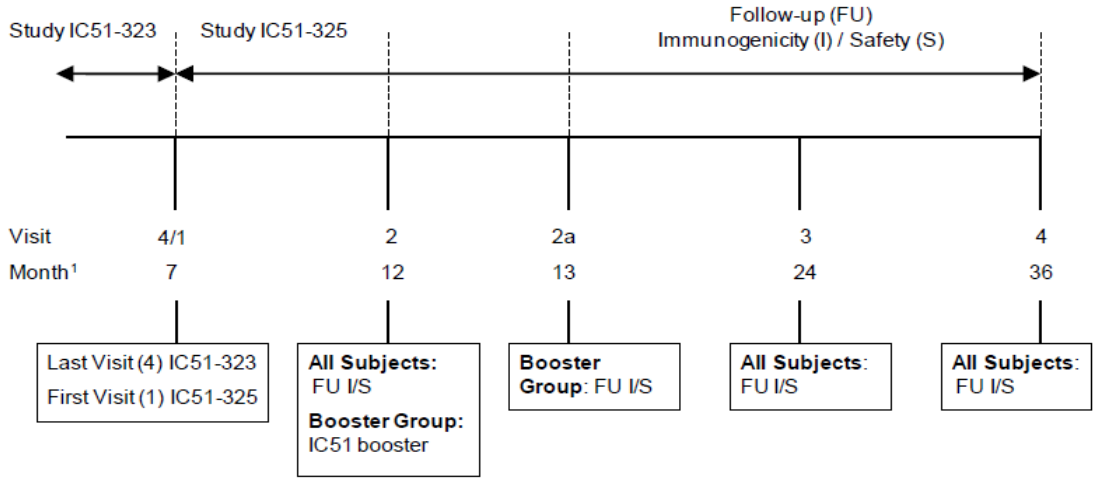
To assess the immune response (GMTs and SCRs) 28 days after one single booster vaccination with the purified inactivated JE vaccine IC51 administered at 12 months after the primary immunization in a pediatric population from JEV-endemic regions.

3.3 Design

The study was an open-label randomized phase 3 follow-up to assess the long-term immunogenicity and safety of IC51 vaccine administered in a parent study IC51-323 in 2 doses, 28 days apart, in pediatric population of a JEV-endemic region (Philippines) (ref. Statistical Review Memo, BLA STN 125280/125, dated May 3, 2013, for greater details about IC51-323). Three hundred children from study IC51-323, stratified by age, who received two IC51 vaccinations and were part of the study's immunogenicity subset, consenting for long-term follow-up with or without opting for boosting, were randomized (1:1) into the non-booster and booster groups. Subjects who were in the dose-finding run-in phase in IC51-323 were included only when they had received the confirmed dose of 0.5 mL. The IC51 dose for boosting depended on age at which the booster dose was administered. Subjects aged ≥ 14 months to < 3 years at visit 2 in IC51-325 received 0.25 mL dose and subjects with age ≥ 3 to < 18 years at that

visit received 0.50 mL dose. Please refer to Figure 1 and Table 1 for further details. Children in the non-booster group (N=150) were followed up for three years after primary vaccination, and those who received booster (N=150) after 1 year of primary vaccination were followed up for additional two years.

Figure 1



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

Source: CSR addendum Month 36 (IC51-325) page 28 of 161

Table 1 Age stratification

Age at First IC51 Dose (Visit 1 in Study IC51-323)	**Age at Enrolment (Visit 1 in Study IC51-325)**	**Age at Booster Dose (Visit 2 in Study IC51-325)**	**Planned Number of Subjects in Study IC51-325**		
			Booster Group	**Non-booster Group**	**Overall**
All Age Groups			150	150	300
≥ 2 months to < 1 year	≥ 9 months to < 1 year and 7 months	≥ 14 months to < 2 years	15	15	30
≥ 1 year to < 2 years	≥ 1 year and 7 months to < 2 years and 7 months	≥ 2 years to < 3 years	65	65	130
≥ 2 years to < 11 years	≥ 2 years and 7 months to < 11 years and 7 months	≥ 3 years to < 12 years	40	40	80
≥ 11 years to < 17 years	≥ 11 years and 7 months to < 17 years and 7 months	≥ 12 years to < 18 years	30	30	60

Source: CSR addendum Month 36 (IC51-325) page 34 of 161.

3.4 Results

3.4.1 Immunogenicity

Table 2 below provides a summary of immunogenicity (seroprotection and GMT) results at different time points after the primary vaccinations, for subjects with and without booster dose. Among the randomized subjects, immunogenicity results between the booster and non-booster groups were largely comparable as of Month 12, pre-booster.

In the month following booster, seroconversion rate rose to 100% for both booster doses and remained at that level for two years since booster. The GMT with 0.25 mL dose rose from the pre-booster level of 53 to 2911 in the month post-booster, declined to 572 in the following 12 month, and declined further to 427 in another 12 months. The GMT with booster dose 0.50 mL seemed lower compared to 0.25 mL, in its display of rise and decline over the same period. In the non-booster group the seroprotection continued at about 90% at Month 36 compared to 100% in the booster group (Table 2).

When considered by age groups, the seroconversion of 100% following the booster was seen in all age groups, in each of the subsequent two years (Month 24, Month 36) (applicant's Table referenced below). The GMTs, however, displayed higher values in the younger age group. Subjects who were 2 months to <1 year old and received booster dose 0.25 mL had post-booster GMT (95% CI) of 4076 (2403, 6913) at Month 13, which reduced to 622 (271, 1432) at Month 24 and to 535 (248, 1152) at Month 36. The GMTs appeared lowest for subjects of 12 years to <17 years old. Despite having higher booster dose of 0.50 mL, these older subjects had GMTs 890 (537, 1474) at Month 13, which reduced to 231 (135, 396) at month 24 and to 231 (143, 374) at Month 36 (CSR addendum Month 36, IC51-325, Table 11.4, page 83-84 of 161).

The increased levels of immunogenicity in the younger age group compared to the older age groups was seen in the non-booster group as well. The subjects who were 2 months to < 1 year old, had seroprotection rate and GMT(95% CI), respectively, as [100% and 66(50,88)] at Month 12 pre-booster, [100%, 92(50,167)] at Month 24, and [100%, 81(57,116)] at Month 36. For subjects of 12 years to 17 years old, these respective values were [93%, 51(36,72)] at Month 12 pre-booster, [85%, 39(21,71)] at Month 24, and [88%, 45(27,76)] at Month 36 (CSR addendum Month 36, IC51-325, Table 11.9, pages 98-99 of 161).

Table 2. Seroconversion* and Geometric Mean Titers after Primary Immunization with IC51, by Treatment Group, Intent-to-treat Population

	Booster group N=150	**Non-booster group N=150**
Visit 1 (Day 0) of Study IC51-323, Pre-Primary Series	**N=150**	**N=149**
Seroconversion: n (%) (95% CI)	19 (12.7) (8.3,18.9)	15 (10.1) (6.2, 15.9)
GMT(SD), (95%CI)	6.47 (0.328) (5.73, 7.31)	6.17 (0.355) (5.41, 7.05)
Median (Min, Max)	5.00 (5.0, 328.0)	5.00 (5.0, 2878.0)
Visit 3 (Day 56) of Study		
IC51-323, Post-Primary Series[a]	**N=49[a]**	**N=49[a]**
Seroconversion: n (%)(95% CI)	49 (100.0) (92.7, 100.0)	49 (100) (92.7, 100.0)
GMT(SD)(95% CI)	240.7 (0.44) (179.4, 323.0)	178.4 (0.48) (130.0,244.9)
Median (Min, Max)	209.0 (43.0, 2936.0)	160.0 (20.0, 1326.0)
Visit 1 (Month 7)	**N=150**	**N=150**
Seroconversion: n (%)(95% CI)	134 (89.3) (83.4, 93.3)	129 (86.0) (79.5, 90.7)
GMT(SD)(95% CI)	52.0 (0.54) (42.5, 63.5)	41.8 (0.52) (34.5, 50.8)
Median (Min, Max)	56.00 (5.0, 3882.0)	50.0 (5.0, 4650.0)
Visit 2 (Month 12), Pre-booster	**N=148**	**N=149**
Seroconversion: n (%)(95% CI)	139 (93.9) (88.8, 96.8)	134 (89.9) (84.1, 93.8)
GMT(SD), (95%CI)	53.4 (0.48) (44., 63.8)	45.5 (0.50) (37.8, 54.8)
Median (Min, Max)	55.0 (5.0, 776.0)	48.0 (5.0, 4385.0)

Visit 2a (Month 13), Study IC51-325, Post-booster	**IC51 0.25 mL**	**IC51 0.50 mL**	
	N=81	N=67	-
Seroconversion: n (%) (95% CI)	81(100.0) (95.5, 100.0)	67(100.0) (94.6, 100.0)	-
GMT(SD), 95%CI	2910.8 (0.52) (2235.1, 3791.0)	1365.9 (0.58) (987.6, 1889.0)	-
Median (Min, Max)	3128.0 (129.0, 41226.0)	1363.0 (90.0, 32280.0)	-
Visit 3 (Month 24), Post-booster	**80**	**67**	**N=146**
Seroconversion: n (%) (95% CI)	80(100) (95.4, 100.0)	67 (100) (94.6, 100)	130 (89.0) (82.9, 93.1)
GMT(SD), 95%CI	572.3 (0.65) (409.8, 799.4)	302.1(0.62) (213.3, 428.0)	49.8 (0.54) (40.6, 61.1)
Median (Min, Max)	516.3 (29.0, 32096.0)	268.0 (22.0, 7516.0)	52.5 (5.0, 3139.0)
Visit 4 (Month 36), Post-booster	**N=76**	**N=67**	**N=142**
Seroconversion: n (%) (95% CI)	76 (100.0) (95.2, 100.0)	67(100.0) (94.6, 100.0)	128 (90.1) (84.1, 94.0)
GMT(SD), 95%CI	427.5 (0.59) (313.0, 583.8)	279.6 (0.59) (200.6, 389.9)	59.4 (0.53) (48.4, 72.8)
Median (Min, Max)	384.0 (26.0, 14629.0)	272.0 (17.0, 7373.0)	63.0 (5.0, 2732.0)

Abbreviations: CI, confidence interval; N, number of subjects with data; n, number of subjects; PRNT50, serum dilution giving 50% reduction in plaques in a plaque reduction neutralization test;SD, standard deviation

[a] In Study IC51-323, not all subjects were included in the immunogenicity subgroup.

*NOTE 1: Seroconversion was defined as a PRNT50 titer ≥ 1:10. NOTE 2: 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 SD was based on the log-transformed value. NOTE 3: The minimum dilution factor was 10, values of < 10 have been replaced with 5 in this table.

Source: Adapted from CSR addendum Month 36, IC51-325, Tables 11.8 and 11.2, pages 95-96 and 77-78 of 161.

Conclusion. It appeared that the booster at Month 12 was highly immunogenic and offered 100% seroprotection for the two subsequent years. Also, in non-boosters, those who were 2 months to < 1 year old remained 100% sero-protected for as long as three years (Month 36) since the primary vaccination, in contrast to the older subjects who showed attenuation pre-booster titer and the seroconversion rate declined to 88% at Month 36.

3.4.2 Safety (Long-term)

All AEs reported as not recovered/not resolved at Month 7 (i.e., Visit 4 in Study IC51-323/Visit 1 in this study IC51-325) and all new AEs reported up to Visit 4 (Month 36) were included in the analysis. For the booster group, all AEs reported from after the booster dose at Month 12 up to Month 36 were included in the analysis (CSR addendum Month 36, IC51-325, page 116). These are summarized in Table 3 below by booster and non-booster groups

Table 3. Summary of adverse events in non-booster group (from Month 7 up to Month 36) and booster group (from booster dose up to Month 36), Safety Population

	Non-booster† N=150 n(%) [95%CI]	Booster IC51 0 25 mL‡ N=81 n (%) [95% CI]	Booster IC51 0 5 mL‡ N=67 n (%) [95% CI]	Total (booster doses)‡ N= 150 n (%) [95% CI]
Number of subjs with at least one:				
Solicited[1] AE	-	12 (14 8) [7 9, 24 4]	17 (25 4) [15 5, 37 5]	29 (19 3) [13 3, 26 6]
Unsolicited AE	100 (66 7) [58 5, 74 1]	49 (60 5) [49 0, 71 2]	35 (52 2) [39 7, 64 6]	84 (56 0) [47 7, 64 1]
Unsolicited/solicited AE with				
Seveiry grade 1	85 (56 7) [48 3, 64 7]	35 (43 2) [32 2, 54 7]	34 (50 7) [38 2, 63 2]	69 (46 0) [37 8, 54 3]
Seveiry grade 2	12 (8 0) [4 2, 13 6]	12 (14 8) [7 9, 24 4]	7 (10 4) [4 3, 20 3]	19 (12 7) [7 8, 19 1]
Seveiry grade 3	2 (1 3) [0 2, 4 7]	3 (3 7) [0 8, 10 4]	1 (1 5) [0 0, 8 0]	4 (2 7) [0 7, 6 7]
Seveiry grade 4	1 (0 7) [0 0, 3 7]	0	0	0
SAE	3 (2 0) [0 4, 5 7]	5 (6 2) [2 0, 13 8]	2 (3 0) [0 4, 10 4]	7 (4 7) [1 9, 9 4]
Medically-attended AE	64 (42 7) [34 6, 51 0]	35 (43 2) [32 2, 54 7]	17 (25 4) [15 5, 37 5]	52 (34 7) [27 1, 42 9]
AE that lead to death	0	0	0	0

Source: Adapted from Table 12.2† and Table 12.4‡ (CSR addendum Month 36, IC51-325, pages 117, 120).

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

Non-booster dose group

In the non-booster group, overall, 66.7% of subjects (100/150) reported one or more unsolicited AEs and 42.7% of subjects (64/150) reported one or more medically-attended AEs (Table 3). The AEs, whether solicited or unsolicited, were by and large mild in intensity (grade 1) in the non-booster and booster groups.

The reported unsolicited AEs included several infections and infestations, of which three most frequent were upper respiratory tract infections, gastroenteritis, nasopharyngitis and rhinitis in

ages <3 years (CSR addendum, IC51-325, Tables 12.7 and 12.6, pages 125 and 124). In higher age groups (≥3 years) the infections with dominant presence were nasopharyngitis, urinary tract infection, varicella and rhinitis (CSR addendum, IC51-325, Tables 12.9 and 12.8, pages 127 and 126). Overall, by age groups, the unsolicited AE rates (CSR addendum, IC51-325, Table 12.3, page 118) were: 80% in age ≥2 months to <1 year, 71.7% in age ≥1 year to <3 years, 56.3% in age ≥3 years to <12 years, and 48.1% in age ≥12 years to <17 years. For medically-attended AEs, the rates in these respective age groups were 66.7%, 48.9%, 12.5% and 25.9%. Of the total 3 SAEs reported (Table 3), 1 occurred in age ≥1 year to <3 years and 2 occurred in age ≥12 years to <17 years. The investigator did not consider the SAEs to be related to the study vaccine. Additionally, one subject was reported to have 2 potentially life-threatening (grade 4) SAEs (injury and traumatic pneumothorax) (CSR addendum Month 36, IC51-325, pages 119 and 136).

Booster dose group

From Table 3, in the booster group, overall 56.0% of subjects (84/150) reported unsolicited AEs. These rates were 60.5% and 52.2% in dose groups 0.25 mL and 0.50 mL, respectively. In the applicant's age-wise breakdown (Table referenced below), these AEs had the following rates: 60% in age ≥9 months to <3 years, 59% in age ≥3 years to <12 years and 44.8% in age ≥12 years to <18 years (CSR addendum Month 36, IC51-325, Table 12.5, page 121).

Of the unsolicted AEs, upper respiratory infection, nasopharygitis and bronchitis were most frequent in age ≥9 months to <3 years, and in age ≥3 years to <12 years and ≥12 years to <18 years, upper respiratory track infection, nasopharyngitis/UTI and influenza like illnesses/cough, pyrexia were mostly reported (CSR addendum Month 36, IC51-325, Tables 12.10, 12.11, 12.12, pages 129-134).

For AEs that were medically-attended, overall 34.7% of subjects (52/150) had such AEs. In dose groups 0.25 mL and 0.50 mL, respectively, these AE rates were 43.2% and 25.4%. The rates in the order of age groups as above were 42.5%, 31.6% and 17.2% (CSR addendum Month 36, IC51-325, Table 12.5, page 121).

Seven subjects had SAEs after the booster dose. Two subjects reported SAEs of abscess and dengue fever, and 5 subjects reported SAEs: gastroenteritis, bronchopneumonia and urinary tract infection between Month 13 and Month 36. Except for the AE of abscess, which the investigator considered to be related to the study vaccine, the other AEs were not considered to be related.

Additionally, the study reported no deaths. However, one subject with age ≥3 years to <12 years reported AESI of pruritus 5 days after receiving a booster dose of IC51 0.5 mL. The event was reported as mild in intensity (grade 1) and was considered by investigator to be related to the study vaccine. The event was given no treatment and resolved the following day (CSR addendum Month 36, IC51-325, pages 138).

Conclusion. Overall, from Table 3, the general safety profiles for the booster and non-booster groups did not differ substantively and implied no long-term safety concerns from the booster. The observed AEs, overall, were considered by the applicant to be in line with expectations in

pediatric population in a developing country setting. Any final considerations about safety, however, is deferred to the medical officer.

4. STUDY IC51-324

4.1 Title

"Long Term Immunity and Safety Following Vaccination with the Japanese Encephalitis Vaccine IC51 (IXIARO®, JESPECT®) in a Pediatric Population in Non-endemic Countries. Uncontrolled, Phase 3 Follow-Up Study."

4.2 Primary Objective

To assess long-term immunity following vaccination with purified inactivated JE vaccine IC51 in terms of GMTs and rate of subjects with a PRNT50 ≥ 1:10 in a pediatric population from regions where JE is not endemic.

4.3 Design

The non-endemic countries stated were the United States, Europe and Australia. As with study IC51-325, study IC51-324 also was an open-label, long-term immunogenicity and safety follow-up of subjects who were a part of the immunogenicity subset in a parent study IC51-322 where pediatric subjects of age ≥2 months to <18 years received 2 injections of IC51 at 28 days interval with primary endpoint taken as safety assessed at 6 months following the last dose of primary vaccination. Study IC51-324 assessed 23 children and had follow-up visits at 12, 24, and 36 months after the first vaccination in the parent study IC51-322. Thus, the study design for IC51-324 was the same as that for IC51-325 (Figure 1) except that the boosting was not a part in IC51-324/IC51-322. The 23 subjects comprised the safety/ITT population, and had the following age (at first IC51 dose) distribution: 1 subject with age ≥2 months to <3 years, 3 subjects with age ≥3 years to <12 years, and 19 subjects with age ≥12 years to <18 years. Small numbers in younger age groups presents limitation in age group comparisons. Six of these subjects were from Australia, 7 from Europe (Germany) and 10 from the United States of America.

4.4 Results

4.4.1 Immunogenicity

For immunogenicity analysis based on the ITT population, the study reported that the seroprotection rates were 100% (23/23), 89.5% (17/19), 91.3% (21/23) and 89.5% (17/19), respectively, at 56 days, 12, 24 and 36 months after the first vaccination of IC51. At these respective time points, the GMT (95% CI)s were 384 (248, 595), 48 (29, 80), 75 (46, 124), and 61(35, 106) (Clinical Overview, page 8-9 of 17, and Final CSR, IC51-324,Tables 11.5-11.6, pages 41-43).

Overall, the small pediatric cohort from JEV non-endemic region reflected a decrease in antibody titers from around 12 months of primary series, and the seroprotection rate that reduced

to about 89% at 12 months continued at that level up to 36 months after the first injection. This pattern of long term immunity for 3 years following primary vaccination was observed as well from endemic population. The sharp decline of antibody titers at 12 months suggests a booster at that time point. The decision of boosting is a clinical call with benefit and risk considerations.

Conclusion deferred to section 5 below.

4.4.2. Safety

All AEs reported as not recovered/not resolved at Month 7 (i.e., Visit 4 in Study IC51-322/Visit 1 in study IC51-324) and all new AEs reported up to Visit 4 (Month 36) were included in the analysis (CSR IC51-324, page 47). The reporting period for AEs is the same as that for the non-booster group in IC51-325.

Of the total 23 subjects, 8 (34.8%) subjects reported AEs between Month 7 and Month 36. The AEs included 2 SAEs, tonsillitis (moderate with severity grade 2) and severe staphylococcal infection, and a severe (grade 3) AE of radius fracture. Also, seven subjects reported medically-attended AEs. None of these AEs were considered by the investigator to be related to the study vaccine. No AEs of special interest were predefined and no death was reported.

The AEs as reported from a small pediatric cohort from JEV non-endemic regions suggested no long-term safety concern about the IC51 vaccination for JEV, but is subject to medicalofficer's viewpoint.

Conclusion deferred to section 5 below.

5. OVERALL SUMMARY AND CONCLUSIONS (IC51-325 & IC51-224)

1. Overall, the submission supports that the general safety profiles of the booster and non-booster groups did not differ substantively and implied no long-term safety concerns from the booster. The observed AEs, by and large, were considered by the applicant to be in line with expectations in pediatric population in a developing country setting. In non-endemic subjects as well, where no death was reported and none of the AEs were considered by the study investigator to be related to the study vaccine, no long-term safety concern was discerned. Any decision about safety, however, is deferred to the medical officer.

2. Following the primary vaccination with IC51, the immune responses, in general, attenuated at Month 12 pre-booster. The onset of attenuation preceded, most likely by about 6 months (Table 2).

3. Booster at Month 12 was highly immunogenic. Seroconversion (PRNT50 $\geq$1:10) rate rose to 100% in the month following the booster and remained at that level for two subsequent years,

regardless of booster doses (0.25 mL, 0.50 mL) used. GMTs showed concomitant decline from its post booster peak (Table 2).

4. Among the non-booster subjects, the GMTs had continued decline and the seroconversion rate reduced to about 90% at Month 12 pre-booster in both endemic and non-endemic regions and stayed at that level for the next 24 months, describing a general pattern of long-term immunity from IC51.

5. Younger children of age ≥2 months to <1 year and without booster displayed 100% seroprotection persisting for 3 years since primary series, in contrast to the older subjects without booster whose seroconversion rate reduced to about 90% at Month 12 with GMT declined to 45 in the next 24 months (section 3.4.1). I defer the approval decision to the medical officer, based on clinical risk and benefit considerations.