DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION

BLA STN 125280

DATE: 05/02/2013

BLA/SUPPLEMENT NUMBER: STN 125280/125

PRODUCT NAME: IXIARO® (Japanese Encephalitis Vaccine IC51)

SPONSOR: Intercell AG

INDICATION: Prevention of Japanese Encephalitis in Pediatric Population

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1. EXECUTIVE SUMMARY

1.1 Overview.

The IC51 vaccine (IXIARO®) was licensed in the U.S. in March 2009 for active immunization against Japanese Encephalitis (JE) virus for adults. The current submission is initiated as a basis for pediatric development of the IC51 vaccine, and aims at establishing safety of IC51 in children from 2 months to 18 years of age in JE endemic regions (study IC51-323 and IC51-221), including children of non-endemic regions planning travel to regions where JE is endemic (study IC51-322). The study evaluates as well the vaccine's appropriate dose and immunogenicity among children 3-12 years of age.

The pivotal study (IC51-323) in the pediatric development was based on a total of about 1869 subjects, used Prevnar® and HAVRIX® as active comparators, and had each subject in the study for a duration of approximately 8 months. Each subject in the IC51 treatment group was vaccinated twice with a 28-day interval. Day 56 following the first of two scheduled vaccinations was the time point when safety was measured as the primary endpoint. The IC51 vaccinees had 2 injections by Day 56. In the Prevnar and HAVRIX groups, respectively, each vaccinee received 2 injections or 1 injection by Day 56 from the first injection. HAVRIX's 2nd injection was at Month 7 from the first injection, and as such it did not contribute to safety experience for the Day 56 measurements. Greater details appear in Figure 2.3 and Table 2.3.1.

The study supports that the general safety profile of IC51 through Day 56 was comparable with that of the control, Prevnar, among children aged from 2 months to 1 year. Among children aged 1-18 years, the serious or medically attended AE rates at Day 56 across the study's treatment and control (HAVRIX®) groups were comparable within age subgroups. For the solicited AEs, despite comparable rates for AEs post-dose 1 between treatment groups, significant excess in solicited AE rates through Day 56 was observed in IC51 vaccinees compared to HAVRIX in age subgroups 1-3 years and 3-12 years. This excess is likely explained by the difference between treatment groups in the number of study vaccinations received during the safety follow-up period. Also, both of the IC51 dose groups of 0.25 mL and 0.5 mL had comparable general safety profiles. The majority of AEs were mild, and no death related to the treatment vaccine was reported.

The immunogenicity analyses were the secondary objectives. Based on the study's immunogenicity subgroup, the study supports that the IC51 vaccine in both doses was highly immunogenic and induced protective antibody titers in overwhelming majority of subjects (> 95.0%) particularly at Day 56 following first vaccination. At Month 7, the immunogenicity generally appeared to have attenuated, most notably among the IC51 0.25 mL vaccinees aged 3-12 years, where the seroconversion rate dropped from 95.9% (at Day 56) to 77.1% (at Month 7). Among children aged 3-12 years, the IC51 0.5 mL dose likely induced higher immune response compared to the lower 0.25 mL dose, both at Day 56 and Month 7. This finding along with the comparable safety profiles of these doses support appropriateness of the 0.5 mL dose for further pediatric development.

1.2 Clinical Studies.

This review covers three studies, IC51-323 (N=1869), IC51-221 (N=60) and IC51-322 (N=60), that gathered pediatric data. Study IC51-323, which was the largest one, enrolling 1869 subjects from Philippines,investigated safety as the primary endpoint, and assessed immunogenicity in secondary analyses in a randomized subgroup for immunogenicity. The study used data at Day 56 and Month 7 following first IC51 vaccination.

Study IC51-221 was conducted in a single site in Bangalore, India to primarily explore immunogenicity of two doses: IXIARO adult dose of 0.5 mL and half adult dose, each with 24 subjects. JE is endemic in India.

Study IC51-322 is ongoing in the United States, Europe, and Australia in healthy subjects planning travel to regions where JE is endemic. It has slower than expected recruitment of subjects. As requested by CBER, the applicant provided interim results from 60 subjects out of 100 planned. This study addressed immunogenicity as its primary analysis, as was done in study IC51-221.

1.3 Statistical Methods.

Safety.
The frequencies of any AEs, SAEs, solicited AEs and serious or medically-attended AEs and local and systemic AEs were summarized. The influence of pre-existing JE virus (JEV) antibodies and pre-existing dengue virus (DENV) antibodies on AE was assessed in the logistic regression analysis of AEs. The AE rates were evaluated using exact 95% confidence intervals.

Immunogenicity.
The plaque reduction neutralization test (PRNT) was used to determine the serum dilution giving 50% reduction in virus plaques (PRNT50). The PRNT50 was measured at baseline and at different time points of interest. The seroconversion rate (SCR) was the percentage of subjects with PRNT50 greater than or equal to 1:10 (PRNT-positive subjects). The geometric mean titer (GMT) for PRNT50 and the related 95% confidence interval (CI) were computed by exponentiating, respectively, the mean and the 95% CI limits of the log-transformed PRNT50 values. The SCRs were evaluated using exact 95% confidence intervals.

1.4 Reviewer's Main Conclusions and Recommendations.

Safety.
The primary objective of the submission was to assess safety of the IC51 vaccine through Day 56 following the first vaccination. Overall, the study supports that, among children 2 months to 1 year of age, the general safety profile through Day 56 in the IC51 0.25 mL dose group was comparable with that of the Prevnar group. In children 1-18 years old, serious or medically attended AE rates across the study's treatment groups were comparable within age subgroups.

For solicited AEs, significant excess in rates through Day 56 in the IC51 vaccinees compared to those receiving HAVRIX was observed in the age subgroups of 1-3 years and 3-12 years, despite that the solicited AE rates post-dose 1 did not significantly differ between the treatment groups. This excess is likely explained by the difference between treatment groups in the number of study vaccinations received during the safety follow-up period. Additionally, both of the IC51 dose groups had comparable general safety profiles. The majority of AEs were mild, and no death related to treatment vaccine was reported.

Immunogenicity.

The immunogenicity analyses were the secondary objectives. Based on the study's immunogenicity subset of subjects, the study supports that the IC51 vaccine in both doses of 0.25 mL and 0.5 mL was highly immunogenic, leading to protective antibody titers in the overwhelming majority (> 95.0%) of subjects, particularly at Day 56 after the first vaccination. At Month 7, the geometric mean antibody titers attenuated, but still maintained protective antibody levels (PRNT50 $\geq$ 1:10) in more than three-fourths of subjects. Because of the comparable safety profiles of the two doses and with higher levels of imunogenicity at the higher dose, the study supports appropriateness of the proposed 0.5 mL dose of IC51 for further pediatric development.

2. STUDY IC51-323

2.1 Title of Study. Safety and Immunogenicity of the Japanese Encephalitis Vaccine IC51 (IXIARO®) in a Pediatric Population, Open Label, Randomized, Active Controlled, Phase III Study.

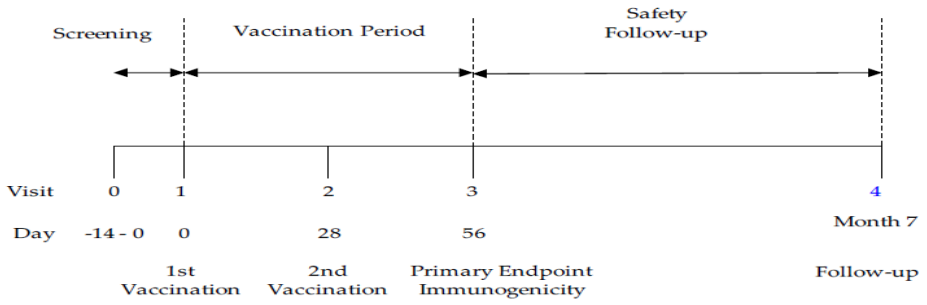
2.2 Primary Objective. To assess safety of IC51 through 56 days following the first of two scheduled doses administered 28 days apart in a pediatric population from endemic regions.

Secondary Objectives.

1. To assess safety of IC51 through 7 months following the first vaccination.
2. To assess immunogenicity of IC51 in terms of geometric mean titers (GMTs) and seroconversion rates (SCRs) at Day 56.
3. To establish the appropriate IC51 dose, 0.25 mL or 0.5 mL, for subjects aged ≥ 3 to < 12 years.
4. To assess age dependent differences in the safety and immunogenicity profile of IC51.
5. To assess differences in the safety and immunogenicity of IC51 in subjects with no baseline immunity and subjects with pre-existing immunity against JEV and dengue virus (DENV).

2.3 Study Design and Methods. A basic scheme of the study design is presented in Figure 2.3 below**.**

Figure 2.3



Source: Interim Study Report, IC-322, 13 Nov 2012, page 21 of 69.

The study was an open label, randomized, active-controlled Phase III study in children aged ≥ 2 months to < 18 years. It was conducted in South East Asia (Philippines and Malaysia) in a planned number of up to 6 sites. JE is endemic in the region. Below are some key features of the study.

1a. The healthy, screened subjects were randomized after informed consent forms were signed. The allocation for randomization was age-dependent. Subjects aged ≥ 2 months to < 1 year were randomized 2:1 to IC51 (0.25 mL dose) or the active control Prevnar® (0.5 mL dose). Subjects aged ≥ 1 year to < 3 years and ≥ 12 to < 18 years were randomized 3:1 to IC51 (0.25 mL dose for < 3 years, 0.5 mL dose for ≥ 12 years), or the active control HAVRIX®720 (0.5 mL dose).

1b. For subjects aged ≥ 3 to < 12 years, a dose-finding run-in phase was performed in parallel recruitment and study conduct for the other age groups. A total of 200 subjects were randomized 1:1 to either the 0.25 mL or the 0.5 mL dose of IC51. The appropriate dose was then determined from the interim analysis based on the Day 56 safety and immunogenicity results. After this dose-finding run-in phase, 300 further subjects in this age group were randomized 2:1 to receive either the appropriate IC51 dose (200 subjects) or HAVRIX (0.5 mL) (100 subjects). The total planned enrollees were 1867. Table 2.3.1 provides further details.

Table 2.3.1: Number of subjects in age and treatment groups, Total N=1867

Treatment group	IC51	Dose	HAVRIX	Dose	Prevnar	Dose
Total # of subjects in different groups	1409 (495)[1]		393		65	
Subjects in age group ≥ 2 months to < 1 year	130 [2] (30) [1]	0.25 mL	-	-	65 [2]	0. 5 mL
Subjects in age group ≥ 1 year to < 3 years	639 (125) [1]	0.25 mL	213	0.5 mL	-	-
Subjects in age group ≥ 3 to <12 years	100 (100)[1,3]	0.25 mL	-	-	-	-
	100 (100)[1,3]	0.5 mL	-	-	-	
	200 [4]	0.25/0.5 mL [4]	100	0.5 mL	-	-
Subjects in age group ≥ 12 years to < 18 years	240 (140)[1]	0.5 mL	80	0.5 mL		

1 Number of subjects in immunogenicity subgroup.

2 at least 30 subjects (IC51) and 15 subjects (Prevnar®) aged ≥ 2 to <6 months.

3 200 children in total / 100 children per dose group will be enrolled from this age group for the dose finding run-in phase.

4 The dose confirmed in the dose finding run-in phase will be administered to additional 200 children in this age group, so that in the end a total of 300 children aged ≥ 3 to < 12 years will have received the appropriate dose.

Source: Adopted from Clinical Study Protocol IC51-323 Final Version 2.0, 22nd Feb 2010, Table 2, page 36/84.

2. Immunogenicity assessment was the secondary analysis. It was planned to be carried out in a subgroup of 495 subjects. During the randomization process, the subjects in the IC51 treatment group were randomly selected for inclusion in the immunogenicity subgroup. The subgroup comprised as follows: 30 subjects aged ≥ 2 months to < 1 year; 125 subjects aged ≥ 1 year to < 3 years; 140 subjects aged ≥ 12 to < 18 years, and 200 subjects aged ≥ 3 to < 12 years who were enrolled during the dose-finding run-in phase. Table 2.3.1 provides details.

3. Study duration per subject was approximately 8 months. Each subject in the IC51 treatment group was vaccinated twice within a period of approximately 28 days. Subjects in the comparator groups were vaccinated with Prevnar or HAVRIX, depending on children's ages (Table 2.3.1), within a period of 7 months. As of Day 56, which is the time point for measuring the primary endpoint for safety, the IC51 and Prevnar vaccinees each had 2 injections and HAVRIX vaccinees had 1 injection contributing to safety experience. The study did not collect safety data after the first 60 minutes of HAVRIX's second vaccination (at Month 7).

4. Subjects (or parent/guardian) were issued diaries to record adverse events (AEs). Safety data were collected throughout the study, while immunogenicity data were collected periodically from the subgroup of 495 subjects.

5. As mentioned earlier, the planned number of subjects for enrollment was 1867. The subjects actually enrolled were 1869, with 1411 included in the IC51 group providing safety data (Table 2.3.2). The applicant considered this safety sample size to be sufficient for the pediatric development program for IC51. The sample size was not based on power considerations but rather that if a certain AE is not observed, the given sample size will provide 95% confidence that the respective AE does not occur with more than a rate of 3/1411 or 0.21%.

Table 2.3.2: Analysis Populations

	IC51 0.25 mL N=871 n (%)	IC51 0.5 mL N=541 n (%)	Prevnar® N=64 n (%)	HAVRIX®720 N=393 N(%)	Total N=1869 n (%)
Safety Population	871 (100.0)	540 (99.8) [a]	64 (100.0)	394 (100.3) [a]	1869 (100.0)
ITT Population	255 (29.3)	241 (44.5)	0	0	496 (26.5)
PP Population	237 (27.2)	232 (42.9)	0	0	469 (25.1)

Abbreviations: ITT, intent-to-treat; N, number of enrolled subjects; PP, per-protocol.
[a] One subject was randomized to IC51 0.5 mL but was vaccinated with HAVRIX 720.
Source: Adapted from Table 11.1, Clinical Study Report, Final v2.0, 13 Nov 2012, page 82/221

6. Analysis Populations: *Safety Population* included all subjects who entered the study and received at least 1 vaccination. It comprised all 1869 randomized subjects.

Intent-to-treat Population included all subjects randomized into the immunogenicity subgroup who received at least 1 vaccination of IC51. The ITT Population comprised 496 subjects. Subjects were analyzed according to the treatment group to which they were randomized, rather than by the actual vaccine they received.

Per-protocol Population included all subjects in the ITT Population unless they were considered to have a major protocol violation/deviation.

A total of 27 subjects from the ITT Population were excluded from the PP Population. All were excluded because of major protocol violations/deviations, where missing PRNT samples or values were most common. The PP Population comprised 469 subjects.

7. Statistics based on Primary and Secondary endpoints: The proportion of subjects experiencing SAEs and medically-attended AEs through Day 56 following the first vaccination was the study's primary endpoint statistic, with main secondary ones being (1) JEV neutralizing antibody GMTs and seroconversion rates (percentage of subjects with neutralizing antibody titer $\geq$ 1:10) at Day 56 and at Month 7 following the first vaccination, and proportion of subjects experiencing (2) SAEs and medically-attended AEs through Month 7 following the first vaccination, (3) solicited local and systemic AEs assessed for 7 consecutive days after vaccination (except for Month 7) and (4) unsolicited AEs through 56 days and 7 months following the first vaccination.

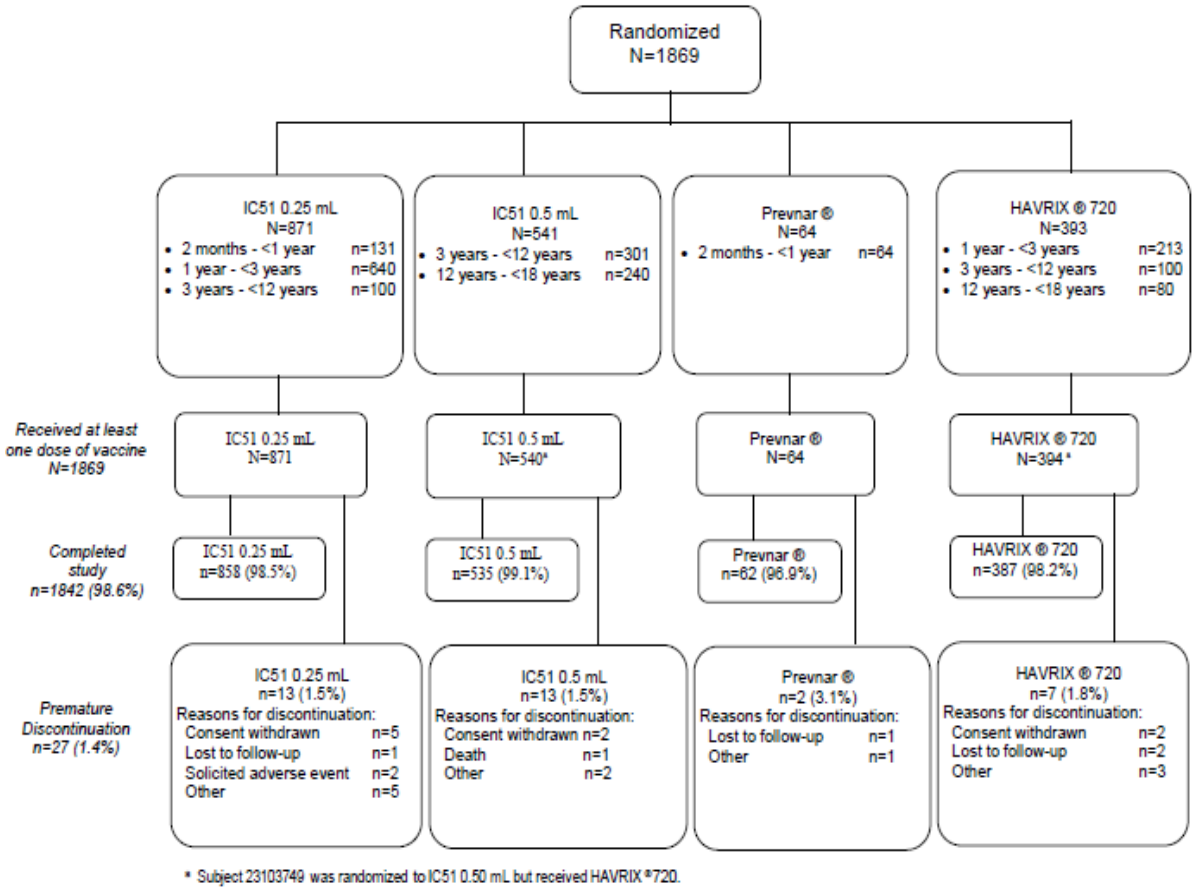
For AEs that were non-quantifiable, a grading-scale was used, such as grade 1 (mild, i.e., symptoms causing no or minimal interference with social and functional activities), grade 2 (moderate), grade 3 (severe), and grade 4 (potentially-life threatening), to describe the AE status.

2.4 Results.

2.4.1 Disposition of Subjects.

All 1869 subjects who were randomized received at least 1 dose of study vaccine. Of these, 871 subjects were in the IC51 0.25 mL group; 540 subjects were in the IC51 0.5 mL group; 64 subjects were in the Prevnar® group; and 394 subjects were in the HAVRIX®720 group (Figure 2.4.1). Also, 195 subjects were administered the study vaccines in the ≥ 2 months to < 1 year age group. The number of vaccinees were 853 in the 1-3 years age group, 501 in the 3-12 years age group, and 320 in the 12-18 years age group. In the age intervals the upper ends were not inclusive.

Figure 2.4.1



Source: Adapted from Clinical Study Report, Final v2.0, 13 Nov 2012, page 70/221

The proportion of subjects completing the study was very high. In the individual study groups, the proportions ranged from 96.9% in the Prevnar group to as high as 99.1% in the IC51 0.5 mL group. A total of 27 subjects (1.4%) prematurely discontinued. These cases and the reasons for discontinuation are also shown in Figure 2.4.1 (bottom panel).

2.4.2 Demographic Characterisitcs. Table 2.4.2 provides the general demographic characteristics of study subjects. The subjects were Asian and had mostly similar proportions of males and females across the treatment groups. However, age was a determining factor for

subject's treatment group. This made the observed differences between groups in terms of weight, height and body mass index (BMI) to be expected.

Table 2.4.2: Demographic Data, Safety Population

	IC51 0.25 mL N=871	IC51 0.5 mL N=540	Prevnar® N=64	HAVRIX®720 N=394	Total N=1869
Age at Visit 1 (years)					
n	871	540	64	394	1869
Mean (SD)	2.41 (2.164)	10.64 (4.099)	0.67 (0.215)	5.98 (5.164)	5.48 (5.056)
Median	1.92	10.90	0.67	2.86	2.68
Min, Max	0.2, 11.9	3.1, 17.8	0.2, 1.0	1.0, 17.9	0.2, 17.9
Sex (n, %)					
Male	422 (48.5)	291 (53.9)	34 (53.1)	197 (50.0)	944 (50.5)
Female	449 (51.5)	249 (46.1)	30 (46.9)	197 (50.0)	925 (49.5)
Race (n, %)					
Asian	871 (100.0)	540 (100.0)	64 (100.0)	394 (100.0)	1869 (100.0)
Caucasian	0	0	0	0	0
Other	0	0	0	0	0
Weight (kg)					
n	871	538	64	394	1867
Mean (SD)	11.29 (5.308)	31.24 (14.991)	7.58 (1.261)	19.87 (13.925)	18.72 (13.935)
Median	10.00	28.00	7.60	12.85	12.00
Min, Max	4.8, 55.0	9.3, 91.0	4.5, 11.0	6.0, 94.0	4.5, 94.0
Height (cm)					
n	869	538	64	394	1865
Mean (SD)	82.79 (15.948)	132.14 (22.621)	66.81 (4.970)	104.53 (29.423)	101.07 (30.439)
Median	80.00	133.00	66.75	90.00	88.00
Min, Max	19.7, 155.0	77.0, 179.0	54.5, 79.0	67.0, 172.0	19.7, 179.0
BMI (kg/m^2)					
n	869	538	64	394	1865
Mean (SD)	16.24 (6.827)	16.76 (3.358)	17.03 (2.665)	16.34 (2.838)	16.44 (5.191)
Median	15.80	16.00	16.60	16.00	15.90
Min, Max	9.2, 206.1	8.0, 35.5	10.5, 25.5	7.1, 34.8	7.1, 206.1

Abbreviations: BMI, body mass index; N, number of subjects in the Safety Population; n, number of subjects with data; SD, standard deviation. Source: Reviewer's calculations based on applicant's data, study IC51-323.

2.4.3 Baseline JEV and DENV Status. Table 2.4.3 provides this information in some detail. A total of 293 (15.7%) subjects had pre-existing JEV antibody titer ≥ 1:10, which is seropositivity at baseline. This proportion seropositive at baseline was 4.5% in the IC51 0.25 mL group, 31.3% in the IC51 0.5 mL group, 9.4% in the Prevnar group, and 20.1% in the HAVRIX group. With regard to the DENV pre-existing antibodies, the overall proportion of subjects seropositive at baseline was 37.4%, while in the individual study groups, these proportions, respectively, were 17.7%, 67.4%, 29.7%, and 41.1%. The current descriptive analyses do not explore the differences in baseline seropositive (JEV and DENV) proportions between individual study groups, but the groups had underlying age differences.

Table 2.4.3: Baseline JEV and DENV Serological Data, overall and by age Group, Safety Population

	IC51 0.25 ml N=871 n (%)	IC51 0.5 ml N=540 N (%)	Prevner N=64 n (%)	HAVRIX 720 N=394 n (%)	Total N=1869 n (%)
Entire study population ‡					
Pre-existing JEV immunity					
seropositive	39 (4.5)	169 (31.3)	6 (9.4)	79 (20.1)	293 (15.7)
seronegative	828 (95.1)	371 (68.7)	58 (90.6)	313 (79.4)	1570 (84.0)
not accessable	4 (0.5)	0	0	2 (0.5)	6 (0.3)
Pre-existing DENV antibodies					
seropositive	154 (17.7)	364 (67.4)	19 (29.7)	162 (41.1)	699 (37.4)
seronegative	699 (80.3)	166 (30.7)	43 (67.2)	221 (56.1)	1129 (60.4)
not accessable	10 (1.1)	7 (1.3)	1 (1.6)	7 (1.8)	25 (1.3)
missing	8 (0.9)	3 (0.6)	1 (1.6)	4 (1.0)	16 (0.9)
Age group 2m to < 1 yr ‡	N=131		N=64		N=195
Pre-existing JEV immunity					
seropositive	8 (6.1)		6 (9.4)		14 (7.2)
seronegative	123 (93.9)		58 (90.6)		181 (92.8)
not accessable	0		0		0
Pre-existing DENV antibodies					
seropositive	25 (19.1)		19 (29.7)		44 (22.6)
seronegative	100 (76.3)		43 (67.2)		143 (73.3)
not accessable	4 (3.1)		1 (1.6)		5 (2.6)
missing	2 (1.5)		1 (1.6)		3 (1.5)
Age group 1-18 yrs †	N=740	N=540		N=394	N=1674
Pre-existing JEV immunity					
seropositive	31 (4.2)	169 (31.3)		79 (20.0)	279 (16.7)
seronegative	705 (95.3)	371 (68.7)		313 (79.4)	1389 (83.0)
not accessable	4 (0.5)	0		2 (0.5)	6 (0.3)
Pre-existing DENV antibodies					
seropositive	129 (17.4)	364 (67.4)		162 (41.1)	655 (39.1)
seronegative	599 (80.9)	166 (30.7)		221 (56.1)	986 (58.9)
not accessable	6 (0.8)	7 (1.3)		7 (1.8)	20 (1.2)
missing	6 (0.8)	3 (0.6)		4 (1.0)	13 (0.8)

‡ Adapted from Table 10.4, Clinical Study Report, Final v2.0, 13 Nov 2012, page 77/221. † Reviewer's calculations based on applicant's data, study IC51-323.

2.4.4 Safety Through Day 56.

2.4.4.1 Solicited AE. A summary of AEs reported through Day 56 is provided in Table 2.4.4.1 for subjects from ≥2 months to <1 year of age, and in Table 2.4.4.2 for those from ≥1 year to < 18 years of age. No death was reported in either of the two age groups during follow-up.

Table 2.4.4.1 Summary of Adverse Events through Day 56 (Visit 3) Reported for Subjects Aged ≥ 2 months to < 1 year, Safety Population

	IC51 0.25 mL N=131 n(%) [95% CI]	Prevner N=64 n(%) [95% CI]	Total N=195 n(%) [95% CI]
Number of subjects with AEs≥1:			
Solicited or unsolicited	110 (84.0) [76.5,89.8]	56 (87.5) [76.9, 94.5]	166 (85.1) [79.3, 89.8]
Solicited	76 (58.2) [49.1, 66.6]	38 (59.4) [46.4, 71.5]	114 (58.5) [51.2, 65.5]
Unsolicited	95 (72.5) [64.0, 80.0]	42 (65.6) [52.7, 77.0]	137 (70.3) [63.3, 76.6]
Unsolicited AE that was:			
probably related	5 (3.8) [1.3, 8.7]	0 (0) [0, 5.6]	5 (2.3) [0.8, 5.9]
possibly related	5 (3.8) [1.3, 8.7]	2 (3.1) [0.4, 10.8]	7 (3.6) [1.5, 7.3]
Solicited/unsolcited AE with severity grade of			
Grade 1	68 (51.9) [43.0, 60.7]	41 (64.1) [51.1, 75.7]	109 (55.9) [48.6, 63.0]
Grade 2	35 (26.7) [19.4, 35.2]	11 (17.2) [8.9, 28.7]	46 (23.7) [17.8, 30.2]
Grade 3	6 (4.6) [1.7, 9.7]	4 (6.3) [1.7, 15.2]	10 (5.1) [2.5, 9.2]
Grade 4	1 (0.8) [0.0, 4.2]	0 (0) [0.0, 5.6]	1 (0.5) [0.0, 2.8]
SAE	0 (0.0) [0.0, 2.8]	1 (1.6) [0.0, 8.4]	1 (0.5) [0.0, 2.8]
Related SAE	0 (0.0) [0.0, 2.8]	0 (0.0) [0.0, 5.6]	0 (0.0) [0.0, 1.9]
Serious or medically attended AE	50 (38.2) [29.8, 47.1]	27 (42.2) [29.9, 55.2]	77 (39.5) [32.6, 46.7]
Medically-attended AE	50 (38.2) [29.8, 47.1]	27 (42.2) [29.9, 55.2]	77 (39.5) [32.6, 46.7]
Related Medically-attended AE	3 (2.3) [0.5, 6.5]	2 (3.1) [0.4, 10.8]	5 (2.6) [0.8, 5.9]
Unsolicited AE of special interest	6 (4.6) [1.7, 9.7]	4 (6.3) [1.7, 15.2]	10 (5.1) [2.5, 9.2]
Related Unsolicited AE of special interest	0 (0.0) [0.0, 2.8]	0 (0.0) [0.0, 5.6]	0 (0.0) [0.0, 1.9]
AE leading to discontinuation	0 (0.0) [0.0, 2.8]	0 (0.0) [0.0, 5.6]	0 (0.0) [0.0, 1.9]
AE leading to death	0 (0.0) [0.0, 2.8]	0 (0.0) [0.0, 5.6]	0 (0.0) [0.0, 1.9]

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in the Safety Population; n, number of subjects; SAE, serious adverse event. NOTE 1: Only AEs with a causality of possibly or probably related were considered related to the vaccine. NOTE 2: Percentages are based on the number of subjects in the Safety Population. NOTE 3: P-value (where applicable and when numbers were sufficient) is from a Fishers exact test comparing the number of subjects with the event across the treatment groups. NOTE 4: CI is an exact confidence interval for a percentage. Source: Adapted from Table 12.1, Clinical Study Report, Final v2.0, 13 Nov 2012, page 103/221

Table 2.4.4.2: Summary of Adverse Events Through Day 56 (Visit 3) Reported for Subjects Aged ≥ 1 Year to < 18 Years, Safety Population

	IC51 0.25 mL N=740 n (%) [95% CI]	IC51 0.5 mL N=540 n (%) [95% CI]	HAVRIX®720 N=394 n (%) [95% CI]	p-value	IC51 Total N=1280 n (%) [95% CI]	Total N=1674 n (%) [95% CI]
Number of subjects with at least one:						
Solicited or unsolicited AE	530 (71.6) [68.2, 74.8]	264 (48.9) [44.6, 53.2]	235 (59.6) [54.6, 64.5]	<0.001	794 (62.0) [59.3, 64.7]	1029 (61.5) [59.1, 63.8]
Solicited AE	339 (45.8) [42.2, 49.5]	183 (33.9) [29.9, 38.1]	116 (29.4) [25.0, 34.2]	<0.001	522 (40.8) [38.1, 43.5]	638 (38.1) [35.8, 40.5]
Unsolicited AE	436 (58.9) [55.3, 62.5]	159 (29.4) [25.6, 33.5]	183 (46.4) [41.4, 51.5]	<0.001	595 (46.5) [43.7, 49.3]	778 (46.5) [44.1, 48.9]
Unsolicited AE that was:						
Probably related	9 (1.2) [0.6, 2.3]	1 (0.2) [0.0, 1.0]	5 (1.3) [0.4, 2.9]	0.079	10 (0.8) [0.4, 1.4]	15 (0.9) [0.5, 1.5]
Possibly related	34 (4.6) [3.2, 6.4]	6 (1.1) [0.4, 2.4]	10 (2.5) [1.2, 4.6]	<0.001	40 (3.1) [2.2, 4.2]	50 (3.0) [2.2, 3.9]
Solicited or unsolicited AE with severity grade of:						
Grade 1	378 (51.1) [47.4, 54.7]	221 (40.9) [36.7, 45.2]	196 (49.7) [44.7, 54.8]		599 (46.8) [44.0, 49.6]	795 (47.5) [45.1, 49.9]
Grade 2	102 (13.8) [11.4, 16.5]	35 (6.5) [4.6, 8.9]	26 (6.6) [4.4, 9.5]		137 (10.7) [9.1, 12.5]	163 (9.7) [8.4, 11.3]
Grade 3	48 (6.5) [4.8, 8.5]	8 (1.5) [0.6, 2.9]	13 (3.3) [1.8, 5.6]		56 (4.4) [3.3, 5.6]	69 (4.1) [3.2, 5.2]
Grade 4	2 (0.3) [0.0, 1.0]	0 [0.0, 0.7]	0 [0.0, 0.9]		2 (0.2) [0.0, 0.6]	2 (0.1) [0.0, 0.4]
SAE	6 (0.8) [0.3, 1.8]	0 [0.0, 0.7]	4 (1.0) [0.3, 2.6]	0.045	6 (0.5) [0.2, 1.0]	10 (0.6) [0.3, 1.1]
Related SAE	0 [0.0, 0.5]	0 [0.0, 0.7]	0 [0.0, 0.9]		0 [0.0, 0.3]	0 [0.0, 0.2]
Serious or medically-attended AE	178 (24.1) [21.0, 27.3]	28 (5.2) [3.5, 7.4]	56 (14.2) [10.9, 18.1]	<0.001	206 (16.1) [14.1, 18.2]	262 (15.7) [13.9, 17.5]
Medically-attended AE	178 (24.1) [21.0, 27.3]	28 (5.2) [3.5, 7.4]	56 (14.2%) [10.9, 18.1]	<0.001	206 (16.1) [14.1, 18.2]	262 (15.7) [13.9, 17.5]
Related medically-attended AE	11 (1.5) [0.7, 2.6]	1 (0.2) [0.0, 1.0]	4 (1.0) [0.3, 2.6]	0.047	12 (0.9) [0.5, 1.6]	16 (1.0) [0.5, 1.5]
Unsolicited AE of special interest	32 (4.3) [3.0, 6.1]	11 (2.0) [1.0, 3.6]	13 (3.3) [1.8, 5.6]	0.073	43 (3.4) [2.4, 4.5]	56 (3.3) [2.5, 4.3]
Related unsolicited AE of special interest	2 (0.3) [0.0, 1.0])	0 [0.0, 0.7]	2 (0.5) [0.1, 1.8]	0.282	2 (0.2) [0.0, 0.6]	4 (0.2) [0.1, 0.6]
AE that led to discontinuation	2 (0.3) [0.0, 1.0]	0 [0.0, 0.7]	0 [0.0%, 0.9]	0.506	2 (0.2) [0.0, 0.6]	2 (0.1) [0.0, 0.4]
AE that led to death	0 [0.0, 0.5]	0 [0.0, 0.7]	0 [0.0, 0.9]		0 [0.0, 0.9]	0 [0.0, 0.2]

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in the Safety Population; n, number of subjects; SAE, serious adverse event.

NOTE 1: Only AEs with a causality of possibly or probably related were considered related to the vaccine. NOTE 2: Percentages are based on the number of subjects in the Safety Population. NOTE 3: P-value (where applicable and when numbers were sufficient) was from a Fishers exact test comparing the number of subjects with the event across the treatment groups. NOTE 4: CI was an exact confidence interval for a percentage.

Source: Adapted from Table 12.2, Clinical Study Report, Final v2.0, 13 Nov 2012, page 104/221

In the younger age group, based on the solicited AEs with the IC51(0.25 mL) vaccinees the rate was 58.2% (95% CI: 49.1%, 66.6%) compared to 59.4% (95% CI: 46.4%, 71.5%) among those receiving Prevnar (control vaccine). The two groups, IC51 and Prevnar, showed no significant difference in solicited rates through Day 56.

In the older age group (Table 2.4.4.2), 339 subjects receiving IC51 with dose 0.25 mL reported solicited AEs, yielding a rate of 45.8% (95% CI: 42.2%, 49.5%). This solicited AE rate was significantly higher compared to that reported for the IC51 0.5 mL dose (33.9%, 95% CI: 29.9%, 38.1%) or for the HAVRIX control arm (29.4%, 95% CI: 25.0%, 34.2%). To explore if these crude differences could be influenced by the underlying age distributions of the treatment groups, the AE rates were compared within age subgroups, as in Table 2.4.4.3. The reduced AE rate in HAVRIX was evidenced after the age-breakdown as well. As Table 2.4.4.3 shows, in the age group 1-3 years, the rate for solicited AEs was higher for the IC51 0.25 mL vaccinees (47.3%, 95% CI: 43.4%, 51.3%) compared to the control, HAVRIX, vaccinees (33.3%, 95% CI: 27.0%, 40.1%). In the 3-12 year age group, the IC51 vaccinees, overall, had this AE rate as 129/400 or 32.3% (95% CI: 27.7%, 37.1%) compared to 14.9% (95% CI: 8.6%, 23.3%) in the HAVRIX control group. The results imply significant excess of these AEs in the IC51 vaccinees in the age subgroups of 1-3 years and 3-12 years. However, it should be noted that this excess appears with a background that the IC51 vaccinees were administered 2 injections compared to 1 injection for HAVRIX - as of Day 56 of first vaccination, and the solicited AE rates post-dose 1 in both vaccines were comparable (IC51: 32.0%, 409/1280, 95% CI: 29.4%, 34.6%; HAVRIX: 29.4%, 116/394, 95% CI: 25.0%, 34.2%) (Table 14.3.4.1, Clinical Study Report, Final v2.0, 13 Nov 2012, page 3301 of 7569).

Table 2.4.4.3: Solicited AE rates through Day 56, by Children Age ≥1 year **and < 18 years and Treatment Groups, Safety Population**

Age subgroup*	IC51 0.25 mL n/N, % (95% CI)	IC51 0.5 mL n/N, % (95% CI)	HAVRIX 720 n/N, % (95% CI)
≥1 yr to <3 yrs	303/640, 47.3 (43.4, 51.3)	-	71/213, 33.3 (27.0, 40.1)
≥3 yrs to <12 yrs	36/100, 36.0 (26.6, 46.2)	93/300, 31.0 (25.8, 36.6)	15/ 101, 14.9 (8.6, 23.3)
≥12 yrs to <18 yrs	-	90/240, 37.5 (31.4, 44.0)	30/80, 37.5 (26.9, 49.0)

Source. Reviewer's compilation from Tables 14.3.1.1, Clinical Study Report, Final v2.0, 13 Nov 2012, pages 395-406 of 7569.
* Used by the applicant.

2.4.4.2a Solicited AE by Center. Since safety through Day 56 after the first vaccination was the study's primary objective, it was of interest to see how results varied by centers. This was addressed based on the solicited AE rate, a dominant safety metric in the study. The results are presented in Table 2.4.4.4a and show that the solicited AE rates did not significantly vary between centers for any of the treatment groups.

Table 2.4.4.4a: Number of Subjects with Solicited AEs and Rates through Day 56 (Visit 3), by Center, Safety Population

Subjects' age from 2 months to 1 year

Study Center	IC51 0.25 mL n/N (%) [95% CI]	Prevnar n/N (%) [95% CI]	Total n/N (%) [95% CI]
Center 1	11/22 (50.0) [28.2, 71.8]	5/12 (41.7) [15.2, 72.3]	16/34 (47.0) [(29.8, 64.9)
Center 3	46/75 (61.6) [49.4, 72.4]	23/36 (63.4) [46.2, 79.2]	69/111 (62.2) [52.5, 71.2]
Center 4	19/34 (55.9) [37.9, 72.8]	10/16 (62.5) [35.4, 84.8]	29/50 (58.0) [43.2, 71.8]

Subjects' age from 1 year to 18 years

Study Center	IC51 0.25 mL n/N (%) [95% CI]	IC51 0.5 mL n/N (%) [95% CI]	HAVRIX n/N (%) [95% CI]	Total n/N (%) [95% CI]
Center 1	94/230 (40.9) [34.4, 47.5]	56/182 (30.8) [24.2, 38.0]	28/107 (26.7) [18.2, 35.6]	178/519 (34.3) [30.2, 38.6]
Center 3	169/329 (51.4) [45.8, 56.9]	66/164 (40.3) [32.7, 48.2]	50/136 (36.8) [28.7, 45.5]	285/629 (45.3) [41.4, 49.3]
Center 4	76/181 (42.0) [34.7, 49.5]	61/194 (31.4) [25.0, 38.5]	38/151 (25.2) [18.5, 32.9]	175/526 (33.3) [29.3, 37.5]

Source. Reviewer's calculations based on applicant's data, study IC51-323.

2.4.4.2b Solicited AE by Demographic Subgroup. With the study (pivotal) conducted in the Philippines, the race category was only Asian. The solicited AE rate was an important safety metric and it was of interest to see its pattern for the demographic characteristics of gender and age. The Table 2.4.4.4b provides solicited AE rates by gender, under the studied pediatric population's two broad age groups, 2 months to < 1 year and 1-18 years. In children < 1 year of age, the boys, overall, appeared to have higher solicited AE rates compared to girls, but the difference was not notable. It appeared otherwise in the older age group but, again, the rates between boys and girls did not differ notably, except for the IC51 0.5mL vaccinees.

Table 2.4.4.4b: Number of Subjects with Solicited AEs and Rates through Day 56 (Visit 3), by Gender, Safety Population

Subjects' age from 2 months to 1 year

Gender	IC51 0.25 mL n/N (%) [95% CI]	Prevnar n/N (%) [95% CI]	Total n/N (%) [95% CI]
Male	43/67 (64.2) [51.5, 75.5]	22/34 (64.7) [46.5, 80.3]	65/101 (64.4) [54.2, 73.6]
Female	33/64 (51.6) [38.7, 64.3]	16/30 (53.3) [34.3, 71.7]	49/94 (52.1) [41.6, 62.5]

Subjects' age from 1 year to 18 years

Gender	IC51 0.25 mL n/N (%) [95% CI]	IC51 0.5 mL n/N (%) [95% CI]	HAVRIX n/N (%) [95% CI]	Total n/N (%) [95% CI]
Male	161/355 (45.4) [40.1, 50.7]	81/291 (27.8) [22.8, 33.3]	49/197 (24.9) [19.0, 31.5]	291/843 (34.5) [31.3, 37.8]
Female	178/ 385 (46.2) [41.2, 51.4]	102/249 (41.0) [34.8, 47.4]	67/197 (34.0) [27.4, 41.1]	347/831(41.8) [38.4, 45.2]

Source. Reviewer's calculations based on applicant's data, study IC51-323.

2.4.4.3 SAEs.

On Day 56 post first vaccination, no SAEs for the younger age group (Table 2.4.4.1) were reported in the IC51 0.25 mL dose group (0%, 95% CI: 0.0%, 2.8%), but in the Prevnar group an SAE was reported for one subject (1.6%, 95% CI: 0.0%, 8.4%). In the older age group (Table 2.4.4.2), SAEs were reported for 6 subjects receiving IC51 0.25 mL (0.8%, 95% CI: 0.3%,

1.8%), with none in the IC51 0.5 mL group (0%, 95% CI: 0.0%, 0.7%), and 4 subjects in the HAVRIX control group (1.0%, 95% CI: 0.3%, 2.6%). None of these SAEs were adjudicated by study investigators as related to the study vaccine.

The above reported SAEs through Day 56 (for one subject of age ≥2 months to <1 year and for 10 subjects of age 1-18 years) are listed (following PT names) in Table 2.4.4.5. Febrile convulsion and upper respiratory tract infection seemed to be the most frequent SAE types reported.

Table 2.4.4.5: Serious adverse events at Day 56, Safety population.

Age group: 2 months - 1year

	IC51 0.25 ml	3:Prevnar	Total
Number of subjects with ≥ 1 SAEs	0	1	1
SAEs (PTNAME):			
Dermatitis Contact	-	1	1
Febrile Convulsion	-	1	1
Upper Respiratory Tract Infection	-	2	2
Total	-	4	4

Age group: 1-18 years

	IC51 0.25 ml	IC51 0.50 ml	HAVRIX 720	Total
	N=740	N=540	N=394	N=1674
	n (%)	n (%)	n (%)	n (%)
Number of subjects with ≥ 1 SAEs	6(0.8)	0	4(1.0)	10(0.6)
SAEs (PTNAME):				
Abscess Limb	1		0	1
Alanine Aminotransferase Increased	1		0	1
Aspartate Aminotransferase Increased	1		0	1
Blood Alkaline Phosphatase Increased	1		0	1
Bronchopneumonia	2		0	2
Cellulitis	1		0	1
Cough	2		0	2
Dengue Fever	1		0	1
Diarrhoea	1		0	1
Dyspnoea	0		2	2
Fall	1		0	1
Febrile Convulsion	2		2	4
Gastroenteritis	1		1	2
Haematoma	1		0	1
Pharyngotonsillitis	1		1	2
Pneumonia	1		0	1
Upper Respiratory Tract Infection	3		3	6
Urinary Tract Infection	2		0	2
Total	23		9	32

Source. Reviewer's calculations based on applicant's data, study IC51-323.

One death was reported following Day 56. It was a fatal SAE of disseminated intravascular coagulation, bacterial meningitis pneumonia reported for a 12-year old male subject receiving IC51 0.5 mL. The study investigator did not consider it related to the study vaccine.

2.4.4.4 Medically-Attended AEs.

Again from Table 2.4.4.1, 50 subjects from ≥2 months to <1 year of age who received IC51 0.025 mL had serious or medically attended AEs, with the AE rate 38.2% (95% CI: 29.8% - 47.1%). In the Prevnar group, this rate was 42.2% (95% CI: 29.9% - 55.2%) based on 27 subjects with similar AEs.

Among subjects from 1 year to <18 years of age (Table 2.4.4.2), serious or medically attended AEs occurred to 178 subjects (24.1%, 95% CI: 21.0%-27.3%) in the IC51 0.25 mL group, compared to 28 subjects in the IC51 0.5 mL group (5.2%, 95% CI: 3.5% - 7.4%) and 56 subjects in the HAVRIX group (14.2%, 95% CI: 10.9% -18.1%). It appears that serious or medically attended AEs in the 1-18 year-old subjects had the highest rate of occurrence in the IC51 0.25 mL group, followed by HAVRIX, and IC51 0.5 mL as the lowest group. The apparent differences in these AE rates across treatment groups, which could potentially be influenced by the underlying age distributions in the treatment groups, were explored in age subgroups as in Table 2.4.4.6. The results indicated no significant difference in treatment groups when the rates were compared within individual age subgroups.

Table 2.4.4.6: Serious or Medically Attended AE rates through Day 56, by Children Age ≥1 year **and < 18 years and Treatment Groups, Safety Population**

Age subgroup	IC51 0.25 mL n/N, % (95% CI)	IC51 0.5 mL n/N, % (95% CI)	HAVRIX 720 n/N, % (95% CI)
≥1 yr to <3 yrs	171/640, 26.7 (23.3, 30.3)	-	47/213, 22.1 (16.7, 28.2)
≥3 yrs to <12 yrs	7/100, 7.0 (2.9, 13.9)	24/300, 8.0 (5.2, 11.7)	6/ 101, 5.9 (2.2, 12.5)
≥12 yrs to <18 yrs	-	4/240, 1.7 (0.5, 4.2)	3/80, 3.8 (0.8, 10.6)

Source. Reviewer's compilation from Tables 14.3.1.1, Clinical Study Report, Final v2.0, 13 Nov 2012, pages 395-406 of 7569

2.4.4.5 Solicited Local and Systemic Adverse Events within 7 Days of First Vaccination.

Table 2.4.4.7 summarizes solicited local and systemic AEs for subjects ≥2 months and <1 year of age by maximum severity grade and treatment arm. A total of 25 subjects, i.e., a proportion of 25/131, or 19.1% (95% CI: 12.7% - 26.9%) receiving IC51 0.25 mL had local AEs within 7 days of first vaccination, compared to a proportion of 20/63 or 31.7% (95% CI: 20.6% - 44.7%) in the Prevnar group. In both treatment groups, the most frequently reported solicited local AEs were injection site redness (IC51 0.25 L, 17.6%, 95% CI: 11.5% - 25.2%; Prevnar, 25.4%, 95% CI: 15.3% - 37.9%). These local AEs were mostly mild, i.e., of grade 1, and none were grade 3 or grade 4. These AE rates in each age group were comparable between arms.

Table 2.4.4.7: Solicited Adverse Events Experienced by Subjects Aged ≥ 2 Months to < 1 Year within 7 Days after the First Vaccination by Maximum Severity, Safety Population

	IC51 0.25 mL N=131	IC51 0.25 mL N=131	IC51 0.25 mL N=131	IC51 0.25 mL N=131	IC51 0.25 mL N=131	Prevnar N=64[a]	Prevnar N=64[a]	Prevnar N=64[a]	Prevnar N=64[a]	Prevnar N=64[a]	
Severity grade[b] ➢	1 %	2 %	3 %	All % (n/N)	All [95% CI]	1 %	2 %	3 %	All % (n/N)	All [95% CI]	p-value
Any Local AE	16.0	3.1	0	19.1 (25/131)	[12.7, 26.9]	23.8	7.9	0	31.7 (20/63)	[20.6, 44.7]	0.069
Pain (without touching)	na	na	na	na	na	na	na	na	na	na	na
Itching[c]	na	na	na	na	na	na	na	na	na	na	na
Tenderness (upon touching)	2.3	0.8	0	3.1 (4/131)	[0.8, 7.6]	11.1	1.6	0	12.7 (8/63)	[5.6, 23.5]	0.021
Hardening	0	0	0	0 (0/131)	[0.0, 2.8]	1.6	6.3	0	7.9 (5/63)	[2.6, 17.6]	0.003
Swelling	0.8	0.8	0	1.5(2/131)	[0.2, 5.4]	4.8	1.6	0	6.3 (4/63)	[1.8, 15.5]	0.089
Redness	15.3	2.3	0	17.6 (23/131)	[11.5, 25.2]	19.0	6.3	0	25.4 (16/63)	[15.3, 37.9]	0.251
Any Systemic AE	25.2	9.9	0.8	35.9 (47/131)	[27.7, 44.7]	31.7	4.8	3.2	39.7 (25/63)	[27.6, 52.8]	0.636
Irritability	13.0	2.3	0	15.3 (20/131)	[9.6, 22.6]	9.5	1.6	1.6	12.7 (8/63)	[5.6, 23.5]	0.828
Nausea	9.1	0	0	9.1 (1/11)	[0.0, 4.2]	0	0	0	0 (0/9)	[0.0, 5.7]	1.000
Vomiting	6.9	0.8	0	7.6 (10/131)	[3.7, 13.6]	4.8	1.6	0	6.3 (4/63)	[1.8, 15.5]	1.000
Diarrhea	8.4	2.3	0.8	11.5 (15/131)	[6.6, 18.2]	4.8	1.6	0	6.3 (4/63)	[1.8, 15.5]	0.313
Flu-like symptoms[c]	na	na	na	na	na	na	na	na	na	na	na
Excessive fatigue	1.5	1.5	0	3.1 (4/131)	[0.8, 7.6]	4.8	3.2	0	7.9 (5/63)	[2.6, 17.6]	0.153
Muscle pain	na	na	na	na	na	na	na	na	na	na	na
Rash	8.4	0	0	8.4 (11/131)	[4.3, 14.5]	9.5	0	0	9.5 (6/63)	[3.6, 19.6]	0.791
Headache	na	na	na	na	na	na	na	na	na	na	na
Loss of appetite	3.8	1.5	0	5.3 (7/131)	[2.2, 10.7]	7.9	1.6	0	9.5 (6/63)	[3.6, 19.6]	0.358
Fever	17.6	6.1	0	23.7 (31/131)	[16.7, 31.9]	22.2	1.6	1.6	25.4 (16/63	[15.3, 37.9]	0.858

Abbreviations: AE, adverse event; CI, confidence interval; n/N, number of subjects with an event/number of assessable subjects in the Safety Population; na, not assessable.

[a] Subject 23101319 in the Prevnar group was administered study vaccine but did not return a solicited AE diary, hence only 63 subjects were assessable.

[b] Grade 4 is not shown in the table; no subject had a Grade 4 solicited AE within 7 days after vaccination. Only the maximum severity experienced between Days 0 and 6 was presented for each subject.

[c] One subject was assessable but had no symptoms.

NOTE 1: Percentages are based on the number of subjects who were able to be assessed. NOTE 2: P-value is from a Fishers exact test comparing the overall number of subjects with the event across the treatment groups. NOTE 3: CI is an exact confidence interval for a percentage.

Source: Adapted from Clinical Study Report, Final v2.0, 13 November 2012

Systemic AEs were experienced by 35.9% (47/131) (95% CI: 27.7% - 44.7%) of subjects in the IC51 0.25 mL group, compared to 39.7% (25/63) (95% CI: 27.6% - 52.8%) in the Prevnar group, implying no overall statistical difference in rates between the two arms. The lack of difference was reflected in major systemic AEs such as irritability, diarrhea, and fever. The respective systemic AEs were mostly mild (grade 1).

The above summary for the local and systemic AEs was obtained also for subjects of age 1-18 years and is provided in Table 2.4.4.8 and Table 2.4.4.9. Overall, the local AEs in this age group occurred at a rate of 11.4% (84/740) (95% CI: 9.2% - 13.9%) in the IC51 0.25 mL group, compared to 16.5% (89/540) (95% CI: 13.5% - 19.9%) in the IC51 0.5 mL group and 13.7% (54/394) (95% CI: 10.5%-17.5%) in the HAVRIX group. The rates of local AEs between IC51 and HAVRIX appeared comparable. The local AEs like injection redness, pain and swelling were dominant, and mostly were mild (grade 1) in terms of maximum severity. For these subjects (Table 2.4.4.9), the systemic AEs occurred with overall rates 27.8% (95% CI: 24.6%-31.2%), 15.9% (95% CI:12.9%-19.3%) and 19.3% (95% CI: 15.5%, 23.5%), respectively, in the groups IC51 0.25 mL, IC51 0.5 mL and HAVRIX720.

Also, the overall proportion of subjects experiencing local (Table 2.4.4.8) and systemic (Table 2.4.4.9) AEs for the IC51 (combined doses) versus HAVRIX comparison were respectively 13.5% (173/1280) versus 13.7% (54/394), and 22.8% (292/1280) vs 19.3% (76/394). The comparisons showed no significant differences in overall local and systemic AE rates between IC51 and HAVRIX.

AEs such as fever, diarrhea, and flu-like symptoms were dominant, and had comparable rates between IC51 and HAVRIX groups.

Table 2.4.4.8: Solicited Local Adverse Events Experienced by Subjects Aged ≥ 1 Year to < 18 Years within 7 Days after the First Vaccination by Maximum Severity, Safety Population

	IC51 0.25 mL N=740	IC51 0.25 mL N=740	IC51 0.25 mL N=740	IC51 0.25 mL N=740	IC51 0.5 mL N=540	IC51 0.5 mL N=540	IC51 0.5 mL N=540	IC51 0.5 mL N=540	HAVRIX 720 N=394	HAVRIX 720 N=394	HAVRIX 720 N=394	HAVRIX 720 N=394		IC51 Total N=1280	IC51 Total N=1280	IC51 Total N=1280	IC51 Total N=1280
Severity Grade[a] ➢	1 %	2 %	3 %	All % (n/N) [95% CI]	1 %	2 %	3 %	All % (n/N) [95% CI]	1 %	2 %	3 %	All % (n/N) [95% CI]	p-value	1 %	2 %	3 %	All % (n/N) [95% CI]
Any Local AE	10.1	1.2	0	11.4 (84/740) [9.2, 13.9]	15.7	0.6	0.2	16.5 (89/540) [13.5, 19.9]	13.5	0.3	0	13.7 (54/394) [10.5, 17.5]	0.031	12.5	0.9	0.1	13.5 (173/1280) [11.7, 15.5]
Pain (without touching)	3.8	0	0	3.8 (10/264) [0.6, 2.5]	9.2	0.6	0	9.8 (52/533) [7.3, 12.4]	6.9	0.4	0	7.3 (17/233) [2.5, 6.8]	<0.001	7.4	0.4	0	7.8 (62/797) [3.7, 6.2]
Itching	1.4	0	0	1.4 (4/279) [0.1, 1.4]	1.1	0	0	1.1 (6/532) [0.4, 2.4]	0	0	0	0 (0/242) [0.0, 0.9]	0.083	1.2	0	0	1.2 (10/811) [0.4, 1.4]
Tenderness (upon touching)	3.1	0.3	0	3.4 (25/740) [2.2, 4.9]	6.7	0.2	0	6.9 (37/540) [4.9, 9.3]	5.8	0.3	0	6.1 (24/394) [3.9, 8.9]	0.010	4.6	0.2	0	4.8 (62/1280) [3.7, 6.2]
Hardening	0.8	0.3	0	1.1 (8/740) [0.5, 2.1]	1.3	0	0	1.3 (7/540) [0.5, 2.7]	0.3	0	0	0.3 (1/394) [0.0,1.4]	0.256	1.0	0.2	0	1.2 (15/1280) [0.7, 1.9]
Swelling	2.0	0.5	0	2.6 (19/740) [1.6, 4.0]	1.1	0	0.2	1.3 (7/540) [0.5, 2.7]	2.8	0	0	2.8 (11/394) [1.4, 4.9]	0.191	1.6	0.3	0.1	2.0 (26/1280) [1.3, 3.0]
Redness	5.8	0.3	0	6.1 (45/740) [4.5, 8.1]	2.0	0	0	2.0 (11/540) [1.0, 3.6]	5.6	0	0	5.6 (22/394) [3.5, 8.3]	<0.001	4.2	0.2	0	4.4 (56/1280) [3.3, 5.6]

Abbreviations: AE, adverse event; CI, confidence interval; n/N, number of subjects with an event/number of assessable subjects in the Safety Population.

[a] Grade 4 is not shown in the table; no subject had a Grade 4 solicited AE within 7 days after vaccination. Only the maximum severity experienced between Days 0 and 6 was presented for each subject.

NOTE 1: Percentages are based on the number of subjects who were able to be assessed. NOTE 2: P-value is from a Fishers exact test comparing the overall number of subjects with the event across the treatment groups.

NOTE 3: CI is an exact confidence interval for a percentage.

Source. Clinical Study Report, Final v2.0, Nov 2012, page 121 of 221.

Table 2.4.4.9: Solicited Systemic Adverse Events Experienced by Subjects Aged ≥ 1 Year to < 18 Years within 7 Days After the First Vaccination by Maximum Severity, Safety Population

	IC51 0.25 mL N=740	IC51 0.25 mL N=740	IC51 0.25 mL N=740	IC51 0.25 mL N=740	IC51 0.5 mL N=540	IC51 0.5 mL N=540	IC51 0.5 mL N=540	IC51 0.5 mL N=540	HAVRIX 720 N=394	HAVRIX 720 N=394	HAVRIX 720 N=394	HAVRIX 720 N=394		IC51 Total N=1280	IC51 Total N=1280	IC51 Total N=1280	IC51 Total N=1280
Severity Grade[a] ➢	1 %	2 %	3 %	All % (n/N) [95% CI]	1 %	2 %	3 %	All % (n/N) [95% CI]	1 %	2 %	3 %	All % (n/N) [95% CI]	p-value	1 %	2 %	3 %	All % (n/N) [95% CI]
Any Systemic AE	21.1	4.9	1.9	27.8(206/740) [24.6, 31.2]	13.1	2.2	0.6	15.9 (86/540) [12.9, 19.3]	15.7	2	1.5	19.3 (76/394) [15.5, 23.5]	<0.001	17.7	3.8	1.3	22.8 (292/1280) [20.5,25.2]
Irritability	5.8	0.9	0.1	6.9 (51/740) [5.2, 9.0]	0.7	0.2	0	0.9 (5/540) [0.3, 2.1]	3.3	0.3	0	3.6 (14/394) [2.0, 5.9]	<0.001	3.7	0.6	0.1	4.4 (56/1280) [3.3, 5.6]
Nausea	1.5	0.3	0.3	2.1 (7/327) [0.4, 1.9]	1.1	0	0	1.1 (6/531) [0.4, 2.4]	0	0.8	0	0.8 (2/257) [0.1, 1.8]	0.713	1.3	0.1	0.1	1.5 (13/858) [0.5, 1.7]
Vomiting	2.8	0.7	0.1	3.6 (27/740) [2.4, 5.3]	1.5	0	0	1.5 (8/540) [0.6, 2.9]	2.8	0.3	0.3	3.3 (13/394) [1.8, 5.6]	0.049	2.3	0.4	0.1	2.7 (35/1280) [1.9, 3.8]
Diarrhea	5.5	0.7	0.1	6.4 (47/740) [4.7, 8.4]	0.4	0.2	0	0.6 (3/540) [0.1, 1.6]	3	0	0.3	3.3 (13/394) [1.8, 5.6]	<0.001	3.4	0.5	0.1	3.9 (50/1280) [2.9, 5.1]
Flu-like symptoms	5.2	0	0.4	5.6 (15/267) [1.1, 3.3]	1.7	0.6	0	2.3 (12/532) [1.2, 3.8]	6.3	0.4	0	6.7 (16/239) [2.3, 6.5]	0.112	2.9	0.4	0.1	3.4 (27/799) [1.4, 3.1]
Excessive fatigue	1.9	0.4	0	2.3 (17/740) [1.3,3.7]	1.1	0.6	0	1.7 (9/540) [0.8, 3.1]	0.8	0.3	0	1.0 (4/394) [0.3, 2.6]	0.309	1.6	0.5	0	2.0 (26/1280) [1.3, 3.0]
Muscle pain	1.3	0.9	0	2.2 (5/227) [0.2, 1.6]	2.3	0.4	0	2.6 (14/531) [1.4, 4.3]	2.7	0.5	0	3.2 (7/221) [0.7, 3.6]	0.016	2	0.5	0	2.5 (19/758) [0.9, 2.3]
Rash	3.4	0.3	0	3.6 (27/740) [2.4, 5.3]	0.9	0	0	0.9 (5/540) [0.3, 2.1]	1.3	0.3	0	1.5 (6/394) [0.6, 3.3]	0.003	2.3	0.2	0	2.5 (32/1280) [1.7, 3.5]
Headache	2.6	0.4	0	3.0 (7/234) [0.4, 1.9]	3.6	0.6	0	4.1 (22/531) [2.6, 6.1]	4.5	0	0	4.5 (10/224) [1.2, 4.6]	<0.001	3.3	0.5	0	3.8 (29/765) [1.5, 3.2]
Loss of appetite	3.8	1.1	0.3	5.1 (38/740) [3.7, 7.0]	1.5	0	0	1.5 (8/540) [0.6, 2.9]	2.8	0.3	0.3	3.3 (13/394) [1.8, 5.6]	0.001	2.8	0.6	0.2	3.6 (46/1280) [2.6, 4.8]
Fever	15.4	2.6	1.5	19.5 (144/740) [16.7, 22.5]	5.7	1.3	0.6	7.6 (41/540) [5.5, 10.2]	9.1	1.5	1.3	11.9 (47/394) [8.9, 15.5]	<0.001	11.3	2	1.1	14.5 (185/1280) [12.6, 16.5]

Abbreviations: AE, adverse event; CI, confidence interval; n/N, number of subjects with an event/number of assessable subjects in the Safety Population.

[a] Grade 4 is not shown in the table; no subject had a Grade 4 solicited AE within 7 days after vaccination. Only the maximum severity experienced between Days 0 and 6 was presented for each subject.

NOTE 1: Percentages are based on the number of subjects who were able to be assessed. NOTE 2: P-value is from a Fishers exact test comparing the overall number of subjects with the event across the treatment groups.
NOTE 3: CI is an exact confidence interval for a percentage. Source. Clinical Study Report, Final v2.0, Nov 2012, page 122 of 221.

2.4.4.6 Association between Pre-existing JEV and DENV status and AE Rate at Day 56.

The occurrence of AEs on or prior to Day 56 were analyzed to assess the influence of pre-existing JEV and DENV status as covariates, by using logistic regression. The results, in age-stratifications, are presented in Table 2.4.4.10. As the Table shows, the AE rate at Day 56

Table 2.4.4.10: Analysis of Adverse Event Rate to Visit 3 (Day 56) by Treatment Group with Covariate Adjustment for Age, Pre-Existing JEV Status and Pre-Existing DENV Status, Safety Population

Strata/Covariate	Odds Ratio	95% CI	p-value
Strata: >= 2 months to < 1 year			
Age	12.497	[1.110; 140.69]	0.041
Pre-existing JEV Status (Seropositive / Seronegative)	0.630	[0.146; 2.714]	0.535
Pre-existing DENV Status (Positive / Negative)	1.586	[0.457; 5.510]	0.468
Treatment Group (IC51 0.25 ml / Prevnar)	0.761	[0.307; 1.885]	0.555
Strata: >= 1 year to < 18 years			
Age	0.961	[0.933; 0.989]	0.008
Pre-existing JEV Status (Seropositive / Seronegative)	0.964	[0.711; 1.307]	0.813
Pre-existing DENV Status (Positive / Negative)	0.610	[0.472; 0.788]	<0.001
Treatment Group (IC51 0.5 ml / HAVRIX 720)	0.847	[0.630; 1.139]	0.045
Treatment Group (IC51 0.25 ml / HAVRIX 720)	1.255	[0.947; 1.664]	0.020
Treatment Group (IC51 0.5 ml / IC51 0.25 ml)	0.675	[0.491; 0.928]	0.015

Source: Adapted from Clinical Study Report, IC-323, Section 14 Table 14.3.2.3.
NOTE: Only treatment emergent adverse events (AEs) starting on or prior to Visit 3 are included in this table. NOTE: Odds Ratios and Confidence Intervals and p-values were obtained from a logistic regression model with age, pre-existing JEV and DENV status as covariates and treatment group as the main effect.
NOTE: Seropositive is defined as a PRNT50 titer >= 1:10 at Visit 0, Seronegative is defined as a PRNT50 titer < 1:10 at Visit 0.

among children of age > 2 months to 1 year did not have significant association with pre-existing JEV status (OR=0.63; 95% CI: 0.15, 2.71). Nor was the association significant with the pre-existing DENV status (OR=1.59; 95% CI: 0.46, 5.51) in the same age group. Both these results were adjusted for the age and treatment effects within strata. Contrastingly, however, the pre-existing immunity to DENV among the 1-18 year-old subjects was significantly associated with decreased AE occurrences at Day 56 (OR=0.61, 95% CI: 0.47, 0.79), after similar adjustment for age and treatment effects.

2.4.5 Safety through Month 7.

This section summarizes the safety results based on solicited AEs, SAEs and serious or medically-attended AEs occurring through Month 7 after the first vaccination. Table 2.4.5.1 and Table 2.4.5.2 present these results for subjects from 2 months to 1 year of age and for subjects from 1 year to 18 years of age, respectively.

Table 2.4.5.1: Summary of Adverse Events through Month 7 (Visit 4) Reported for Subjects Aged ≥ 2 months to < 1 year, Safety Population

	IC51 0.25 mL N=131 n(%) [95% CI]	Prevner N=64 n(%) [95% CI]	Total N=195 n(%) [95% CI]
Number of subjects with AEs≥1:			
Solicited or unsolicited	115 (87.8) [80.9, 92.9]	58 (90.6) [80.7, 96.5]	173 (88.7) [83.4, 92.8]
Solicited	76 (58.0) [49.1, 66.6]	44 (68.8) [55.9, 79.8]	120 (61.5) [54.3, 68.4]
Unsolicited	101 (77.1) [68.9, 84.0]	52(81.3) [69.5, 89.9]	153 (78.5) [72.0, 84.0]
Unsolicited AE that was:			
probably related	5 (3.8) [1.3, 8.7]	1 (1.6) [0.0, 8.4]	6 (3.1) [1.1, 6.6]
possibly related	5 (3.8) [1.3, 8.7]	3 (4.7) [1.0, 13.1]	8 (4.1) [1.8, 7.9]
Solicited/unsolcited AE with severity grade of			
Grade 1	69 (52.7) [43.8, 61.5]	35 (54.7) [41.7, 67.2]	104 (53.3) [46.1, 60.5]
Grade 2	36 (27.5) [20.0, 36.0]	17 (26.6) [16.3, 39.1]	53 (27.2) [21.1, 34.0]
Grade 3	8 (6.1) [2.7, 11.7]	6 (9.4) [3.5, 19.3]	14 (7.2) [4.0, 11.8]
Grade 4	2 (1.5) [0.2, 5.4]	0 [0.0, 5.6]	2 (1.0) [0.1, 3.7]
SAE	2 (1.5) [0.2, 5.4]	1 (1.6) [0.0, 8.4]	3 (1.5) [0.3, 4.4]
Related SAE	0 [0.0, 2.8]	0 [0.0, 5.6]	0 [0.0, 1.9]
Serious or medically attended AE	64 (48.9) [40.0, 57.7]	38 (59.4) [46.4, 71.5]	102 (52.3) [45.1, 59.5]
Medically-attended AE	64 (48.9) [40.0, 57.7]	38 (59.4) [46.4, 71.5]	102 (52.3) [45.1, 59.5]
Related Medically-attended AE	3 (2.3) [0.5, 6.5]	2 (3.1) [0.4, 10.8]	5 (2.6) [0.8, 5.9]
Unsolicited AE of special interest	6 (4.6) [1.7, 9.7]	6 (9.4) [3.5, 19.3]	12 (6.2) [3.2, 10.5]
Related Unsolicited AE of special interest	0 [0.0, 2.8]	0 [0.0, 5.6]	0 [0.0, 1.9]
AE leading to discontinuation	0 [0.0, 2.8]	0 [0.0, 5.6]	0 [0.0, 1.9]
AE leading to death	0 [0.0, 2.8]	0 [0.0, 5.6]	0 [0.0, 1.9]

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in the Safety Population; n, number of subjects; SAE, serious adverse event. NOTE 1: Only AEs with a causality of possibly or probably related were considered related to the vaccine. NOTE 2: Percentages are based on the number of subjects in the Safety Population. NOTE 3: P-value (where applicable and when numbers were sufficient) was from a Fishers exact test comparing the number of subjects with the event across the treatment groups. NOTE 4: CI was an exact confidence interval for a percentage. Source: Adapted from Table 12.3, Clinical Study Report, Final v2.0, 13 Nov 2012, page 106/221

Table 2.4.5.2: Summary of Adverse Events to Month 7 (Visit 4) Reported for Subjects Aged ≥ 1 Year to < 18 Years, Safety Population

≥ 1 Year to < 18 Years	IC51 0.25 mL N=740 n (%) [95% CI]	IC51 0.5 mL N=540 n (%) [95% CI]	HAVRIX®720 N=394 n (%) [95% CI]	p-value	IC51 Total N=1280 n (%) [95% CI]	Total N=1674 n (%) [95% CI]
Number of subjects with at least one:						
Solicited or unsolicited AE	592 (80.0) [76.9, 82.8]	307 (56.9) [52.6, 61.1]	262 (66.5) [61.6, 71.1]		899 (70.2) [67.6, 72.7]	1161 (69.4) [67.1, 71.6]
Solicited AE	339 (45.8) [42.2, 49.5]	183 (33.9) [29.9, 38.1]	125 (31.7) [27.2, 36.6]		522 (40.8) [38.1, 43.5]	647 (38.6) [36.3, 41.0]
Unsolicited AE	530 (71.6) [68.2, 74.8]	219 (40.6) [36.4, 44.8]	227 (57.6) [52.6, 62.5]	<0.001	749 (58.5) [55.8, 61.2]	976 (58.3) [55.9, 60.7]
Unsolicited AE that was:						
Probably related	9 (1.2) [0.6, 2.3]	1 (0.2) [0.0, 1.0]	5 (1.3) [0.4, 2.9]	0.079	10 (0.8) [0.4, 1.4]	15 (0.9) [0.5, 1.5]
Possibly related	34 (4.6) [3.2, 6.4]	7 (1.3) [0.5, 2.7]	10 (2.5) [1.2, 4.6]	0.002	41 (3.2) [2.3, 4.3]	51 (3.0) [2.3, 4.0]
Solicited or unsolicited AE with severity grade of:						
Grade 1	412 (55.7) [52.0, 59.3]	243 (45.0) [40.7, 49.3]	206 (52.3) [47.2, 57.3]		655 (51.2) [48.4, 53.9]	861 (51.4) [49.0, 53.9]
Grade 2	120 (16.2) [13.6, 19.1]	46 (8.5) [6.3, 11.2]	38 (9.6) [6.9, 13.0]		166 (13.0) [11.2, 14.9]	204 (12.2) [10.7, 13.8]
Grade 3	58 (7.8) [6.0, 10.0]	15 (2.8) [1.6, 4.5]	18 (4.6) [2.7, 7.1]		73 (5.7) [4.5, 7.1]	91 (5.4) [4.4, 6.6]
Grade 4	2 (0.3) [0.0, 1.0]	3 (0.6) [0.1, 1.6]	0 [0.0, 0.9]		5 (0.4) [0.1, 0.9]	5 (0.3) [0.1, 0.7]
SAE	14 (1.9) [1.0, 3.2]	7 (1.3) [0.5, 2.7]	10 (2.5) [1.2, 4.6]	0.403	21 (1.6) [1.0, 2.5]	31 (1.9) [1.3, 2.6]
Related SAE	0 [0.0, 0.5]	1 (0.2) [0.0, 1.0]	0 [0.0, 0.9]	0.558	1 (0.1) [0.0, 0.4]	1 (0.1) [0.0, 0.3]
Serious or medically-attended AE	266 (35.9) [32.5, 39.5]	72 (13.3) [10.6, 16.5]	101 (25.6) [21.4, 30.2]	<0.001	338 (26.4) [24.0, 28.9]	439 (26.2) [24.1, 28.4]
Medically-attended AE	266 (35.9) [32.5, 39.5]	71 (13.1) [10.4, 16.3]	101 (25.6) [21.4, 30.2]	<0.001	337 (26.3) [23.9, 28.8]	438 (26.2) [24.1, 28.3]
Related medically-attended AE	11 (1.5) [0.7, 2.6]	2 (0.4) [0.0, 1.3]	4 (1.0) [0.3, 2.6]	0.124	13 (1.0) [0.5, 1.7]	17 (1.0) [0.6, 1.6]
Unsolicited AE of special interest	42 (5.7) [4.1, 7.6]	19 (3.5) [2.1, 5.4]	17 (4.3) [2.5, 6.8]	0.191	61 (4.8) [3.7, 6.1]	78 (4.7) [3.7, 5.8]
Related unsolicited AE of special interest	2 (0.3) [0.0, 1.0]	0 [0.0, 0.7]	2 (0.5) [0.1, 1.8]	0.282	2 (0.2) [0.0, 0.6]	4 (0.2) [0.1, 0.6]
AE that led to discontinuation	2 (0.3) [0.0, 1.0]	0 [0.0, 0.7]	0 [0.0, 0.9]	0.506	2 (0.2) [0.0, 0.6]	2 (0.1) [0.0, 0.4]
AE that led to death	0 [0.0, 0.5]	1 (0.2) [0.0, 1.0]	0 [0.0, 0.9]	0.558	1 (0.1) [0.0, 0.4]	1 (0.1) [0.0, 0.3]

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in the Safety Population; n, number of subjects; SAE, serious adverse event.

NOTE 1: Only AEs with a causality of possibly or probably related were considered related to the vaccine. NOTE 2: Percentages are based on the number of subjects in the Safety Population. NOTE 3: P-value (where applicable and when numbers were sufficient) was from a Fishers exact test comparing the number of subjects with the event across the treatment groups. NOTE 4: CI was an exact confidence interval for a percentage. Source: Clinical Stud. Report, IC51-323, Table 12.4, Page 107/221.

As the younger age group (Table 2.4.5.1) shows, the rates for solicited AEs, SAEs, and serious or medically attended AEs were by and large similar between the IC51 0.25mL dose group and the Prevnar control group. In the older age group (Table 2.4.5.2), a total of 338 subjects experienced serious or medically attended AEs with IC51 and a total of 101 subjects had similar AEs with HAVRIX. This led to overall, serious or medically-attended AE rates of 26.4% (95% CI: 24.0 - 28.9) for IC51 compared to 25.6% (95% CI: 21.4 - 30.2) for HAVRIX, showing no significant AE rate differences between the two treatment groups. The AE rate differences were also not significant within the age subgroups (Table 2.4.5.3).

Table 2.4.5.3: Serious or Medically Attended AE rates through Month 7, by Children Age ≥1 year **and < 18 years and Treatment Groups, Safety Population**

Age subgroup	IC51 0.25 mL n/N, % (95% CI)	IC51 0.5 mL n/N, % (95% CI)	HAVRIX 720 n/N, % (95% CI)
≥1 yr to <3 yrs	251/640, 39.2 (35.4, 43.1)	-	83/213, 39.9 (32.4, 45.9)
≥3 yrs to <12 yrs	15/100, 15.0 (8.6, 23.5)	55/300, 18.3 (14.1, 23.2)	11/ 101, 10.9 (5.6, 18.7)
≥12 yrs to <18 yrs	-	17/240, 7.1 (4.2, 11.1)	7/80, 8.8 (3.6, 17.2)

Source. Reviewer's compilation from Tables 14.3.1.2, Clinical Study Report, Final v2.0, 13 Nov 2012, pages 407-426 of 7569.

The study did not collect safety data following the HAVRIX's second vaccination (at 7 months after the first vaccination), except for the first 60 minutes of its administration. This resulted in adding no substantive new information to the HAVRIX's solicited safety data reported as of Day 56 and analyzed earlier in Table 2.4.4.3.

Also, 3 subjects in the younger age group (Table 2.4.5.1) and 31 subjects in the older age group (Table 2.4.5.2) had SAEs. These SAEs are listed in Table 2.4.5.4. It appeared that, overall, the upper respiratory tract infection had the highest frequency of occurrence followed by Febrile Convulsion and Bronchopneumonia and Gastroenteritis. Additionally, there were two AEs of Kawasaki's disease in the older group of subjects 1-18 years of age within 56 days of surveillance. The majority of the reported AEs were mild (grade 1).

Table 2.4.5.4: Serious adverse events at Month 7, Safety population.
Age group: 2 months - 1year

	IC51 0.25 ml	IC51 0.50 ml	Prevnar	Total
	N=131	N=0	N=64	N=195
	n (%)	n (%)	n (%)	n (%)
Number of subjects with ≥ 1 SAEs	2 (1.5)	0	1 (1.5)	3 (1.5)
SAEs (PTNAME):				
Dermatitis Contact	0		1	1
Febrile Convulsion	0		1	1
Pneumonia	4		0	4
Pyrexia	2		0	2
Rhinitis	1		0	1
Upper Respiratory Tract Infection	1		2	3
Urinary Tract Infection	1		0	1
Total	9		4	13

Table 2.4.5.4. contd ... /

Age group: 1-18 years

	IC51 0.25 ml	IC51 0.5 ml	HAVRIX 720	Total
	N=740	N=540	N=394	N=1674
	n (%)	n (%)	n (%)	n (%)
Number of subjects with ≥ 1 SAEs	14 (1.9)	7 (1.3)	10 (2.5)	31 (1.9)
SAEs (PTNAME):				
Abscess Limb	1	0	0	1
Alanine Aminotransferase Increased	1	0	0	1
Aphthous Stomatitis	0	0	1	1
Aspartate Aminotransferase Increased	1	0	0	1
Blood Alkaline Phosphatase Increased	1	0	0	1
Bronchitis	0	0	2	2
Bronchopneumonia	3	0	1	4
Cellulitis	1	0	0	1
Cough	3	1	0	4
Dengue Fever	1	1	1	3
Diarrhoea	1	0	0	1
Disseminated Intravascular Coagulation	0	2	0	2
Dizziness	0	1	0	1
Dyspnoea	0	0	2	2
Fall	1	0	0	1
Familial Periodic Paralysis	0	0	2	2
Febrile Convulsion	5	0	3	8
Flushing	0	1	0	1
Folliculitis	1	0	0	1
Food Allergy	0	1	0	1
Furuncle	0	0	2	2
Gastroenteritis	2	0	1	3
Gingivitis	0	0	1	1
Haematoma	1	0	0	1
Hepatitis A	1	0	0	1
Herpangina	1	0	0	1
Hyponatraemia	0	0	1	1
Injury	0	1	0	1
Kawasaki's Disease	0	2	0	2
Lymphadenitis	0	1	0	1
Meningitis Bacterial	0	1	0	1
Muscular Weakness	0	0	1	1
Nasopharyngitis	1	0	0	1
Pharyngotonsillitis	1	1	1	3
Pneumonia	2	1	4	7
Pyrexia	0	2	0	2
Rhinitis	1	0	1	2
Stillbirth	0	1	0	1
Strabismus	0	1	0	1
Toothache	0	1	0	1
Typhoid Fever	0	1	0	1
Upper Respiratory Tract Infection	12	2	11	25
Urinary Tract Infection	4	0	0	4
Viral Upper Respiratory Tract Infection	0	1	0	1
Vision Blurred	0	1	0	1
Total	46	24	35	105

Source. Reviewer's calculations based on applicant's data, study IC51-323.

2.4.6 Safety Summary and Conclusions.

1. Based on safety data through Day 56 after the first vaccination, the IC51 vaccinees from 2 months to 1 year of age had a solicited AE rate of 58.2% (95% CI: 49.1% - 66.6%), serious or medically-attended AE rate of 38.2% (95% CI: 29.8% - 47.1%) and an overall AE rate of 84% (95% CI: 76.5% - 89.8%) (Table 2.4.4.1). The observed rates in the age group were comparable with Prevnar, the comparator vaccine.

2a. Among subjects from 1 to 18 years of age, the solicited AE rates through Day 56 were 45.8% (95% CI: 42.2% - 49.5%) in the IC51 0.25 mL group, 33.9% (95% CI: 29.9% - 38.1%) in the IC51 0.5 mL group, and 29.4% (95% CI: 25.0% - 34.2%) in the HAVRIX control group (Table 2.4.4.2). The results, when further examined in age subgroups, implied significant excess of solicited AE occurrences in the IC51 vaccinees compared to HAVRIX in the age subgroups of 1-3 years and 3-12 years (Table 2.4.4.3). But the overall solicited AE rates post-dose 1 appeared comparable between IC51 (32.0%, 95% CI: 29.4%, 34.6%) and HAVRIX (29.4%, 95% CI: 25.0%, 34.2%) (Clinical Study Report, Final v2.0, 13 Nov 2013, Table 14.3.4.1, page 3301 of 7569). The observed excess appears in the context of the IC51 vaccinees administered 2 injections compared to 1 injection for HAVRIX - as of Day 56 after first vaccination. The study did not explore to what extent the excess might be associated with the differential exposure resulting from the difference in the number of administered injections between the two treatment groups.

2b. In the same broader age group of 1-18 year-olds, serious or medically-attended AEs occurred with rates 24.1% (95% CI: 21.0% - 27.3%) in the IC51 0.25 mL group, 5.2% (95% CI: 3.5% - 7.4%) in the IC51 0.5 mL group, and 14.2% (95% CI: 10.9% - 18.1%) in the HAVRIX group. The apparent differences in serious or medically-attended AE rates across treatment groups were not significant when the rates were compared within individual age subgroups (Table 2.4.4.6).

3. Most AEs reported were mild, and both local and systemic AEs within 7 days of the first vaccination were comparable between IC51 and its control group of Prvenar or HAVRIX (Table 2.4.4.7, Table 2.4.4.8, Table 2.4.4.9).

4. The occurrence of AEs on or prior to Day 56 among children from 2 months to 1 year of age did not show significant association with pre-existing JEV status (OR=0.63; 95% CI: 0.15, 2.71) and pre-existing DENV status (OR=1.59; 95% CI: 0.46, 5.51), in logistic regression analyses (Table 2.4.4.10) after adjusting for the age and treatment effects. However, after similar adjustment, pre-existing immunity to DENV among the 1-18 year-old subjects was significantly associated with decreased AE occurrence at Day 56 (OR=0.61, 95% CI: 0.47, 0.79).

5. In conclusion, among children from 2 months to 1 year of age, the general safety profile through Day 56 in the IC51 0.25 mL dose group was comparable with that of Prevnar. In children 1-18 years of age, serious or medically attended AE rates between study groups were comparable, within age subgroups. But for solicited AEs, significant excess in AE occurrences in the IC51 vaccinees compared to HAVRIX was observed in age subgroups of 1-3 and 3-12 year-olds. Both IC51 dose groups had comparable, general safety profiles.

2.4.7 Immunogenicity.

Immunogenicity was studied in a randomly selected (*ref*. section 2.3, point 2 for details) subset of 495 subjects, and the dataset contained titer information at baseline, Day 56, and Month 7. The seroconversion rate (SCR) was the proportion of subjects who met the seroconversion criterion (i.e., PRNT50 titer ≥ 1:10). The geometric mean titers (GMTs) and their 95% CIs were calculated using log10-transformed titers. The ITT subjects comprised the primary analyses for immunogenicity assessment. Results from the PP population were stated to be similar (Clinical Study Report, Final v2.0, 13 Nov 2013, page 91 of 221). The vaccination with IC51, comprising 2 doses of either 0.25 mL or 0.5 mL, given approximately 28 days apart appeared to have produced a robust immune response at Day 56 in the majority of subjects. Descriptive results are provided in Table 2.4.7.1.

Table 2.4.7.1: Seroconversion and GMTs by Treatment Group, Stratified by Age Groups, ITT Population

	IC51 0.25 ml 2m to < 1yr	IC51 0.25 ml 1 to <3 yrs	IC51 0.25 ml 3 to <12 yrs	IC51 0.5 ml 3 to <12 yrs	IC51 0.5 ml 12 to 18 yrs
Baseline†					
Seroconversion					
N	30	124	100	101	140
n (%)	3 (10.0)	4 (3.2)	12 (12.0)	17 (16.8)	64 (45.7)
95% CI	[2.1, 26.5]	[0.9, 8.0]	[6.4, 20.0]	[10.1, 25.6]	[37.3, 54.3]
GMTs					
N	30	124	100	101	140
Geom mean	5.9	5.5	6.1	6.5	13.1
95% CI	[4.8, 7.4]	[5.0, 6.1]	[5.4, 6.8]	[5.7, 7.4]	[10.7, 16.0]
Day 56 (Visit3)‡					
Seroconversion					
N	28	120	98	100	137
n (%)	28 (100.0)	119 (99.2)	94 (95.9)	100 (100.0)	137 (100.0)
95% CI	[87.9, 100.0]	[95.4, 99.9]	[90.0, 98.4]	[96.3, 100.0]	[97.3, 100.0]
GMTs					
N	28	121	98	100	137
Geom mean	457.9	258.9	113.9	213.7	175.6
95% CI	[283.5, 739.6]	[214.4, 312.6]	[89.9, 144.3]	[175.6, 260.0]	[147.8, 208.7]
Month 7 (Visit 4)‡					
Seroconversion					
N	28	124	96	100	137
n (%)	28 (100.0)	106 (85.5)	74 (77.1)	91 (91.0)	133 (97.1)
95% CI	[87.9, 100]	[78.2, 90.6]	[67.7, 84.4]	[83.8, 95.2]	[92.7, 98.9]
GMTs					
N	28	125	96	100	137
Geom mean	88.6	38.9	28.8	43.6	86.6
95% CI	[61.5, 127.8]	[31.8, 47.7]	[22.6, 36.5]	[35.6, 53.4]	[70.7, 106.0]

† Reviewer's calculations based on applicant's data, study IC51-323., ‡Adapted from Table 11.5 Clinical Study Report , IC51-323, Final v2.0, 13 Nov 2012, page 89/221.

2.4.7.1 Seroconversion Rates and Geometric Mean Titers by age Groups.

As Table 2.4.7.1 shows (2nd panel), in the IC51 0.25 mL group and in subjects aged ≥ 2 months to < 1 year, 100% (95% CI: 87.9% - 100%) of N=28 subjects seroconverted and had a GMT of 457.9 (283.5 - 739.6) at Day 56. In the same treatment group, those who were aged ≥ 1 year to < 3 years had a seroconversion rate of 99.2% (95% CI: 95.4% - 99.9%) and GMT of 258.9 (95% CI: 214.4 - 312.6), and those who were aged ≥ 3 years to < 12 years had a seroconversion rate of 95.9% (95% CI: 90.0% - 98.4%) and GMT of 113.9 (95% CI: 89.9 - 144.3). In the IC51 0.5 mL group, these seroconversion rate and GMT figures were, respectively, 100.0% (95% CI: 96.3% - 100.0%) and 213.7 (95% CI: 175.6 - 260.0) in age ≥ 3 years to <12 years, and 100.0% (95% CI: 97.3% - 100.0%) and 175.6 (95% CI: 147.8 – 208.7) in age ≥ 3 years to <12 years. It appears that, at Day 56, the SCR from either dose of IC51 was robust regardless of the age group, but the higher dose could have led to a higher level of response. Also, in both doses, the GMT showed a tendency to decline with age, but with level still remaining higher with the higher dose.

At Month 7 of the study visit, in the IC51 0.25 mL group and in subjects aged ≥ 2 months to < 1 year, the seroconversion rate persisted at 100% (95% CI: 87.9% - 100.0%) and GMT was 88.6 (95% CI: 61.5 - 127.8). In the same treatment group, the subjects ≥ 1 year to < 3 years of age had a seroconversion rate of 85.5% (95% CI: 78.2% - 90.6%) and GMT of 38.9 (95% CI: 31.8 – 47.7), and the subjects ≥ 3 year to < 12 years of age had a seroconversion rate of 77.1% (95% CI: 67.7% - 84.4%) and GMT of 28.8 (95% CI: 22.6 – 36.5). At the same visit of Month 7, those who received the IC51 0.5 mL dose and were ≥ 3 years to < 12 years old had a seroconverison rate of 91.0% (95% CI: 83.8% - 95.2%) and GMT of 43.6 (95% CI: 35.6 - 53.4), and those who were ≥ 12 years to < 18 years old had respective immunogenicity measures of 97.1% (95% CI: 92.7 – 98.9%) and 86.6 (95% CI: 70.7 - 106.0).

Overall, the selected IC51 doses induced robust immune responses in the selected age groups at Day 56, but at Month 7 the results indicated that the responses were attenuated.

Additionally, among subjects ≥ 3 years to < 12 years of age, those who received the IC51 dose 0.5 mL displayed higher immune responses compared to those who received the lower dose IC51 0.25 mL (ref. Table 2.4.7.1), column 4 vs column 5, 2nd & 3rd panel), at both time points of Day 56 and Month 7.

2.4.7.2 Immunogenicity by Pre-Existing JEV and DENV Antibodies.

A summary of the SCRs and GMTs stratified by pre-existing JEV immunity is provided in Table 2.4.7.2. Table 2.4.7.3 provides this summary when stratification was based on pre-existing DENV antibodies.

Table 2.4.7.2: Seroconversion and Geometric Mean Titers by Treatment Group, stratified by Pre-existing JEV Immunity, ITT Population.

	IC51 0.25 ml Seropositive at baseline	IC51 0.25 ml Seronegative at baseline	IC51 0.5 ml Seropositive at baseline	IC51 0.5 ml Seronegative at baseline
Day 56 (Visit 3)				
Seroconversion				
N	17	229	79	158
n (%)	17 (100.0)	224 (97.8)	79 (100.0)	158 (100.0)
95% CI	[81.6, 100.0]	[95.0, 99.1]	[95.4, 100.0]	[97.6, 100.0]
GMTs				
Geom mean	201.2	200.9	168.0	203.3
95% CI	[102.5, 394.7]	[171.5,235.2]	[133.0, 212.3]	[173.9, 237.5]
Month 7 (Visit 4)				
Seroconversion				
N	18	230	79	158
n (%)	18 (100.0)	190 (82.6)	78 (98.7)	146 (92.4)
95% CI	[82.4, 100.0]	[77.2, 87.0]	[93.2, 99.8]	[87.2, 95.6]
GMTs				
Geom mean	77.1	36.3	97.9	52.8
95% CI	[54.1, 109.9]	[31.1, 42.3]	[75.6, 126.9]	[44.1, 63.0]

Adapted from Table 11.7, Clinical Study Report , IC51-323, Final v2.0, 13 Nov 2012,, page 93 of 221.

From Table 2.4.7.2 (1st panel), with the seroconversion rate exceeding 95% and with GMTs ranging from 168.0 to 203.3, robust immune responses for both doses of the IC51 vaccine were evidenced at Day 56, regardless of the vaccinees' JEV sero-status at baseline. This suggests that immune responses at Day 56 due to the IC51 doses were not influenced by pre-existing JEV sero-status.

At Month 7 (Table 2.4.7.2, 2nd panel), the SCRs with the IC51 doses of 0.25 mL and 0.5 mL were, respectively, 100% (95% CI: 82.4% - 100%) and 98.7% (95% CI: 93.2% - 99.8%) among the JEV seropositve subjects at baseline. Among those who were JEV seronegative at baseline, these SCRs in the respective dose groups were 82.6% (95% CI: 77.2% - 87.0%) and 92.4% (95% CI: 87.2% - 95.6%).

Additionally, at Month 7, the GMTs generally were reduced from the Day 56 levels, in both IC51 dose groups. Yet, the baseline seropositive subjects maintained, on average, >1-fold increase in titers compared to the seronegative subjects. These fold-increases were 2.04 (95% CI: 1.16 - 3.58) in the IC51 0.25 mL group and 1.59 (95% CI: 1.16 - 2.18) in the IC51 0.5 mL group, after adjusting for the center and baseline titer effects in an analysis of covariance performed by the applicant (ref. Table 11.8, page 95 of 221, Clinical Study Report, Final v2.0, 13 Nov 2012). The results indicate some considerable persistence of antibodies in baseline seropositive subjects compared to baseline seronegative subjects, at Month 7.

As for pre-existing JEV, the SCR at Day 56 with either a 0.25 mL or 0.5 mL dose of IC51 remained high, exceeding 95%, regardless of the DENV sero-status at baseline (Table 2.4.7.3, 1st panel). But the GMT level seemed suppressed with the baseline DENV seropositivity, in either dose of the vaccinees IC51. Based on the applicant's similar covariance analysis as above, and after adjusting for the center and baseline titer effects, the IC51 0.25 mL titer ratio in subjects with pre-existing DENV was 0.43-fold lower (95% CI: 0.31-0.59) compared to those who were

Table 2.4.7.3: Seroconversion and Geometric Mean Titers by Treatment Group, Stratified by Pre-existing Dengue Fever Virus Immunity, ITT Population.

	IC51 0.25 ml Seropositive at baseline	IC51 0.25 ml Seronegative at baseline	IC51 0.5 ml Seropositive at baseline	IC51 0.5 ml Seronegative at baseline
Day 56 (Visit 3)				
Seroconversion				
N	72	167	153	81
n (%)	69 (95.8)	165 (98.8)	153(100.0)	81(100.0)
95% CI	[88.5, 98.6]	[95.7, 99.7]	[97.6, 100.0]	[95.5, 100.0]
GMTs				
Geom mean	106.3	263.3	154.4	285.6
95% CI	[80.0, 141.2]	[222.0, 312.3]	[132.2, 180.3]	[229.9, 354.8]
Month 7 (Visit 4)				
Seroconversion				
N	72	169	153	81
n (%)	62 (86.1)	139 (82.2)	148 (96.7)	73 (90.1)
95% CI	[76.3, 92.3]	[75.8, 87.3]	[92.6, 98.6]	[81.7, 94.9]
GMTs				
Geom mean	41.4	36.9	68.8	57.9
95% CI	[31.3, 54.6]	[30.8, 44.2]	[57.2, 82.7]	[44.3. 75.9]

Adapted from Table 11.9, Clinical Study Report , IC51-323, Final v2.0, 13 Nov 2012, page 96/221.

without pre-existing DENV, at Day 56. The ratio was 0.49-fold lower (95% CI: 0.38-0.65) for the IC51 0.5 mL titer at the same visit of Day56 (ref. Table 11.10, page 98 of 221, Clinical Study Report, Final v2.0, 13 Nov 2012). The results indicate greater immune response in subjects with baseline DENV seronegativity compared to those who were DENV seropositive at baseline. No such change was observed at Month 7, but the SCR was above 80% regardless of the pre-existing DENV status and doses of IC51 received.

Overall, the pre-existing JEV antibodies did not seem to have differential effect on IC51 immune response at Day 56, but at Month 7, it was associated with better persistence of the vaccine's antibodies compared to absence of such pre-existing JEV antibodies. However, pre-existing DNV antibodies were associated with lower GMTs at Day 56, but the effect leveled off at Month 7.

2.4.7.3 Immunogenicity Summary.

The immunogenicity analyses were the secondary objectives. The analyses based on the data from the immunogenicity subset indicated the following:

1. The IC51 vaccine induced, at Day 56, protective antibody titers in an overall proportion of 99.0% of children aged 2 months to 18 years who received age-appropriate IC51 doses. At Month 7, however, the proportion protected seemed to have reduced, with the largest reduction being from 95.9% (at Day 56) to 77.1% (at Month 7) among the IC51 0.25 mL vaccinees from 3 to 12 years of age (Table 2.4.7.1).

2. The GMTs declined, overall, with children's age. The GMT was highest at 457.9 among the youngest children on Day 56, but declined to 88.6 at Month 7. Such reductions were present in other age/dose groups as well (Table 2.4.7.1).

3. Among children aged 3-12 years, the IC51 0.5 mL dose induced higher immune response compared to the lower 0.25 mL dose, both at Day 56 and Month 7. This, coupled with the comparable safety profiles between doses, supports appropriateness of the 0.5 mL dose (Table 2.4.7.1) for further pediatric program development.

4. Pre-existing JEV antibodies did not appear to have influenced the immune response at Day 56, but they were associated with better persistence of the vaccine's antibodies at Month 7, and this was so despite an overall decline in GMTs at Month 7 (Table 2.4.7.2). In contrast, the pre-existing DNV seropositive children had substantively lower GMT compared to the pre-existing DNV seronegative group at Day 56, but the effect, by and large, leveled off at Month 7 (Table 2.4.7.3).

2.5 Study Conclusions.

2.5.1 Safety.

The primary objective of the study was to assess safety of the IC51 vaccine through Day 56 after the first vaccination. The study supports that, among children 2 months to 1 year of age, the general safety profile through Day 56 in the IC51 0.25 mL dose group was comparable with Prevnar. In children 1-18 yearsold , serious or medically attended AE rates across the study's treatment groups were comparable, within age subgroups. But for solicited AEs, despite comparable AE rates post-dose 1, significant excess in solicited AE rates through Day 56 in the IC51 vaccinees compared to HAVRIX was observed in the age subgroups of 1-3 years and 3-12 years. This excess is in the context where the vaccinees in the HAVRIX, Prevnar and IC51 groups, respectively, had 1, 2, and 2 injections contributing to the safety data at Day 56 following the first injection in each group. Also, both of the IC51 dose groups had comparable, general safety profiles. The majority of AEs were mild, and no death related to treatment vaccine was reported.

2.5.2 Immunogencicity.

The immunogenicity analyses were the secondary objectives. Based on the study's immunogenicity subset of subjects, the study supports that the IC51 vaccine in both doses was highly immunogenic and induced protective antibody titers in the overwhelming majority of subjects, particularly at Day 56 from first vaccination. At Month 7, however, immune responses seemed to have attenuated, with the greatest magnitude of decline being among the IC51 0.25 mL vaccinees aged 3 to 12 years, where the seroconversion rate dropped from 95.9% at Day 56 to 77.1% at Month 7.

Among children aged 3-12 years, the IC51 0.5 mL dose induced higher immune response compared to the lower 0.25 mL dose, at both Day 56 and Month 7. This result along with the comparable safety profiles of these doses supports appropriateness of the 0.5 mL dose for further pediatric program development.

Pre-existing JEV antibodies did not appear to be associated with immune response at Day 56, but they appear to have been associated with better persistence of the vaccine's antibodies at Month 7. In contrast, in the pre-existing DNV seropositive children, the GMT at Day 56 was substantively lower compared to the pre-existing DNV seronegative group, but the effect leveled off at Month 7.

3. STUDIES IC51-221 & IC51-322

3.1 Background and Designs.

Study IC51-221 was a single-site, open-label, randomized, active-controlled, Phase-II study conducted in a JE endemic region: Bangalore, India. The study assessed for its primary objective the immunogenicity at Day 56 following the first of two IXIARO vaccinations 28 days apart. The IC51 vaccination was in one of two doses, 0.25 mL and 0.5 mL. The comparator vaccine was the locally available JenceVac^{TM} vaccine administered on the schedule of Day 0/7/28. The study was based on a total of 60 children aged 1 to 3 years and had the mean ± SD age of 2 ± 0.6 years for children.

Study IC51-322 was an uncontrolled, open label study in a non-endemic population, with the same primary objective of assessing the IC51 vaccine's immunogenicity at Day 56 following the first of two vaccinations given on Day 0/28 in children aged 2 months to 18 years in the U.S., Europe, and Australia. This study had slower recruitment than expected, was continuing as of the BLA submission, but submitted per guidance from CBER the interim data from 60 subjects out of 100 planned. The subjects had an average age of 12.5 years, were mostly Caucasian (83.3%), and females (56.7%).

3.2 Results.

Immunogenicity. The primary endpoint results on immunogenicity from the two studies are summarized in **Table 3.2**.

Table 3.2: Summary of Immunogenicity Results at Day 56 from IC51-221 and IC51-322 studies, ITT Populations

	IC51-221[@] 1 yr - < 3 yrs, IXIARO 0.25 mL [1]	**IC51-221[@] 1 yr - < 3 yrs, IXIARO 0.5 mL [2]**	**IC51-322[*] 3 yrs - < 12 yrs, IXIARO 0.5 mL**	**IC51-322[*] 12 yrs - < 18 yrs, IXIARO 0.5 mL**
Seroconversion				
N	24	24	11	35
n (%)	23 (95.8)	23 (95.8)	11(100.0)	35 (100.0)
95% CI	[78.9, 99.9]	[78.9, 99.9]	[71.5, 100.0]	[90.0, 100.0]
GMTs				
Geom mean	208.8	216.0	498.8	292.3
95% CI	[113.0, 385.9]	[129.3, 361.1]	[201.8, 1232.8]	[225.7, 378.4]

[1]0.25 mL vaccine containing 3 mcg per dose, [2]0.5 mL vaccine containing 6 mcg per dose (adult dose)
Source. [@] Inactivated JE Vaccine Phase-II (IC51-221) Report, pages 74,79. [*] Table 5, Clinical Overview, page 19-20 of 33,

In Study IC51-221, conducted in an endemic population, the SCR and GMT were, respectively, 95.8% (95% CI: 78.9% - 99.9%) and 208.8 (95% CI: 113.0, 385.9) with the IXIARO 0.25 mL

dose in the age group 1-3 years. In the same age group, and with higher dose IXIARO 0.5 mL, the SCR and GMT were, respectively, 95.8% (95% CI: 78.9% - 99.9%) and 216.0 (95% CI: 129.3, 361.1).

The Study IC51-322 provides immunogenicity results for fewer subjects from a non-endemic population, but still reflects high levels of antibody response at Day 56, as evidenced from Table 3.2 above (last two columns).

Based on the results above, studies IC51-221 and IC51-322 provide additional evidence, albeit with limited sample size and incompletion of study, that the IC51 vaccine is highly immunogenic in the enrolled pediatric population.

Safety.
The safety objectives were addressed by the secondary analyses in both studies. In IC51-221, 8 subjects of a total of 48 (16.7%, 95% CI: 7.5% - 30.2%) receiving either 0.25 mL or 0.5 mL dose of IXIARO had adverse events, in comparison to 4/12 (33.3%, 95% CI: 9.9% - 65.1%) in the control vaccine group. Injection site tenderness was the most frequent adverse event reported and occurred to overall 13.3% subjects, with no significant rate differences between the 3 treatment groups (IXIARO 0.25 mL, IXIARO 0.5 mL, and JenceVac control) (ref. Table 2, Clinical Overview, page 9 of 33).

In IC51-322, 40 subjects (66.7%) had one or more AEs reported through Day 56 from the first vaccination. Most of the AEs were mild (60%). Serious or medically-attended AEs happened to 3 (5.0%) subjects. One SAE, type 1 diabetes mellitus, was potentially life-threatening. The applicant considered this unlikely to be related to treatment vaccine (ref. Clinical Overview, BLA Sequence 0137, page 23 of 33). Injection site pain (18.2%), injection site tenderness (30.9%), and muscle pain (27.3%) were the most frequent local or systemic AEs reported within 7 days of the first vaccination.

Demographic Subgroup Analysis for Safety.
This analysis was already performed for the pivotal IC51-323 study (Section 2.4.4.2b). The study IC51-221 being of phase-II (India) had only 60 subjects. The study IC51-322 which also has 60 planned subjects is still ongoing in Australia, U.S. and Europe. Given the limited sample size in each of these studies, the evaluation by demographic subgroups in study regions will be potentially of limited value and as such is not performed.

3.3 Summary And Conclusions.

1. Immunogencity assessment was the primary objective in studies IC51-221 and IC51-322, conducted in JE endemic (age group 3-12 years) and JE non-endemic regions (age group 2 months - 18 years), respectively. The data were of limited sample size and the study IC51-322 was ongoing at the time of the BLA submission because of slow recruitment.

2. Overall, the results showed that both IC51 doses of 0.25 mL and 0.5 mL were highly immunogenic, leading to protective (PRNT50 ≥ 1:10) antibody titers at Day 56 in respective age/dose groups.

3. The safety profiles of the doses raised no general safety concern.

4. OVERALL SUMMARY AND CONCLUSIONS

1. The assessment of safety experience by Day 56 following the first of two vaccinations of IC51 given to children > 2 months and < 18 years old was the primary objective of the study.

- Overall, the study supports that, among children 2 months to 1 year of age, the general safety profile through Day 56 in the IC51 0.25 mL dose group was comparable with the that of the Prevnar control group.

- In children 1-18 years old, the overall AE rates of IC51 were comparable to that of the HAVRIX control group. Serious or medically attended AE rates across the study's treatment groups were comparable, within age subgroups. For solicited AEs, despite comparable rates for AEs post-dose 1, significant excess in AE rates in the IC51 vaccinees compared to HAVRIX recipients occurred in the age subgroups of 1-3 years and 3-12 years. This should be interpreted in the context that the IC51 and HAVRIX vaccinees each had, respectively, 2 injections or 1 injection, when assessing the safety experience by Day 56.

2. Most AEs were mild in both IC51 dose groups. No death related to treatment vaccine was reported, and the overall rates for local or systemic reactions between the IC51 and control vaccines were comparable.

3. The IC51 vaccine in both doses of 0.25 mL and 0.5 mL was highly immunogenic, and was associated with protective (PRNT50 ≥ 1:10) antibody titers in the overwhelming majority (> 95.0%) of subjects, particularly at Day 56 from first vaccination. At Month 7, the immune responses appeared to be attenuated.

4. The IC51 0.5 mL dose induced higher immune response than the lower 0.25 mL dose, at both Day 56 and Month 7, for children in the 3-12 years age group. This finding suggests appropriateness of the IC51 0.5 mL dose for further pediatric program development.