13 December 2012
EMA/233708/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ixiaro

Common name: Japanese encephalitis vaccine (inactivated, adsorbed)

Procedure No.: EMEA/H/C/000963/II/0039/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II Group of variations

Pursuant to Article 7.2.(b) of Commission Regulation (EC) No 1234/2008, Intercell AG submitted to the European Medicines Agency on 14 June 2012 an application for a group of variations.

This application concerns the following medicinal product:

Medicinal product:	**Common name:**	**Presentations:**
Ixiaro	Japanese encephalitis vaccine (inactivated, adsorbed)	See Annex A

The following variations were requested in the group:

Variations requested		**Type**
B.II.e.6.a	B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information	IB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed the extension of indication of Ixiaro to the paediatric segment (2 months of age and older) in line with approved PIP EMEA -000559-PIP01-09-M03. Modification of syringe label to include "half dose mark" for administration of a 0.25 ml nominal dose for the paediatric sub-segment 2 months to below 3 years of age in line with the aforementioned PIP. This change is grouped with the indication extension as direct result of the proposed extension. The Package Leaflet and Labelling were proposed to be updated accordingly.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 8.2.

Rapporteur: Jan Mueller-Berghaus

1.2. Steps taken for the assessment

Submission date:	14 June 2012
Start of procedure:	22 July 2012
Rapporteur's preliminary assessment report circulated on:	17 September 2012
Rapporteur's updated assessment report circulated on:	13 October 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	18 October 2012
MAH's responses submitted to the CHMP on:	12 November 2012
Rapporteur's assessment report on the MAH's responses circulated on:	26 November 2012
CHMP opinion:	13 December 2012

Information on Paediatric requirements

The completed studies, development of marked pre-filled syringe and study IC51-323, are considered compliant with the Agency's Decision P/0249/2011) of 25 October 2011.

This partially completed compliance procedure confirmed the compliance of all those studies contained in the agreed paediatric investigation plan that were to be completed by this date.

2. Scientific discussion

2.1. Introduction

IXIARO is licensed in the EU since 31 March 2009. The clinical development program to support licensure of IXIARO in adults consisted of 9 studies in which approx. 4,700 subjects were enrolled and vaccinated. Currently Ixiaro is indicated for active immunization against Japanese encephalitis in adults from 18 years onwards.

JE disease is a potentially debilitating or fatal disease for which there is currently no drug treatment available. Children are the most vulnerable population for JE. The mortality rates can go as high as 30% of symptomatic cases and around 50% of those who survive have permanent neurological sequale. IXIARO is currently indicated only for 18 years and above, hence there is a need for a safe and immunogenic vaccine in this vulnerable population (<18 years).

Intercell received Protocol assistance on the Paediatric Investigational Plan (PIP) of Ixiaro in September 2007 (EMEA/CHMP/SAWP/414690/2007). The PIP received initial PDCO opinion and EMA decision in January 2010. The PDCO has favourably completed the interim compliance check on 16 May 2012 for IXIARO versus the currently effective PIP (EMEA-000559-PIP01-09-M03).

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

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

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

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

2.2. Quality aspects

The vaccine is supplied as a pre-filled syringe containing a 0.5ml single dose. For children aged 2 months to less than 3 years a 0.25ml dose is recommended. As agreed in the approved PIP no separate pharmaceutical development has been initiated but half the dose of the syringe filled with 0.5ml is used without any alteration to the primary container and filled volume. This half dose is applied by means of a printed line and an arrow on the syringe label, the "Half Dose Mark" (HDM).

The approach was justified by the number of doses marketed. Ixiaro is indicated for active immunisation against Japanese encephalitis (JE), which is not endemic in Europe and therefore vaccination is restricted to subjects travelling to endemic regions or laboratory workers at risk of exposure to JEV. The overall maximum number of estimated doses for the overall paediatric population is far less than one single manufacturing lot, and the anticipated number of doses to be used in the age range of 2 months to <3 years, where the half-dose has to be administered, is therefore estimated to be extremely small. This is also confirmed by the enrolment rate in the ongoing paediatric studies conducted in non-endemic countries (including EU) which was very low (only 59 children enrolled after 21 months). The number of children in the age group over 2 months to less than 3 years is even more limited.

A number of options for administration of the 0.25ml dose to children <3 years of age were investigated. The most appropriate option identified was the application of a 0.25ml mark on the 0.5ml syringe label (adult dose). The "half dose mark" (HDM) constitutes a red printed line and an arrow on the syringe label. Details on the label are given in figure 1 and figure 2. No other modifications to the label have been introduced.

Figure 1: Proposed label with Half Dose Mark (EU label)

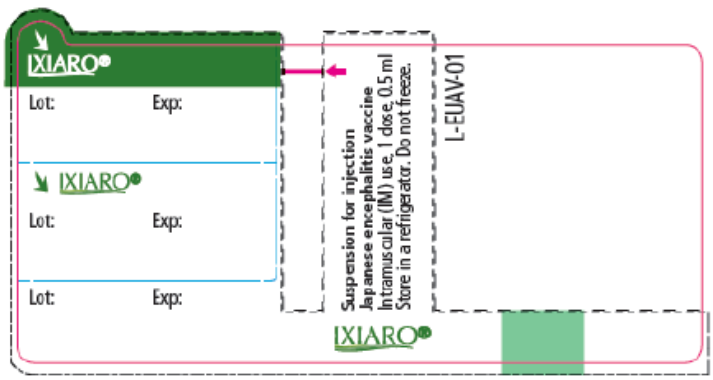


Figure 2: Photograph of syringe with proposed 0.25 ml mark on label

If a 0.25 ml dose is to be administered, 0.25ml of the 0.5ml vaccine content in the syringe is expelled and discarded. This is done by holding the syringe in an upright position and manually expressing the syringe plunger until the plunger tip is aligned with the half dose mark indicated on the syringe label. The remaining volume of vaccine in the syringe can then be administered.

Calculation of target extractable volume for half dose

To assure that the minimum half-dose (0.25 ml) will be achieved, considering the theoretical "worst case" tolerance during labelling operation (based on equipment capability), a target extractable volume of 0.34 ml was calculated.

Exploratory trial runs

Test runs were performed. The labelling was performed in accordance with the normal commercial labelling process with the exception that the labels used included the HDM and that labelling was performed with pre-filled syringes containing a placebo solution. Labelling was initially performed at three target positions: 9mm, 10mm and 11mm. A fourth label position (9.5mm) was added following review of the initial data. For all four label positions a good correlation of label position and extractable volume was demonstrated. The 9.5mm label position provided an extractable volume for the paediatric dosage in line with the 0.34ml target and therefore was chosen as the basis for the position of the HDM.

Qualification (Validation) runs

Intercell performed Qualification studies on the two labeling machines currently used for commercial routine labeling.

It was demonstrated that both labeling machines consistently applied the label within the specified range on to the syringe barrel. This was checked by 100% visual inspection with the IPC gauge. In total, 5,452 syringes were tested and passed the acceptance criterion on both machines.

Paediatric extractable volume results were obtained from 300 syringes on both labeling machines. All of the syringes tested, resulted in extractable volumes of ≥0.25 ml (range 0.28 ml – 0.39 ml).

Implementation of an in-process control for the Half Dose Mark Label Position for Paediatric Dose

The Half Dose Mark label position is checked during the labeling operation using a specially designed In-process control gauge (IPC gauge). A pre-defined range on the IPC gauge allows direct assessment of the correct position of the HDM line relative to the syringe. The IPC gauge is being used in the Qualification labelling runs (done with Placebo filled syringes). The exact number of labelled syringes and sampling time points used for HDM in-process control checks for the commercial labelling process were determined following completion of the qualification runs.

IPC and acceptance criteria for the half-dose labeling were acceptably defined.

Conclusions on the chemical, pharmaceutical and biological aspects

As agreed in the approved PIP no separate pharmaceutical development has been initiated but half the dose of the syringe filled with 0.5ml is used without any alteration to the primary container and filled volume. This half dose is applied by means of a printed line and an arrow on the syringe label, the 'Half Dose Mark'. The exact position of the HDM on the label was defined in an exploratory study. Results of the extractable volume demonstrate that the 9.5mm label position of the HDM ensures that at least 0.25ml remains in the syringe.

Currently qualification and validation studies are performed to verify the results of the exploratory study. Qualification data on the labeling of syringes using two different labeling machines demonstrate that positioning of the HDM label ensures that a minimum volume of at least 0.25ml remains in the syringe after expelling excess vaccine. Labeling by the two machines used (manually and automatic) is comparable.

IPC and acceptance criteria for the half-dose labeling were acceptably defined. The data provided show that during routine production the half dose labeling is satisfactorily performed and controlled. The MAH is committed to inform about any unexpected results and negative trends observed in the validation runs.

The variation is in line with the approved PIP which contains the binding requirement "Development of a marked pre-filled syringe allowing accurate administration of a half dose".

2.3. Immunogenicity /Clinical efficacy aspects

2.3.1. Methods – analysis of data submitted / results

Three clinical trials conducted in children were submitted to support approval of the paediatric indication of Ixiaro, two studies were performed in endemic regions (IC51-221 and IC51-323) and one study is currently conducted in non-endemic countries (IC51-322). The study in non-endemic countries is still ongoing but an interim report was provided.

Evaluation of Ixiaro in children in endemic countries

IC51-221 was an open label phase II trial conducted in a single centre in India to evaluate immunogenicity and safety of two doses of Ixiaro in comparison to another JE-vaccine JenceVac. The study was performed from July 2007 to October 2007.

In study IC51-221 a total of 60 healthy children in the age group ≥ 1 to < 3 years were enrolled and were randomized in a 2:2:1 allocation ratio. Group I (n=24) received two doses of 3 µg (0.25 ml) Ixiaro, group II (n=24) received two doses of 6 µg (0.5 ml) Ixiaro and group III (n=12) received three doses of 0.5 ml JenceVac manufactured by Korean Green Cross Vaccine Corporation, Korea. IXIARO was administered at day 0 and 28, while JenceVac, an inactivated mouse-brain derived vaccine, was administered at day 0, 7 and 28. Primary endpoint was seroconversion rates measured as neutralising antibodies against the IXIARO vaccine strain SA 14-14-2. Seroconversion was defined as a titre of ≥ 1:10, while zero titres are designated the value of 5 for calculations. Secondary endpoints were GMT values and adverse events.

Out of the 60 subjects enrolled there were more male (61.7%) than female subjects (38.3%). At baseline 1 subject each in group I and II and none in the JenceVac group (group III) were seropositive for JEV.

The primary analysis of immunogenicity at day 56 showed seroconversion rates (SCR) of 95.8% in the IC51– 3 µg dose group, 95.8% in the IC51– 6 µg dose group and 91.7% in the JenceVac group. There were no significant differences in SCRs at day 56 between the groups (Table 1).

Table 1: Comparison of SCRs in children aged ≥ 1 to < 3 years (ITT set)

	IXIARO 3 µg (n=24)	IXIARO 6 µg (n=24)	JenceVac (n=12)
Screening	4.2%	4.2%	0%
Day 28	62.5%	62.5%	66.7%
Day 56	95.8%	95.8%	91.7%

The GMT values were in the range of 200-250 for all groups at day 56, which was comparable to the antibody levels found in clinical studies in adults in non-endemic countries (Table 2).

Table 2: Comparison of GMTs as measured by PRNT50 assay in children aged ≥ 1 to < 3 years (ITT set)

	IXIARO 3 µg (n=24)	IXIARO 6 µg (n=24)	JenceVac (n=12)
Screening	5.3	5.2	5
Day 28	23.5	21.1	25.9
Day 56	208.8	216	238.4

A total of 13 adverse events were recorded for all three vaccination groups, most of them were injection site tenderness. A total of 2 subjects (1 subject (4.2%) from IC51-6µg dose group and 1 subject (8.3%) from JenceVac group) had fever post vaccination. All AEs were mild in severity, and no unexpected reactions were observed. There were no clinically significant changes in the laboratory parameters in all the groups. No serious adverse events were reported during the study.

IC51-323 was an open-label, randomized, active-controlled Phase III study to assess the safety of Ixiaro (IC51) in children aged ≥ 2 months to < 18 years, compared to Havrix 720 and to Prevnar, and to establish the immunogenicity of Ixiaro and the appropriate dose (0.25ml or 0.5ml) in children aged ≥ 3 to <12 years.

The study was conducted in three centres in the Philippines from March 2010 to July 2011. Study IC51-323 was initially planned to be performed in centres located in the Philippines and Malaysia, but conduct of the study in Malaysia was not initiated as the request of the national authorities to use another inactivated JEV vaccine as comparator was not feasible for the sponsor.

No JEV vaccine is currently licensed in the Philippines. Justification for not using another inactivated JEV vaccine as comparator in study IC51-323 was provided and the current study design was agreed in discussions of the MAH with PDCO and FDA.

Study objectives

The primary objective was to assess the systemic and local safety profile of Ixiaro (IC51), administered in 2 doses in a 28-day interval, up to Month 7 after the first IC51 vaccination.

Secondary objectives were defined as follows

- To assess the immunogenicity of Ixiaro in terms of GMTs and SCRs at Day 56
- To establish the appropriate dose (0.25 ml or 0.5 ml) for subjects aged ≥ 3 to < 12 years.
- To assess age-dependent differences in the immunogenicity and safety profile of Ixiaro.
- To assess differences in the safety and immunogenicity profile in subjects with no baseline immunity and subjects with pre-existing immunity against JEV and dengue virus (DENV).

Children and adolescents of good general health were to be enrolled in the study provided they met the following eligibility criteria.

- Healthy children and adolescents aged ≥ 2 months to < 18 years at the time of first vaccination.
- Written informed consent provided by the subject's legal representative(s), according to local requirements, and written informed assent of the subject, if applicable.
- Female subjects with either no childbearing potential or, if after onset of menarche, a negative pregnancy test and a willingness to practice a reliable method of contraception.
- Subjects must not have been vaccinated against JEV, yellow fever, West Nile virus or DENV at any time before the study.

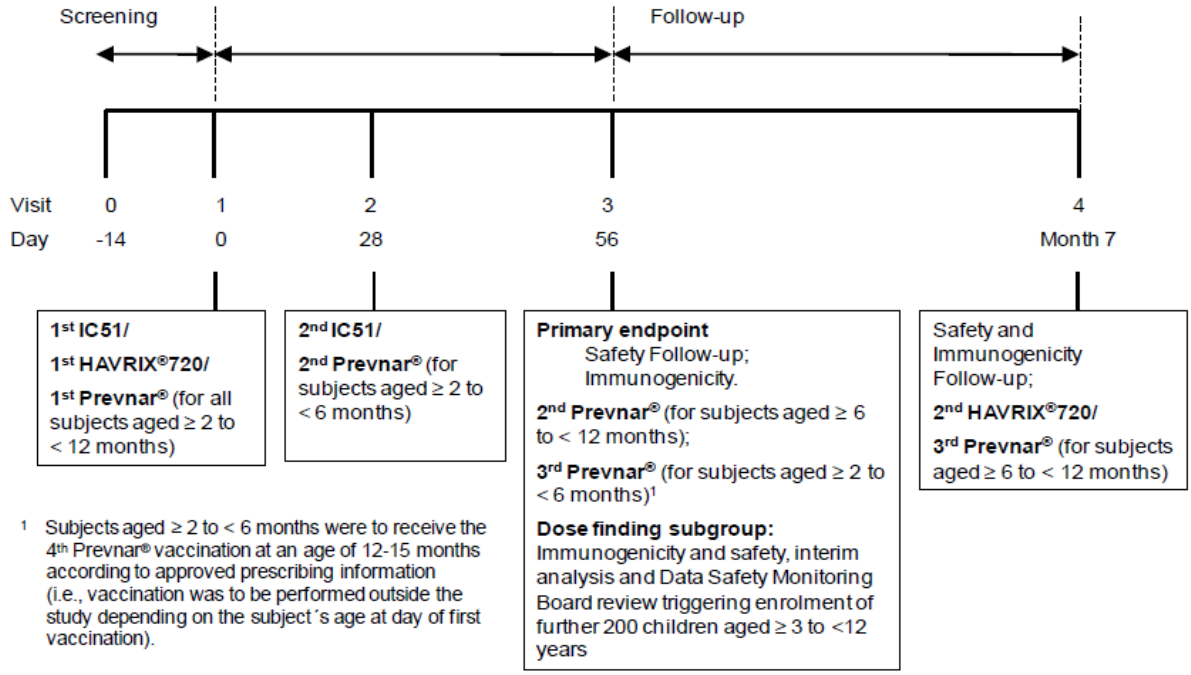
Subjects were randomized as follows:

- Subjects aged ≥ 2 months to < 1 year (195 subjects planned, with at least 45 subjects aged less than 6 months) in a 2:1 ratio to receive IC51 (0.25 ml) or Prevnar (0.5 ml).
- Subjects aged ≥ 1 year to < 3 years (852 subjects planned) and ≥ 12 to < 18 years (320 subjects planned) in a 3:1 ratio to receive IC51 (0.25 ml if < 3 years and 0.5 ml if ≥ 12 years) or Havrix 720 (0.5 ml).

- For subjects aged ≥ 3 to < 12 years, a dose-finding run-in phase was to be performed involving a planned 200 subjects), in parallel to recruitment and study conduct for the other age groups. Subjects were to be randomized 1:1 to receive IC51 at a dose of either 0.25 ml or 0.5 ml, and the appropriate dose was to be determined based on an interim analysis providing Day 56 (Visit 3) safety and immunogenicity results. Immunogenicity data for children with and without pre-existing JEV neutralizing antibodies in this group were to be analyzed, and a Data Safety Monitoring Board (DSMB) was to review the safety data and recommend whether 1 of the 2 doses was deemed more appropriate based on the safety profile. After this run-in phase, 300 further children in this age group were to be randomized 2:1 to receive either the appropriate IC51 dose or Havrix 720.

The study design is summarized in Figure 3.

Figure 3: Study design



Criteria of evaluation

The primary endpoint of the study was the rate of subjects with serious adverse events (SAEs) and medically-attended AEs until Day 56 after the first vaccination.

Secondary endpoints were:

- GMTs for JEV neutralizing antibodies measured using a validated plaque reduction neutralization test (PRNT) and SCR as defined by percentage of subjects with PRNT50 titers of ≥ 1:10 at Days 0 and 56 and at Month 7.
- Rate of subjects with SAEs and medically-attended AEs up to Month 7 after the first vaccination.
- Rate of subjects with solicited local and systemic AEs assessed with a subject diary for 7 consecutive days after each vaccination (except for Month 7).
- Rate of subjects with unsolicited AEs up to Day 56 and up to Month 7 after the first vaccination.

- Rate of subjects with abnormal laboratory parameters (hematology, biochemistry, urinalysis) up to Day 56 and up to Month 7 after the first vaccination.

Analytical tests used for immunogenicity assessment

To determine JEV neutralizing antibody titers and SCRs, blood samples were to be collected from all subjects at Day 0 and, for subjects in the immunogenicity subgroup, at Day 56 and Month 7 or early termination visit. Anti-JEV neutralizing antibodies were measured using an validated PRNT assay established by Intercell and conducted in the Quality Control Clinical Serology laboratories at Intercell Vienna.

To determine the presence of anti-DENV antibodies local laboratories at the study sites were responsible for analyzing these blood samples using the Panbio Dengue Immunoglobulin G (IgG) Indirect Enzyme-linked Immunosorbent Assay (ELISA) for the qualitative detection of IgG antibodies to dengue antigen serotypes (1, 2, 3 and 4).

Retesting of some samples became necessary as one local laboratory (affecting approx. 650 subjects at sites 103 and 104) used the wrong assay until May 2010. It was noted that not all samples could be retested as not enough serum was available for all samples.

Statistical analysis

Safety

Only treatment-emergent AEs (commencing after exposure to study vaccine) were included in the AE summaries. In all tabulations of AEs, the frequency of subjects experiencing a given AE or AEs from a given category, were compared between treatment groups using Fisher's exact test. An overall summary was produced by treatment group and stratified by age group. The summary was repeated stratified by pre existing JEV status, and also by pre-existing DENV status.

The incidence of serious and medically-attended AEs up to Day 56 was analyzed using a logistic regression model. Subjects were categorized Yes/No as to whether they had an SAE or medically-attended AE, age, pre - existing immunity against JEV and pre - existing immunity against DENV were fitted as categorical covariates. The odds ratios were presented with 95% CIs for each effect in the model.

Summaries of solicited local AEs (injection site reactions of pain, itching, tenderness, hardening, swelling, redness) and solicited systemic AEs (headache, muscle pain, flu-like symptoms, excessive fatigue, rash, fever, nausea, vomiting, diarrhea, irritability, loss of appetite) up to and including Day 6 after each vaccination were presented by treatment group and stratified by age group. Percentages were based upon subjects who were assessable.

Immunogenicity

The number and percentage of subjects achieving a PRNT50 ≥ 10 at Day 0, Day 56 and Month 7 were tabulated for each IC51 treatment group along with the 95% two-sided confidence interval (CI) for the percentages.

The number and percentage of subjects with each of 4- and 10-fold increases in PRNT50 titers at Visit 3 (Day 56) and Visit 4 (Month 7) were tabulated for each IC51 treatment group along with the 95% two-sided CI for the percentages.

The effect of vaccine dose (0.25 ml versus 0.5 ml) on the SCR, and the 4- and 10-fold increases in PRNT50 titers at Day 56 and Month 7 were assessed using a Fisher's exact test. The response variable was a binary variable (yes or no) indicating whether a subject had seroconverted. The Mantel-Haenszel type risk difference estimator and associated two-sided 95% CIs were also presented.

The raw GMTs and the 95% CIs for the geometric mean were calculated using log10-transformed titres. The GMTs were summarized at Day 0, Day 56 and Month 7 by treatment group. The GMT ratio and 95% CI for the GMT ratio (IC51 0.5 ml to IC51 0.25 ml) were summarized at Day 56 and Month 7.

The log titres were analyzed at Day 56 and Month 7 using an analysis of covariance (ANCOVA), with covariates including log pre-vaccination PRNT50 titers and center. The anti-log of least square means and the estimated ratio between the vaccines were presented along with the 95% CI.

Subset Analyses: The analyses described above were repeated stratified by pre-existing JEV immunity status (seropositive or seronegative at screening) and by pre-existing DENV antibodies status (positive or negative).

Exploratory Analyses: Within each IC51 treatment group, the log titers were analyzed at Day 56 and Month 7 using an analysis of variance, with age as a factor. To assess whether pre-existing immunity to JEV influences the post-vaccination titers, the log titers were analyzed at Day 56 and Month 7 using an ANCOVA with pre-existing JEV immunity status as a categorical covariate and treatment group as the main effect. This was repeated for pre-existing DENV antibodies status. To assess which covariate was most strongly associated with the increase in post-vaccination titers, within each IC51 treatment group, the log titers were analyzed at Day 56 and Month 7 using an ANCOVA with baseline titer and age as covariates and baseline DENV status as the main effect.

The following study populations were defined

Safety population: All safety analyses were based on the Safety Population, defined as subjects who entered into the study and received at least one vaccination.

Intent-to-treat Population: The ITT Population was the primary analysis population for the immunogenicity analyses and was defined as all subjects randomized into the immunogenicity subgroup, who received at least 1 vaccination. Subjects were analyzed according to the treatment group to which they were randomized, rather than by the actual vaccine they received.

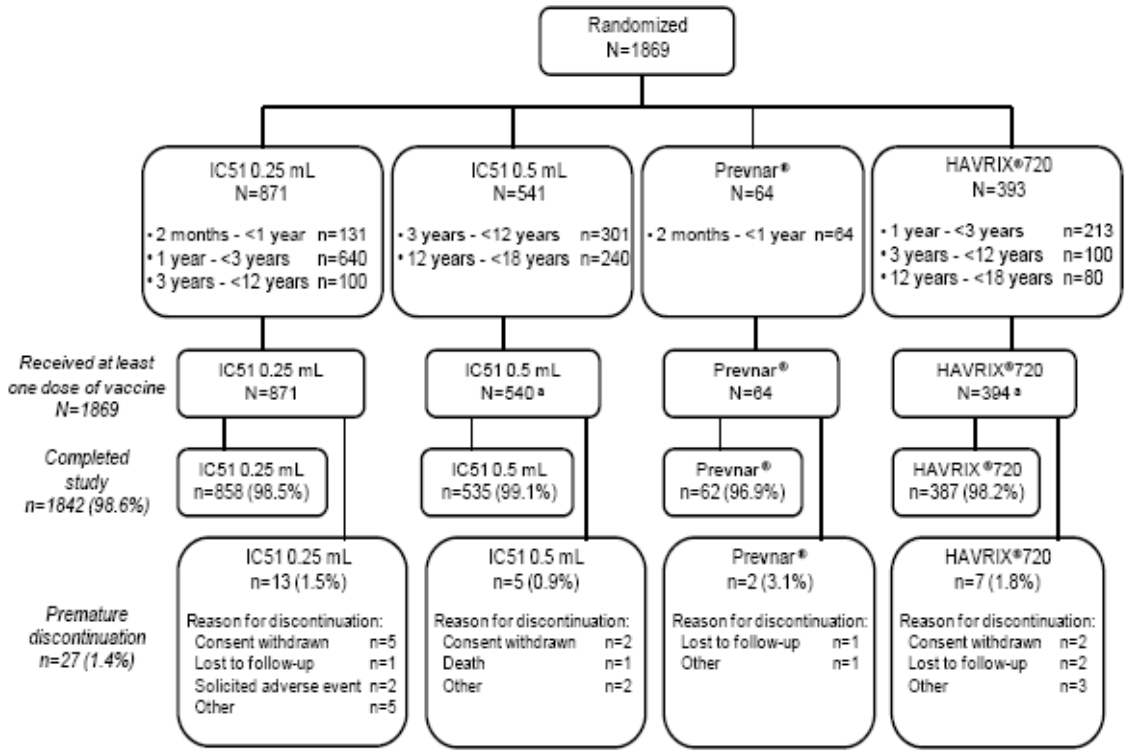
Per–protocol Population: Immunogenicity analyses were repeated for the PP Population and excluded any randomized subjects who were randomized incorrectly or received the wrong study vaccine or dose were considered major protocol deviators and were to be excluded from the PP Population. These and other potential protocol deviations were assessed in a data review meeting and classified into major or minor protocol deviations. Major protocol deviations resulted in a subject's withdrawal from the PP analysis.

Disposition of subjects

Disposition of subjects is displayed in Figure 4.

All 1869 subjects who were randomized received at least 1 dose of study vaccine. A total of 1842 subjects (98.6%) completed the study and 27 (1.4%) prematurely discontinued. The reasons for discontinuation were: consent withdrawn (9 subjects); lost to follow-up (4 subjects); solicited AE (2 subjects, 1 subject with vomiting and 1 subject with headache, both events were considered by the investigator to be related to study vaccine). One subject (0.1%) had a fatal SAE of disseminated intravascular coagulation; the event was considered not related to study vaccine by the investigator. Eleven further subjects (0.6%) discontinued for other reasons, the most common was relocating away from the study site.

Figure 4: Disposition of subjects



[a] Subject 23103749 was randomized to IC51 0.50 mL but received HAVRIX®720.
Source: Table 14.1.1

Table 3 shows the populations analysed. All immunogenicity analyses were carried out using the ITT Population and were repeated using the PP Population as a supportive analysis.

Table 3: Analysis Populations, All Enrolled Subjects

	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)

Baseline characteristics

All subjects enrolled were of Asian origin and there was equal distribution of male and female subjects across the treatment groups. Since age determined disposition of a subject to a treatment group other baseline characteristics like weight, height and BMI differ between the two vaccination groups.

The CHMP noted that in CSR Table 10.2 Demographic data, safety population there must be an error in the 0.25 ml dose column: Height, minimum: 19.7 cm, BMI, maximum 206.1 kg/m2. The error seems to stem from the subject: 23101311 listed with the following data: weight 8.0 kg, height 19.7 cm, BMI 206.1

kg/m2. The MAH provided information on the investigation of outlying values in height and weight of study subjects. It was concluded that these outliers have no significant impact on the average demographic data weight, height and BMI.

A summary of baseline JEV and DENV seropositivity rates was provided for the safety and ITT population. Table 4 summarizes the data by age group for the ITT population. Seropositivity for JEV was defined as a PRNT50 titer of ≥ 1:10. Seropositivity against DENV was defined by a commercial ELISA.

Table 4: Baseline JEV and DENV Serological Data, Overall and by Age Group, ITT Population

	IC51 0.25 mL N=255 n (%)	IC51 0.5 mL N=241 n (%)	Total N=496 n (%)
Entire study population			
Pre-existing JEV immunity			
Seropositive	19 (7.5)	81 (33.6)	100 (20.2)
Seronegative	235 (92.2)	160 (66.4)	395 (79.6)
Not assessable	1 (0.4)	0	1 (0.2)
Pre-existing DENV antibodies			
Positive	76 (29.8)	155 (64.3)	231 (46.6)
Negative	171 (67.1)	83 (34.4)	254 (51.2)
Not assessable	2 (0.8)	0	2 (0.4)
Missing	6 (2.4)	3 (1.2)	9 (1.8)
Age group 2 to <6 months	**N=10**		**N=10**
Pre-existing JEV immunity			
Seropositive	3 (30.0)		3 (30.0)
Seronegative	7 (70.0)		7 (70.0)
Not assessable	0		0
Pre-existing DENV antibodies			
Positive	6 (60.0)		6 (60.0)
Negative	4 (40.0)		4 (40.0)
Not assessable	0		0
Missing	0		0
Age group 6 months to <1 year	**N=20**		**N=20**
Pre-existing JEV immunity			
Seropositive	0		0
Seronegative	20 (100.0)		20 (100.0)
Not assessable	0		0
Pre-existing DENV antibodies			
Positive	2 (10.0)		2 (10.0)
Negative	16 (80.0)		16 (80.0)
Not assessable	1 (5.0)		1 (5.0)
Missing	1 (5.0)		1 (5.0)
Entire age group 2 months to <1 year	**N=30**		**N=30**
Pre-existing JEV immunity			
Seropositive	3 (10.0)		3 (10.0)
Seronegative	27 (90.0)		27 (90.0)
Not assessable	0		0
Pre-existing DENV antibodies			
Positive	8 (26.7)		8 (26.7)
Negative	20 (66.7)		20 (66.7)
Not assessable	1 (3.3)		1 (3.3)
Missing	1 (3.3)		1 (3.3)
Age group 1 to <3 years	**N=125**		**N=125**
Pre-existing JEV immunity			
Seropositive	4 (3.2)		4 (3.2)
Seronegative	120 (96.0)		120 (96.0)
Not assessable	1 (0.8)		1 (0.8)

	IC51 0.25 mL N=255 n (%)	IC51 0.5 mL N=241 n (%)	Total N=496 n (%)
Pre-existing DENV antibodies			
Positive	16 (12.8)		16 (12.8)
Negative	107 (85.6)		107 (85.6)
Not assessable	0		0
Missing	2 (1.6)		2 (1.6)
Age group 3 to <12 years	**N=100**	**N=101**	**N=201**
Pre-existing JEV immunity			
Seropositive	12 (12.0)	17 (16.8)	29 (14.4)
Seronegative	88 (88.0)	84 (83.2)	172 (85.6)
Not assessable	0	0	0
Pre-existing DENV antibodies			
Positive	52 (52.0)	51 (50.5)	103 (51.2)
Negative	44 (44.0)	47 (46.5)	91 (45.3)
Not assessable	1 (1.0)	0	1 (0.5)
Missing	3 (3.0)	3 (3.0)	6 (3.0)
Age group 12 to <18 years	**N=140**		**N=140**
Pre-existing JEV immunity			
Seropositive	64 (45.7)		64 (45.7)
Seronegative	76 (54.3)		76 (54.3)
Not assessable	0		0
Pre-existing DENV antibodies			
Positive	104 (74.3)		104 (74.3)
Negative	36 (25.7)		36 (25.7)
Not assessable	0		0
Missing	0		0

The CHMP commented that the determination of anti JEV and DENV antibody titers at baseline prior vaccination shows that pre-existing maternal antibodies against JEV and DENV are present in a high proportion of small children below 6 months (anti-JEV: 30% and anti-DENV: 60%). In children aged 6 to <1year no JEV antibodies and in only 10% DENV antibodies were found. In contrast from the age of 1 year onwards the number of baseline seropositive subjects increases due to natural infection with JEV or DENV. The seropositivity rates for JEV for children aged 1 to 3 years were comparable to the rates observed in study IC51-221 (3.2% vs 4.2%). The baseline seropositivity rates for children 3 to <12 years of age were generally comparable in the two vaccination groups (0.25ml and 0.5ml). Prior vaccination 12-17% of subjects aged 3-<12 years were found seropositive for JEV and 50-52% were seropositive for DENV. In the age group of the 12 to <18 years old approx. 46% were seropositive for JEV and 74% for DENV.

Immunogenicity evaluation

A summary of SCRs, fold increase rates and GMTs for the two vaccination groups is presented in Table 5 for the ITT Population.

Vaccination with IC51, comprising 2 doses of either 0.25ml or 0.5ml given approximately 28 days apart, resulted in high SCRs with 98% in the 0.25ml and 100% in the 0.5ml treatment group post dose 2. Four-fold increases in titers were observed in 93.5% and 84.4% of subjects 0.25ml and 0.5ml vaccination group, respectively. Comparable GMTs post dose 2 were determined for the 2 vaccination groups (0.25ml: 199.39 and 0.5ml 190.77).

At Month 7, the immune responses had decreased in both treatment groups with SCRs of 83.9% and 94.5% in the 0.25 ml and 0.5ml group respectively. Decline in GMTs was more pronounced in the 0.25ml group (GMT: 37.99) than the 0.5ml vaccination group (GMT: 64.83).

Significant differences between the vaccination groups were found for the fold increase rates post dose 2 and the SCRs at Month 7.

PP Population results were similar to those of the ITT Population at Day 56 and Month 7.

Table 5: Seroconversion rates, Fold Increase rates and GMTs by treatment group, ITT Population

	IC51 0.25 mL N=255	IC51 0.5 mL N=241	Risk Difference Estimates and GMT Ratios
Baseline (Visit 0)			
Seroconversion			
N	254	241	
n (%)	19 (7.5)	81 (33.6)	
95% CI	4.8; 11.4	27.9; 39.8	
Geometric mean titers, value			
Geometric mean (SD)	5.79 (1.802)	9.78 (2.944)	
95% CI for geometric mean	5.38; 6.22	8.53; 11.22	
Median (Min, Max)	5.00 (5.0, 578.0)	5.00 (5.0, 453.0)	
Day 56 (Visit 3)			
Seroconversion			
N	246	237	Risk difference estimate: 0.021
n (%)	241 (98.0)	237 (100.0)	95% CI: 0.003; 0.040
95% CI	95.3; 99.1	98.4; 100	p-value: 0.061
Four-fold increase in titers			Risk difference estimate: -0.050
n (%)	230 (93.5)	200 (84.4)	95% CI: -0.102; 0.001
95% CI	89.7; 96.0	79.2; 88.5	p-value: 0.002
Ten-fold increase in titers			Risk difference estimate: -0.156
n (%)	212 (86.2)	159 (67.1)	95% CI: -0.232; -0.080
95% CI	81.3; 89.9	60.9; 72.8	p-value: <0.001
Geometric mean titers, value			
N	247	237	
Geometric mean (SD)	199.39 (3.387)	190.77 (2.747)	GMT ratio: 0.96
95% CI for geometric mean	171.12; 232.32	167.63; 217.11	95% CI: 0.78; 1.17
Median (Min, Max)	199.00 (5.0, 3194.0)	178.00 (19.0, 3702.0)	
Month 7 (Visit 4)			
Seroconversion			
N	248	237	Risk difference estimate: 0.097
n (%)	208 (83.9)	224 (94.5)	95% CI: 0.037; 0.157
95% CI	78.8; 87.9	90.8; 96.8	p-value: <0.001
Four-fold increase in titers			Risk difference estimate: -0.016
n (%)	175 (70.6)	160 (67.5)	95% CI: -0.101; 0.070
95% CI	64.6; 75.9	61.3; 73.2	p-value: 0.492
Ten-fold increase in titers			Risk difference estimate: -0.016
n (%)	105 (42.3)	92 (38.8)	95% CI: -0.107; 0.075
95% CI	36.4; 48.6	32.8; 45.2	p-value: 0.460
Geometric mean titers, value			
N	249[a]	237	
Geometric mean (SD)	37.99 (3.267)	64.83 (3.242)	GMT ratio: 1.71
95% CI for geometric mean	32.77; 44.04	55.77; 75.36	95% CI: 1.38; 2.11
Median (Min, Max)	46.00 (5.0, 580.0)	62.00 (5.0, 2064.0)	

Stratified by age

SCRs, fold increase rates and GMTs by treatment group following stratification by age group are given in Table 6. SCRs in subjects vaccinated with the 0.25ml dose was 100% in the age group of ≥ 2 months to < 1 year, 99.2% in the age group of ≥ 1 year to < 3 years and 95.9% in the group of ≥ 3 years to < 12 years. For all subjects in the 0.5ml vaccination group stratified by age categories SCRs of 100% were observed. The magnitude of the antibody response in the older age groups within each treatment group was generally lower than that in the younger age groups.

For subjects aged ≥ 3 years to < 12 years, a GMT of 213.67 and of 113.89 was reported post dose 2 in the 0.5ml and 0.25ml dose group respectively. At Month 7 the SCRs observed were 91% and 77.1% for the 0.5ml and 0.25ml dose group, respectively.

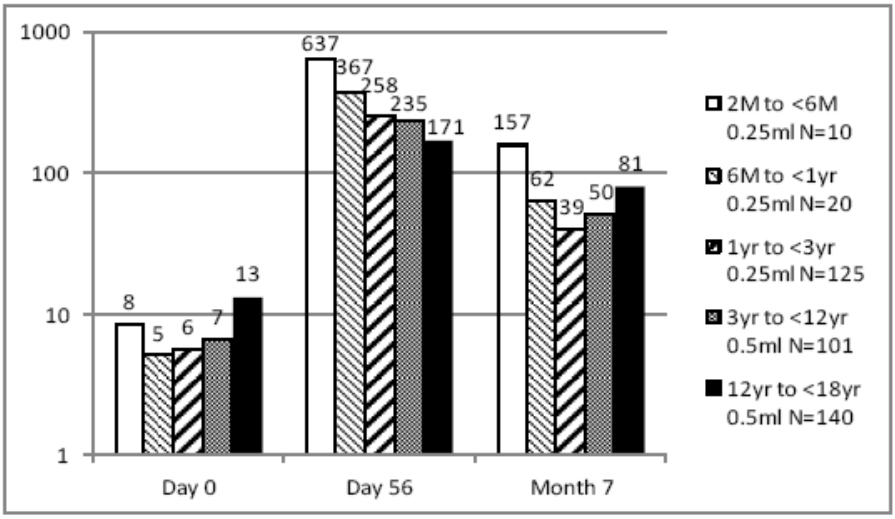
In the ITT Population, the only age group in which both doses were administered and therefore could be compared was the ≥ 3 years to < 12 years group. After adjustment for a pre-defined covariate of center, the estimated ratio between treatments was statistically significant at both Day 56 (1.88-fold higher GMT in the IC51 0.5 mL group; p-value <0.001) and Month 7 (1.51-fold higher GMT in the IC51 0.5 mL group; p-value 0.009).

Further analysis of covariance of GMTs by age group (from ANCOVA with center as a covariate) stratified by treatment group, age appeared to be significantly associated with a decrease in GMTs. In general, the further apart the age group, the more significant the association regardless of treatment group or time since vaccination (Figure 5).

Table 6: Seroconversion, Fold Increase Rates and Raw Geometric Mean Titers by Treatment Group, Stratified by Age Group, Intent-to-treat Population

	IC51 0.25 mL			IC51 0.5 mL	
	2 months to < 1 year	1 year to < 3 years	3 years to < 12 years	3 years to < 12 years	12 years to < 18 years
Day 56 (Visit 3)					
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
Four-fold increase in titers					
n (%)	27 (96.4)	116 (96.7)	87 (88.8)	94 (94.0)	106 (77.4)
95% CI	82.3; 99.4	91.7; 98.7	81.0; 93.6	87.5; 97.2	69.7; 83.6
Ten-fold increase in titers					
n (%)	27 (96.4)	112 (93.3)	73 (74.5)	80 (80.0)	79 (57.7)
95% CI	82.3; 99.4	87.4; 96.6	65.0; 82.1	71.1; 86.7	49.3; 65.6
GMTs					
N	28	121	98	100	137
Geometric mean	457.93	258.90	113.89	213.67	175.63
(SD)	(3.443)	(2.849)	(3.252)	(2.690)	(2.777)
95% CI	283.53; 739.61	214.43; 312.59	89.90; 144.26	175.58; 260.03	147.79; 208.71
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; 100.0	78.2; 90.6	67.7; 84.4	83.8; 95.2	92.7; 98.9
Four-fold increase in titers					
n (%)	24 (85.7)	94 (75.8)	57 (59.4)	71 (71.0)	89 (65.0)
95% CI	68.5; 94.3	67.6; 82.5	49.4; 68.7	61.5; 79.0	56.7; 72.4
Ten-fold increase in titers					
n (%)	20 (71.4)	56 (45.2)	29 (30.2)	42 (42.0)	50 (36.5)
95% CI	52.9; 84.7	36.7; 53.9	21.9; 40.0	32.8; 51.8	28.9; 44.8
GMTs					
N	28	125	96	100	137
Geometric mean	88.63	38.91	28.76	43.60	86.61
(SD)	(2.568)	(3.150)	(3.260)	(2.787)	(3.314)
95% CI	61.49; 127.77	31.75; 47.67	22.64; 36.54	35.58; 53.43	70.74; 106.04

Figure 5: Least square means for the analysis of covariance for GMTs by age group, Intent-to-treat Population



Stratified by baseline JEV seropositivity

A summary of SCR, fold increase rates and GMTs by treatment group stratified by pre-existing JEV immunity is presented in Table 7.

Analysis of covariance for GMTs by pre-existing JEV immunity shows that, there was no significant association with pre-existing JEV immunity status at Day 56. At Month 7, the estimated ratio between JEV serostatus groups was significant in the 0.25 ml group (GMT was 2.04-fold higher in the seropositive group; p-value 0.014) and the 0.5 ml group (GMT was 1.59-fold higher in the seropositive group; p-value 0.004) indicating a better persistence of antibodies in those subjects who were seropositive at baseline.

Table 7: Seroconversion, Fold Increase Rates and Raw Geometric Mean Titers by Treatment group, Stratified by Pre-existing JEV Immunity, Intent-to-treat Population

	IC51 0.25 mL N=255		IC51 0.5 mL N=241	
	Seropositive at Baseline	Seronegative at Baseline	Seropositive at Baseline	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
Four-fold increase in titers				
n (%)	10 (58.8)	220 (96.1)	43 (54.4)	157 (99.4)
95% CI	36.0; 78.4	92.7; 97.9	43.5; 65.0	96.5; 99.9
Ten-fold increase in titers				
n (%)	6 (35.3)	206 (90.0)	16 (20.3)	143 (90.5)
95% CI	17.3; 58.7	85.4; 93.2	12.9; 30.4	84.9; 94.2
GMTs				
Geometric mean	201.15	200.85	168.05	203.26
(SD)	(3.710)	(3.362)	(2.837)	(2.695)
95% CI	102.51; 394.70	171.52; 235.21	133.05; 212.26	173.94; 237.53
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				
Geometric mean	77.12	36.26	97.91	52.76
(SD)	(2.040)	(3.293)	(3.177)	(3.110)
95% CI	54.10; 109.94	31.06; 42.33	75.58; 126.85	44.14; 63.05

Stratified by baseline DENV seropositivity

A summary of SCR, fold increase rates and GMTs by treatment group stratified by pre-existing DENV immunity is presented in Table 8.

The analysis of covariance for GMTs stratified by pre-existing DENV antibodies and stratified by treatment group at Day 56 revealed that the estimated ratio between pre-existing DENV status was significant in the 0.25 ml group (0.43-fold lower GMT in the positive group; p-value < 0.001) and the 0.5 ml group (0.49-fold lower GMT in the positive group; p-value < 0.001) indicating a greater immune response in those subjects who were negative to DENV at baseline. At Month 7 no effect was observed.

Table 8: Seroconversion, Fold Increase Rates and Geometric Mean Titers by Treatment group, Stratified by Pre-existing DENV Antibodies, Intent-to-treat Population

	IC51 0.25 mL N=255		IC51 0.5 mL N=241	
	Positive at Baseline	Negative at Baseline	Positive at Baseline	Negative 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
Four-fold increase in titers				
n (%)	61 (84.7)	162 (97.0)	119 (77.8)	78 (96.3)
95% CI	74.7; 91.2	93.2; 98.7	70.6; 83.6	89.7; 98.7
Ten-fold increase in titers				
n (%)	50 (69.4)	155 (92.8)	84 (54.9)	72 (88.9)
95% CI	58.0; 78.9	87.9; 95.8	47.0; 62.6	80.2; 94.0
GMTs				
Geometric mean	106.29	263.29	154.38	285.62
(SD)	(3.345)	(3.056)	(2.639)	(2.668)
95% CI	80.04; 141.16	221.98; 312.28	132.22; 180.27	229.92; 354.83
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				
Geometric mean	41.36	36.90	68.78	57.95
(SD)	(3.267)	(3.289)	(3.178)	(3.382)
95% CI	31.31; 54.62	30.80; 44.21	57.18; 82.73	44.26; 75.86

Baseline DENV seropositivity seems to negatively impact the antibody responses post dose 2 but not at Month 7.

In order to assess the combined impact of JEV and DENV baseline seropositivity on the immune response to the different doses of Ixiaro, the MAH was asked to provide further analyses stratified by JEV+DENV baseline immunity as well as stratified by JEV+DENV baseline immunity and stratified in age categories of 2 months to 1 year, 1-<3 years, 3-<12 years and 12 -<18 years.

The MAH provided the following analysis:

Combined impact of JEV+DENV baseline immunity could be interpreted as either comparing subjects who tested positive against both viruses with subjects who tested negative against both viruses, or alternatively as subjects testing positive for either virus vs. those testing negative for both viruses. Both these analyses have been performed and are summarized below.

- Subject Disposition According to JEV, DENV and combined JEV / DENV Seropositivity and Age at Baseline

Table 9 provides an overview on the number of subjects per dose group, classified by JEV and DENV serostatus at baseline, overall and stratified by age. In the younger children (0.25 ml dose group, < 3 years) the majority of about two-third of children were seronegative to both viruses while two-third of the older children (0.5 ml dose group, > 3 years) were tested seropositive for at least one or both viruses with one third positive for both.

Table 9: Subject Disposition Classified by JEV and DENV Serostatus at Baseline, Stratified by Age Group, ITT Population, IC51-323

Age Group		IC51 0.25 ml No. (%)	IC51 0.5 ml No. (%)
>= 2 months to < 18 years	Pre-existing DENV and JEV Status		
	JEV-/DEN-	171 (69.2)	72 (30.3)
	JEV-/DEN+	57 (23.1)	86 (36.1)
	JEV+/DEN-	1 (0.4)	10 (4.2)
	JEV+/DEN+	18 (7.3)	70 (29.4)
	Total	247	238
>= 2 months to < 12 months	Pre-existing DENV and JEV Status		
	JEV-/DEN-	20 (71.4)	n.a.
	JEV-/DEN+	5 (17.9)	n.a.
	JEV+/DEN-	0 (0.0)	n.a.
	JEV+/DEN+	3 (10.7)	n.a.
	Total	28	n.a.
>= 1 year to < 3 years	Pre-existing DENV and JEV Status		
	JEV-/DEN-	106 (86.2)	n.a.
	JEV-/DEN+	13 (10.6)	n.a.
	JEV+/DEN-	1 (0.8)	n.a.
	JEV+/DEN+	3 (2.4)	n.a.
	Total	123	n.a.
>= 3 years to < 12 years	Pre-existing DENV and JEV Status		
	JEV-/DEN-	45 (46.9)	45 (45.9)
	JEV-/DEN+	39 (40.6)	37 (37.8)
	JEV+/DEN-	0 (0.0)	1 (1.0)
	JEV+/DEN+	12 (12.5)	15 (15.3)
	Total	96	98
>= 12 years to < 18 years	Pre-existing DENV and JEV Status		
	JEV-/DEN-	n.a.	27 (19.3)
	JEV-/DEN+	n.a.	49 (35.0)
	JEV+/DEN-	n.a.	9 (6.4)
	JEV+/DEN+	n.a.	55 (39.3)
	Total	n.a.	140
Percentages are based on the number of non-missing observations within each stratum (Total) n.a. not applicable – dose not given in respective age group			

In line with the known limited specificity of ELISA based assay kits, which may not discriminate between cross-reactive antibodies directed against different Flaviviruses, there are very few subjects testing positive in the (specific) JEV PRNT assay but negative in the DENV Indirect IgG ELISA (Panbio, AUS). Only 11 subjects overall were JEV PRNT positive but tested DENV ELISA negative. In contrast, there was a significant proportion of about 30% of both dose groups combined that was tested positive in the DENV ELISA only but negative in the JEV PRNT, so those subjects may truly have had exposure to DENV only, without exposure to JEV.

- Impact of JEV and DENV Baseline Seropositivity and Age on the Immune Response to the Different Doses of IXIARO

Following comparison of SCRs and GMTs between subjects who were seronegative for both viruses at baseline and subjects being either seropositive for both viruses ("JEV + DENV positive") or being seropositive for at least one of the viruses ("JEV and / or DENV positive") for the two IXIARO dose groups (0.25ml vs 0.5ml) the following observations were made:

On Day 56, for all age groups combined;

- SCR did not differ substantially between JEV + DENV positive subjects and JEV + DENV negative subjects or between JEV and / or DENV positive subjects and JEV + DENV negative subjects after either dose of IXIARO.
- GMT was higher in JEV + DENV negative subjects compared to JEV + DENV positive subjects and JEV and / or DENV positive subjects after either dose of IXIARO.
- Compared to JEV + DENV positive subjects, JEV and / or DENV positive subjects had a slightly lower SCR (100% vs. 95.9%) and lower GMT (approx. 180 vs. 110) in the 0.25 ml dose group (which included children aged 3-12 years who received this dose during the dose-finding phase). There were no relevant differences in the 0.5 ml group.

On Month 7, for all age groups combined;

- SCR was higher for JEV + DENV positive subjects and also for JEV and / or DENV positive subjects compared to JEV + DENV negative subjects, after either dose of IXIARO.
- In contrast to Day 56, GMT was lower in JEV + DENV negative subjects compared to JEV + DENV positive subjects and JEV and / or DENV positive subjects after either dose of IXIARO.
- Compared to JEV + DENV positive subjects, JEV and / or DENV positive subjects also had a lower SCR (100% vs. 86.3%) and lower GMT (approx. 79 vs. 42) in the 0.25 ml dose group (which included children aged 3-12 years who received this dose during the dose-finding phase). There were no relevant differences in the 0.5 ml group.

In addition further comparisons were presented stratified by age for Day 56 ("JEV + DENV positive" and "JEV and / or DENV positive", Table 10) and Month 7 ("JEV + DENV positive", and "JEV and / or DENV positive", Table 11).

Table 10 Seroconversion and Raw Geometric Mean Titers on Day 56, Stratified by Pre-existing JEV and DENV Serostatus and by Age Group, Intent-to-treat Population

	Day 56 SCR n (%) [95%CI]			Day 56 GMT [95%CI]	
	JEV + DENV Seropositive at Baseline	JEV + DENV Seronegative at Baseline	Fisher Exact	JEV + DENV Seropositive at Baseline	JEV + DENV Seronegative at Baseline
0.25 ml Dose					
			p-value		
< 1 year	2 (100) [34.2, 100]	19 (100) [83.2, 100]	not calculable	949.97 [0.05,1.678E7]	432.65 [239.25, 782.39]
1-<3 years	3 (100) [43.9, 100]	101 (99.0) [94.7,99.8]	1.0000	500.45 [23.28,10760.2]	273.25 [222.72, 335.25]
3- < 12 years	11 (100) [74.1, 100]	44 (97.8) [88.4,99.6]	1.0000	99.23 [57.20, 172.13]	189.12 [133.98, 266.95]
0.5 ml Dose					
3- < 12 years	15 (100) [79.6, 100]	45 (100) [92.1, 100]	not calculable	125.10 [85.71, 182.60]	313.50 [235.96, 416.51]
12-<18 years	53 (100) [93.2, 100]	26 (100) [87.1, 100]	not calculable	163.63 [122.50, 218.56]	243.58 [169.51, 350.04]

	JEV and/or DENV Seropositive at Baseline	JEV + DENV Seronegative at Baseline	Fisher Exact	JEV and/or DENV Seropositive at Baseline	JEV + DENV Seronegative at Baseline
0.25 ml Dose					
			p-value		
< 1 year	7 (100) [64.6, 100]	19 (100) [83.2, 100]	not calculable	411.88 [121.80,1392.86]	432.65 [239.25, 782.39]
1-<3 years	17 (100) [81.6, 100]	101 (99.0) [94.7,99.8]	1.0000	225.53 [134.95, 376.92]	273.25 [222.72, 335.25]
3- < 12 years	46 (93.9) [83.5,97.9]	44 (97.8) [88.4,99.6]	0.6182	71.11 [52.53, 96.26]	189.12 [133.98, 266.95]
0.5 ml Dose					
3- < 12 years	52 (100) [93.1, 100]	45 (100) [92.1, 100]	not calculable	155.27 [119.65, 201.50]	313.50 [235.96, 416.51]
12-<18 years	111 (100) [96.7, 100]	26 (100) [87.1, 100]	not calculable	162.67 [133.84, 197.71]	243.58 [169.51, 350.04]

Table 11 Seroconversion and Raw Geometric Mean Titers on Month 7, Stratified by Pre-existing JEV and DENV Serostatus and by Age Group, Intent-to-treat Population

	Month 7 SCR n (%) [95%CI]			Month 7 GMT [95%CI]	
	JEV + DENV Seropositive at Baseline	JEV + DENV Seronegative at Baseline	Fisher Exact	JEV + DENV Seropositive at Baseline	JEV + DENV Seronegative at Baseline
0.25 ml Dose					
			p-value		
< 1 year	3 (100) [43.9, 100]	18 (100) [82.4, 100]	not calculable	158.31 [42.22, 593.58]	66.91 [42.01, 106.56]
1-<3 years	3 (100) [43.9, 100]	90 (84.9) [76.9,90.5]	1.0000	100.11 [2.38,4216.39]	39.42 [31.69, 49.04]
3- < 12 years	11 (100) [74.1, 100]	30 (68.2) [53.4,80.0]	*0.0484*	60.98 [49.04, 75.82]	24.45 [16.42, 36.42]
0.5 ml Dose					
3- < 12 years	14 (93.3) [70.2,98.8]	38 (84.4) [71.2,92.3]	0.6657	48.84 [29.41, 81.09]	41.54 [29.31, 58.86]
12-<18 years	54 (100) [93.4, 100]	26 (96.3) [81.7,99.3]	0.3333	112.25 [82.01, 153.64]	78.07 [49.69, 122.68]

	JEV and/or DENV Seropositive at Baseline	JEV + DENV Seronegative at Baseline	Fisher Exact	JEV and/or DENV Seropositive at Baseline	JEV + DENV Seronegative at Baseline
0.25 ml Dose					
			p-value		
< 1 year	8 (100) [67.6, 100]	18 (100) [82.4, 100]	not calculable	150.22 [78.48, 287.53]	66.91 [42.01, 106.56]
1-<3 years	15 (88.2) [65.7,96.7]	90 (84.9) [76.9,90.5]	1.0000	40.70 [21.67, 76.42]	39.42 [31.69, 49.04]
3- < 12 years	40 (83.3) [70.4,91.3]	30 (68.2) [53.4,80.0]	0.1412	33.73 [24.57, 46.32]	24.45 [16.42, 36.42]
0.5 ml Dose					
3- < 12 years	50 (96.2) [87.0,98.9]	38 (84.4) [71.2,92.3]	0.0768	44.39 [34.57, 57.01]	41.54 [29.31, 58.86]
12-<18 years	107 (97.3) [92.3,99.1]	26 (96.3) [81.7,99.3]	1.0000	88.84 [70.62, 111.78]	78.07 [49.69, 122.68]

Immunogenicity analysis stratified by baseline immunity and age can be summarized as follows:

On Day 56, when stratified by age;

- SCR was above 97% in all subgroups examined so did not differ substantially between JEV + DENV positive subjects, JEV and / or DENV positive subjects and JEV + DENV negative subjects; with the exemption of 93.9% SCR in the JEV and / or DENV positive subgroup, age stratum 3 - < 12 years (i.e. children who received the 0.25 ml dose during dose finding).
- In all age and dose groups with a meaningful number of subjects, JEV + DENV negative subjects had higher (up to about 2-fold) GMTs compared to JEV + DENV positive subjects and JEV and / or DENV positive subjects after either dose of IXIARO; in some age/dose group combinations the differences even reach statistical significance as the 95%CI for GMT do not overlap.
- Within each age stratum, the groups JEV + DENV positive subjects and JEV and / or DENV positive subjects had similar GMTs;
- In general, the GMTs decreased with increasing age within each of the baseline JEV/DENV status strata; (except for the group aged 3 - < 12 years that received the 0.25 ml dose during dose finding and had the lowest titers for obvious reasons).

At Month 7, when stratified by age;

- In most age and dose groups, SCR was slightly - moderately higher in JEV + DENV positive subjects and JEV and / or DENV positive subjects compared to JEV + DENV negative subjects.
- While data in some age and dose groups are very limited, the JEV + DENV positive subjects seemed to retain higher (up to about 3-fold in the group aged 3 - < 12 years that received the 0.25 ml dose during dose finding) GMTs compared to JEV + DENV negative subjects and higher titers compared to the JEV and / or DENV positive subjects subgroup (which did not show relevant differences in GMT compared to the baseline negative subjects).
- In general, within each JEV/DENV baseline serostatus stratum, the GMTs remained highest in the youngest children followed by the 12 - <18 years group.

In summary, the MAH asserts that the additional analyses support the findings and conclusions drawn on the previous analysis on the impact of baseline JEV seropositivity and DENV seropositivity on immunogenicity. Pre-existing JEV immunity appears to lead to lower GMTs shortly after vaccination but better persistence of antibodies. The effect on GMT shortly after vaccination is not considered clinically relevant, as seroconversion rates i.e. the proportion of subjects that achieve protective titers are high and close to 100% in all groups. Additionally, the GMTs are high in both baseline positive and negative subjects even though they differ. Lower GMTs seen in baseline positive subjects also underline that the results generated in this population from a JEV endemic country does not overestimate the magnitude of immune response in non-endemic populations, and if any would represent an underestimate.

The differences in antibody persistence is regarded of higher practical relevance and studies to determine the persistence of antibodies in children from non-endemic areas are ongoing and will be reviewed jointly with follow-up data from endemic regions to conclude on duration of protection in western children.

Following this clarification, the CHMP remarked that the immunogenicity analysis stratified by baseline serostatus and age revealed that post dose 2 all JEV/DENV naïve subjects except one in the age group of

the 1-3 years old seroconverted. The GMTs were highest in the youngest age group of the 2-<12 months old naïve subjects although only limited data from 19 subjects are available. In the group of the 1-<3 years a lower GMT of 273 was achieved than in the group below 1 year of age. This GMT is comparable to the GMT of 332.1 reported in study IC51-322 for the ITT population and well above the accepted seroprotective titer of 1:10.

Antibody persistence data up to 6 Month after the last dose further indicate that in JEV/DENV naïve subjects the neutralizing response declines slightly faster than in JEV/DENV seropositive subjects.

Evaluation of Ixiaro in children from non-endemic countries

IC51-322 is an ongoing uncontrolled, open-label Phase 3 study to assess immunogenicity and safety of Ixiaro in healthy children aged ≥ 2 months to < 18 years planning to travel to countries where JEV is endemic and JE vaccination would be recommended.

The study is conducted in 11 centres in USA, Germany, Denmark, Sweden and Australia. The study plan foresees that 100 healthy children were to be enrolled, but so far only 60 subjects were treated with Ixiaro, because recruitment has been slower than expected. Upon request of US FDA, an interim report was prepared covering the period of February 2010 to September 2011. This report was submitted to support the extension of the age indication of Ixiaro.

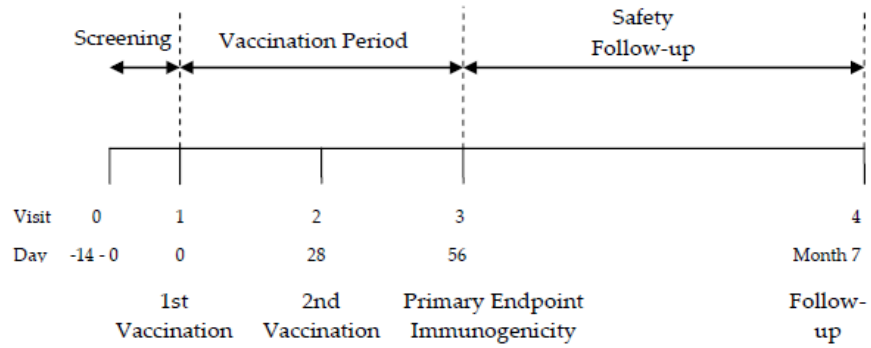
The study was designed to bridge the data obtained from clinical studies with Ixiaro in endemic populations to populations which do not have natural exposure to JEV. Subjects included in the study had to be healthy children and adolescents aged ≥ 2 months to < 18 years at the time of the first vaccination. The subject must be planning to travel to an area where JEV is endemic after completion of the vaccination schedule. Exposure to JE should be avoided until 1 week after the second IC51 dose and subjects should return from travel to JE endemic areas before the Month 7 visit. The planned travel to JE endemic areas should not interfere with the study visits and can take place between Days 35 and 56 or between Day 56 and Month 7.

The age cut-off of 2 months has been chosen to meet the PIP requirements. The doses (0.25 or 0.5 ml) to be investigated in this study were based on the results of study IC51-221 and IC51-323.

In study IC51-322 subjects were to receive Ixiaro as follows:

- Two injections of Ixiaro 0.25 ml (3µg), intramuscularly, at Day 0 and Day 28 for subjects aged ≥ 2 months to < 3 years (half the adult dose).
- Two injections of Ixiaro 0.5 ml (6µg), intramuscularly, at Day 0 and Day 28 for subjects aged ≥ 3 years to < 12 years (the appropriate dose for this age group based on the findings of Study IC51-323).
- Two injections of Ixiaro 0.5 ml (6µg), intramuscularly, at Day 0 and Day 28 for subjects aged ≥ 12 years to < 18 years (full adult dose).

The study design is displayed below.



Three different commercial vaccine lots were used during the study: JEV08K16A, JEV09K35A and JEV10H62A.

Study objectives

The primary study objective is the assessment of immunogenicity by determination of SCRs and GMTs at Day56. Secondary objectives are defined as assessment of the safety profile and of the differences in the immunogenicity and safety profile in subjects depending on age groups, dose groups, TBE vaccination history and travel to JE endemic areas.

Endpoints for the Interim Analysis

The co-primary endpoints in the study are: SCRs as defined by percentage of subjects with PRNT50 titers of ≥ 1:10 at Day 56 and GMTs for JEV neutralizing antibodies measured using a validated PRNT50 assay at Day 56.

Secondary endpoints were:

- SCRs and GMTs at Day 56 and Month 7 stratified according to dose groups, age groups, TBE vaccination history, travel to JE endemic areas, travel to JE endemic areas before Day 56, as well as travel to JE endemic areas after Day 56.
- Rate of subjects with SAEs and medically-attended AEs up to Day 56 and up to Month 7 after the first vaccination.
- Rate of subjects with solicited local and systemic AEs assessed with a subject diary for 7 consecutive days after each vaccination.
- Rate of subjects with unsolicited AEs up to Day 56 and up to Month 7 after the first vaccination.

Statistical analyses

For the immunogenicity analyses the number and percentage of subjects achieving seroconversion at Day 0, Day 56 and Month 7 were tabulated for each Ixiaro dose group, and for both dose groups combined, along with the 95% 2-sided confidence intervals (CI) for the percentages. The raw GMTs and the 95% CIs for the geometric mean were calculated using log10-transformed titers. The log titers were analyzed using an analysis of covariance, with region as a covariate. The descriptive statistics were repeated stratified by dose group and age group. The effect of region on the immune response was analyzed by analysis of covariance on the log PRNT50 titers.

For safety analyses treatment-emergent AEs were summarized. In all tabulations of AEs, the frequencies of subjects experiencing a given AE or AEs from a given category were compared between dose groups using Fisher's exact test. The effect of age on the SAE or medically-attended AE rate, AE rate and the rate of related AEs was analyzed by logistic regression. Results from physical examinations, and vital signs and body temperature measurements were listed only.

The following populations were analysed:

Safety Population comprised all subjects who entered into the study and received at least 1 vaccination.

Intent-to-treat (ITT) Population for the interim analysis comprised all subjects with a Visit 3 that occurred up to and including 15 September 2011.

Per–protocol (PP) Population was based on the ITT Population but excluded any subjects who were major protocol deviators.

Interim results

At the data cut-off point, 28 subjects had been recruited from Europe, 26 subjects from North America and 6 subjects from Australia. The subjects received at least 1 dose of Ixiaro (IC51) and a total of 53 subjects had completed visit 3 and 22 subjects had completed the study. One subject withdrew consent and discontinued prematurely from the study.

	IC51 0.25 mL n (%)	**IC51 0.5 mL n (%)**	**Total n (%)**
Enrolled	5	55	60
Subjects who received at least 1 vaccination	5 (100.0)	55 (100.0)	60 (100.0)
Ongoing in the study and not yet completed Visit 3	0	6 (10.9)	6 (10.0)
Completed Visit 3	5 (100.0)	48 (87.3)	53 (88.3)
Completed the study (Visit 4)	3 (60.0)	19 (34.5)	22 (36.7)
Premature discontinuation from the study	0	1 (1.8)	1 (1.7)
Consent withdrawn	0	1 (1.8)	1 (1.7)

The baseline characteristic by dose group is given in table 12. The mean age of subjects was 1.5 years (median 1.06; range 0.9 to 2.9 years) for the half dose vaccination group and 13.49 (median 15.49; range 3.4 to 17.9 years) for the full dose group. Most subjects were Caucasian (83.3%). The proportion of females (56.7%) was greater than males (43.3%).

Table 12: Baseline characteristics

	IC51 0.25 mL (N=5) n (%)	IC51 0.5 mL (N=55) n (%)	Total (N=60) n (%)
Age at Visit 1 (years)			
n	5	55	60
Mean (SD)	1.53 (0.835)	13.49 (4.285)	12.50 (5.288)
Median (Min, Max)	1.06 (0.9, 2.9)	15.49 (3.4, 17.9)	15.19 (0.9, 17.9)
Sex			
Male	2 (40.0)	24 (43.6)	26 (43.3)
Female	3 (60.0)	31 (56.4)	34 (56.7)
Race			
Asian	2 (40.0)	6 (10.9)	8 (13.3)
White	2 (40.0)	48 (87.3)	50 (83.3)
Black of African heritage or African American	1 (20.0)	1 (1.8)	2 (3.3)
Weight (kg)			
n	5	54	59
Mean (SD)	11.86 (2.971)	49.34 (16.848)	46.17 (19.258)
Median (Min, Max)	11.00 (9.0, 16.6)	54.54 (13.7, 78.5)	54.48 (9.0, 78.5)
Height (cm)			
n	5	53	58
Mean (SD)	82.94 (9.903)	156.47 (23.825)	150.13 (30.953)
Median (Min, Max)	78.00 (72.0, 95.3)	165.10 (93.0, 190.5)	165.05 (72.0, 190.5)
BMI (kg/m^2)			
n	5	53	58
Mean (SD)	17.08 (1.287)	19.14 (2.551)	18.96 (2.529)
Median (Min, Max)	17.40 (15.2, 18.3)	19.90 (14.2, 23.9)	19.40 (14.2, 23.9)

Analysis was performed by dose and age group. Table 13 and Table 14 display the various populations analysed.

Out of the 60 subjects enrolled, 54 subjects were included in the ITT population and 25 in the PP population. The low number of subjects included in the PP population is mostly due to major protocol violations identified as temperature excursions for the study vaccine (21 subjects; 38.9%) and prohibited medication or vaccination (7 subjects; 13.0%).

Table 13: Analysis Populations by Dose Group, All Subjects

	IC51 0.25 mL n (%)	IC51 0.5 mL n (%)	Total n (%)
Safety Population	5 (100.0)	55 (100.0)	60 (100.0)
ITT Population	5 (100.0)	49 (89.1)	54 (90.0)
PP Population	3 (60.0)	22 (40.0)	25 (41.7)

Table 14: Analysis Populations by Age Group, All Subjects

	≥ 2 months to < 3 years n (%)	≥ 3 years to < 12 years n (%)	≥ 12 years to < 18 years n (%)	Total n (%)
Safety Population	5 (100.0)	14 (100.0)	41 (100.0)	60 (100.0)
ITT Population	5 (100.0)	11 (78.6)	38 (92.7)	54 (90.0)
PP Population	3 (60.0)	5 (35.7)	17 (41.5)	25 (41.7)

Immunogenicity results

A summary of SCRs and GMTs at Day 0, Day 56 and Month 7 is presented in Table 15 for the ITT Population.

Table 15: Geometric Mean Titers and Seroconversion Rates by Dose Group, ITT Population

	IC51 0.25 mL	IC51 0.5 mL	Total
Baseline (Visit 0)			
Seroconversion rate			
N	5	49	54
n (%)	0	0	0
95% CI	0.0; 43.4	0.0; 7.3	0.0; 6.6
Geometric mean titers, value			
Geometric mean (SD)	5.00 (1.000)	5.00 (1.000)	5.00 (1.000)
95% CI for geometric mean	5.00; 5.00	5.00; 5.00	5.00; 5.00
Median (min, max)	5.0, 5.0	5.0, 5.0	5.0, 5.0
Day 56 (Visit 3)			
Seroconversion rate			
N	5	46	51
n (%)	5 (100.0)	46 (100.0)	51 (100.0)
95% CI	56.6; 100.0	92.3; 100.0	93.0; 100.0
Geometric mean titers, value			
Geometric mean (SD)	216.18 (1.776)	332.11 (2.560)	318.42 (2.498)
95% CI for geometric mean	105.97; 441.00	251.22; 439.04	246.14; 411.93
Median (min, max)	259.00 (102.0, 457.0)	313.00 (56.0, 7380.0)	307.00 (56.0, 7380.0)
Month 7 (Visit 4)			
Seroconversion rate			
N	2	16	18
n (%)	2 (100.0)	16 (100.0)	18 (100.0)
95% CI	34.2; 100.0	80.6; 100.0	82.4; 100.0
Geometric mean titers, value			
Geometric mean (SD)	47.96 (3.445)	84.00 (2.120)	78.93 (2.199)
95% CI for geometric mean	0.00; 3214485.72	56.28; 125.36	53.34; 116.79
Median (min, max)	47.96 (20.0, 115.0)	103.50 (17.0, 234.0)	103.50 (17.0, 234.0)

The GMT was slightly higher in the PP Population (483.91 [95% CI: 300.46 to 779.36]) at

Day 56 (Visit 3) than in the ITT Population for the 0.5 ml group.

Further analysis of GMTs stratified by age group and travel to endemic areas were performed. Post dose 2, GMT in the ≥ 2 months to < 3 years age group was 216.18 (95% CI: 105.97 to 441.00); in the ≥ 3 to < 12 years group was 498.78 (95% CI: 201.80 to 1232.77); and in the ≥ 12 to < 18 years group was 292.26 (95% CI: 225.74 to 378.39). While GMTs were similar in the youngest and oldest group at Day 56, the wide 95% CI in the middle age group would suggest the mean titer for that group should be treated with caution. This was due to a single extremely high PRNT50 titer of 7380 in Subject 22205010, a 7.1-year-old female.

CHMP commented that there is a large difference in number of subjects between ITT (54 subjects) and PP (25 subjects) populations. As much as 54% of the subjects had a major protocol violation. This was mainly due to unsatisfactory monitoring of temperature during storage of study vaccine (39% of

subjects) and use of another medicine/vaccine (13% of subjects). While emphasis has been on presenting immunogenicity results in the ITT population, the possible impact of using a vaccine which could be of lower quality due to exposure to extreme temperature was not discussed. It is reported that the GMT values of the PP population (GMT 483) was higher than for the ITT population (GMT 332).

The MAH thoroughly discussed the consequences of inappropriate temperature excursions (including excursions of -1.7°C for 24 hours or up to 16°C for 1 hour) and provided further immunogenicity analysis specific for the group of vaccinees having received such vaccine doses (TDP).

The MAH asserted that it is important to note that the sample size of the overall study and hence the PP population was limited. It is therefore probable that due to the low number of subjects the differences between ITT and PP population did not reach statistical significance (see Table 16) as seen by the large degree in overlap of 95% CI's for GMT. The true GMT for the PP population is likely to be between 300 and 780, which would include the 332 observed in the ITT population. Additionally, the lowest and highest observed individual PRNT titer was found in subjects from the PP population, i.e. a subject who received study vaccine stored under the correct conditions between 2-8°C.

Table 16: IC51-322: GMT with IXIARO 0.5 ml Dose on Day 56 for ITT and PP Population

	GMT at Day 56, PP Population	**GMT at Day 56, ITT Population**
n	22	46
Geometric Mean (GMT)	483.91	332.11
95% CI for GM	300.46; 779.36	251.22; 439.04
SD	2.930	2.560
Median	444.19	313.00
Min, Max	56.0, 7380.0	56.0, 7380.0

A total of 36 subjects (66.7%) were associated with at least one protocol deviation/violation up to the data cut-off date of the interim report. Of these, 29 subjects (53.7%) were excluded from the PP population due to major protocol deviations/violations. The most frequently reported major deviations/violations were temperature excursions involving study vaccine administered to 21 subjects (38.9%).

The temperature excursions occurred at 6 study centers and in most cases were the result of the vaccine storage temperature not being monitored using a minimum or maximum thermometer, so it was not possible to confirm that the temperature had been kept within the required temperature range during storage. The storage temperature deviations ranged from short-term excursions where the product was exposed to high temperatures e.g. up to 16°C for 1 hour; to conditions where monitoring was inadequate over longer time periods (e.g. minimum/maximum thermometers not used) and where intermittent, documented spikes in storage temperatures outside the required 2-8°C conditions were estimated to have occurred for periods of between 12-24 hours.

- Antibody Titers in Subjects with Temperature Deviations

Table 17 summarizes the results comparing the GMT measured for PP subjects and the Temperature Deviations Population (TDP). This comparison shows that the sample sizes of the TDP and PP populations are very limited with only 22 for the PP and 21 for the TDP. The 95% CI for GMT in the PP and TDP population overlap. Again, not only the highest but also the lowest observed individual PRNT titer was found in a subject from the PP population, i.e. a subject received study vaccine stored under the correct conditions between 2-8°C.

Table 17: GMTs between subjects in PP population and subjects with major PV temperature excursion for the IC51 0.5 mL treatment group following post dose 2

Visit		PP population (N=22)	Subjects with major PV temperature excursion (N=21)
	Geometric mean	**483.91**	**253.38**
	Median	447.00	277.50
	Min / Max	56.00 / 7380.00	100.00 / 727.00
	95% CI	[300.46, 779.36]	[184.64, 347.73]
	Total	22	18

All subjects in the TDP group seroconverted and a GMT of 253 was determined which is numerically lower as for the PP population (484). However for five subjects exceptionally high titers were reported in the PP group. For one subject having received two vaccine doses stored below 0°C a neutralizing antibody titer of 532 was measured. All subjects in the TDP group had at least a titer of 100, which is well above the accepted neutralizing cut-off titer of 1:10. Since such temperature excursions might also happen regularly in routine practice, the immunogenicity data derived from the ITT population are quite valuable as they most likely reflect antibody titers, which could be expected in the field.

It was noted that the MAH took immediate corrective and preventive actions upon notice of inappropriate vaccine storage.

Although the study aimed to recruit 100 children, it has not been possible to complete the recruitment goal in the 35 months since first study initiation in December 2009, despite considerable efforts and multiple study locations on three continents.

As of 18 October 2012, Intercell has only been able to recruit 95 children (which mirrors the low projected use of IXIARO in the pediatric segment). If recruitment into the study continues at a comparable rate, it is projected that the last subject would be enrolled at approximately end of February 2013; resulting in Last Subject Last Visit in September 2013 and the availability of a final CSR in Q2 2014.

No further interim analysis is planned. As the study design has changed (approved PIP Modification Request EMEA-000559-PIP01-09-M03) and serological samples are no longer collected, the extent of additional immunogenicity data that would become available from an interim analysis is very limited.

Further information provided during assessment on concerns raised by CHMP

- The low number immunogenicity data from children < 1 year, 25 subjects from endemic region (Philippines) and 3 from non-endemic region (Europe) is a concern.

The MAH discussed how one can be confident that the measured immune response is representative for healthy children of that age group in endemic as well as non-endemic regions.

It is acknowledged that the amount of immunogenicity data from children below one year of age is limited. Nonetheless, Intercell is convinced that the available data are sufficient to judge immunogenicity and conclude that IXIARO has a favorable risk benefit profile for the prevention of a potentially deadly or debilitating disease in that age group.

Following considerations were provided:

- The seroconversion rate in IC51-323 in children < 1 year of age was 100%, or 28 of 28 subjects. While the N is indeed low, the resulting 95% CI for the SCR of 87.8-100.1 shows that there is a 95% probability that the SCR is at least about 88%. Even if on hypothesized that the vaccine's SCR was really only 88% in the children < 1 year and the risk-benefit profile would be evaluated based on this rate, the vaccine would probably still be acceptable. In the case of JEV vaccine, seroconversion rate is synonymous with seroprotection rate as the cut-off titer of 1:10 in the neutralization assay (PRNT) is accepted to represent a protective titer. There are other licensed traveler's vaccines which offer protection in that range, e.g. against Cholera (Dukoral SmPC: 85% Protective Efficacy (95%CI: 56 - 95).
- Not only the SCR is high, but also the rate of subject with at least 4- or 10-fold increases in titers is at comparably high levels, 96.4% for both (95%CI: 83.4 - 98.3), the highest rate observed in any age group for 10-fold increase; underlining that the immune response in this age group is very pronounced.
- Of all age groups investigated, GMT was highest in the children < 1 year of age. As the number of subjects is limited, the confidence intervals for the GMT are wider than in an ideal situation where no recruitment concerns exist and higher sample sizes can be obtained. However, while the "true" GMT in this age group may not have been precisely established, even the lower bound of the confidence interval for GMT (284 to 740) in that age group is higher than the GMT in any other age group, again demonstrating a very profound immune response to vaccination with IXIARO in the children below 1 year of age. In addition, a titer of 10 is considered protective, and the limited precision of the GMT may not be a concern with respect to clinical relevance, as even the lower boundary of the 95%CI is at a magnitude 28 times above this cut-off.
- With respect to generalizability of results obtained in a JEV endemic population, reference is made to the response to Questions 7 and 12 which discuss in more detail that the clinically most relevant outcome measure, seroconversion i.e. seroprotection rates, were constantly seen not to be influenced by pre-existing immunity on Day 56

The CHMP commented that although limited data are available in children below 1 year of age there is no indication that the vaccine is not immunogenic in this age group. All subjects seroconverted and high GMTs were observed across the studies.

- While authorization is sought in Europe, the main paediatric study was performed in the Philippines, an endemic country. European population immunogenicity data are available from only 51 children between 2 months and 18 years as reported in the interim report from an on-going study. From the study in Philippines, immunogenicity data are available from 496 children. The MAH should elaborate to what extent the immunogenicity data from an endemic area (Philippines) applies to Europe, a non-endemic region.

The MAH responded that several factors may influence the applicability of data generated in one population to another population, e.g. age, ethnicity, socio-economic factors; but the factor most prominent in the present study is certainly the pre-existing immunity against JEV and DENV that has been observed in the Philippines study population but is not expected to exist in European travelers. The study thus had pre-defined endpoints addressing these factors, i.e. immunogenicity analysis stratified by JEV and DENV baseline status, and by age. In addition, further post-hoc analyses were performed, in which immunogenicity was analyzed separately for subjects who were baseline negative for both JEV and DENV, resulting in a subgroup that from an immunological standpoint should be most comparable to the situation in naïve, European pediatric travelers. Table 18 summarizes immunogenicity on Day 56 stratified by age, for the JEV+DENV positive and JEV+DENV negative subjects from IC51-323, as well as for subjects from IC51-322.

SCR on Day 56 was not impacted by baseline JEV or DENV serostatus and was high in both studies, all age groups and all subjects regardless of their Flavivirus status at baseline. As seroconversion in the case of JEV vaccine translates to seroprotection, this observation is considered to have the highest clinical relevance.

Subjects who were classified as "seropositive" for either JEV, DENV, JEV+DENV or JEV and/or DENV tended to have lower titers shortly after vaccination i.e. on Day 56 compared to seronegative subjects in study IC51-323. Thus, a previously hypothesized memory response in pre-exposed subjects obviously did not occur. The results generated in an endemic population therefore do not overestimate the magnitude of immune response one would see in non-endemic population, if any it would represent an underestimate which certainly would be less of a concern.

Accordingly, when the subjects who were negative to both JEV+DEN are compared to the respective results in subjects in study IC51-322, it appears that titers in IC51-322 are slightly higher where the sample sizes permit interpretation. (Note there was one subject with an extremely high titer of over 7000 in study IC51-322 in the age group 3- <12 years in which GMT is considerably higher compared to JEV+DENV negative subjects in IC51-323; see also response to Question 1). Especially in the adolescents, with 35 subjects the largest age group in study IC51-322, GMTs between the two groups are fairly similar at about 240 (IC51-323 JEV/DENV negative subgroup) and 290 (IC51-322).

Table 18: Seroconversion and Raw Geometric Mean Titers on Day 56, in Study IC51-322 and Study IC51-323 Stratified by Pre-existing JEV and DENV Serostatus and by Age Group, Intent-to-treat Population

	Day 56 SCR n (%) [95%CI]			Day 56 GMT [95%CI]		
	IC51-323 JEV + DENV Seropositive at Baseline	IC51-323 JEV + DENV Seronegative at Baseline	IC51-322 Non-endemic for JEV/DENV	IC51-323 JEV + DENV Seropositive at Baseline	IC51-323 JEV + DENV Seronegative at Baseline	IC51-322 Non-endemic for JEV/DENV
0.25 ml Dose						
< 1 year	2 (100) [34.2, 100]	19 (100) [83.2, 100]	5 (100.0) [56.1, 100.4]	949.97 [0.05,1.678E7]	432.65 [239.25, 782.39]	216.18 [105.97, 441.0]
1-<3 years	3 (100) [43.9, 100]	101 (99.0) [94.7,99.8]		500.45 [23.28,10760.2]	273.25 [222.72, 335.25]	
3- < 12 years	11 (100) [74.1, 100]	44 (97.8) [88.4,99.6]	n.a.	99.23 [57.2, 172.13]	189.12 [133.98, 266.95]	n.a.
0.5 ml Dose						
3- < 12 years	15 (100) [79.6, 100]	45 (100) [92.1, 100]	11 (100.0) [73.9, 100.3]	125.10 [85.71, 182.6]	313.50 [235.96, 416.51]	498.78 [201.8, 1232.77]
12-<18 years	53 (100) [93.2, 100]	26 (100) [87.1, 100]	35 (100.0) [90.0, 100.1]	163.63 [122.5, 218.56]	243.58 [169.51, 350.04]	292.26 [225.74, 378.39]

At Month 7, persistence of immunity appeared to be better in most age and dose groups with SCRs slightly - moderately higher in those groups that contained a significant proportion of JEV positive

subjects (i.e. subgroups "seropositive" for JEV, JEV+DENV or JEV and/or DENV). A similar effect has been demonstrated in adults where prior or concomitant TBE vaccination has been found to impact duration of protection (IC51-303 study report Month 60; submitted as FUM). As duration of protection was found to be lower in a study that was conducted in an entirely TBE-naïve population, IC51-305 submitted as part of variation II-005, the booster recommendation for IXIARO in adults was set based on that lower estimate. Currently, the Month 7 immunogenicity results in study IC51-323 cannot be contrasted to results from the non-endemic population in IC51-322 in a meaningful way, as only 18 children completed that study to the Month 7 time point at the time of the interim analysis. However the data are awaited to conclude on antibody persistence in western populations.

Apart from differing Flavivirus immunity status, ethnic factors could also limit the applicability of data generated in the Philippines to the European pediatric population. Ethnicity has been a factor that has been investigated in the licensure trial in adults for IXIARO, IC51-301. Stratified analysis did not reveal any difference in the immune response to IXIARO (and neither to JE-VAX) at Day 56, with GMTs and SCRs generally similar across different ethnicities (Caucasian, Black or African American, Asian and Other).

Albeit the number of subjects was limited, the immunogenicity results for persons with Asian background observed in study IC51-301 do not indicate an impaired immune response to the vaccine as compared to Caucasians or a difference in response patters to IXIARO and JE-VAX. At Day 56, GMTs and SCRs were generally similar across different races (Caucasian, Black or African American, Asian and Other) in both the IXIARO® and JE-VAX® groups (study IC51-301, post hoc analyses) (Table 19).

Table 19: Seroconversion Rates and Geometric Mean Titers At Day 56 Stratified by Ethnic Origin: Per Protocol Population (Study IC51-301)

Race	SCR[1] n (%)		SCR risk difference[2] % [95% CI]	GMT (n)		GMT ratio estimate[3] [95%CI]
	IXIARO®	JE-VAX®		IXIARO®	JE-VAX®	
Caucasian, N=604	284 (96.3)	293 (94.8)	1.65 [-0.90, 4.19]	234.2	100.0	2.33 [1.93, 2.81]
Black or African American, N=84	43 (97.7)	34 (85.0)	9.98 [-0.69, 20.65]	324.2	114.8	2.89 [1.73, 4.81]
Asian and other, N=47	25 (96.2)	20 (95.2)	-3.33 [-11.86, 5.19]	235.4	109.9	2.13 [1.12, 4.06]
P-value	p=0.5142[4]	p=0.5559[4]		p=0.2588[5]	p=0.8934[5]	

In conclusion, immunogenicity in Flavivirus naïve (i.e. DENV and JEV negative) subjects from study IC51-323 conducted in the Philippines and immunogenicity in Flavivirus-naïve subjects from trial IC51-322 conducted in Europe, US and Australia appear to be well comparable; and analysis based on the entire study population in IC51-323 would also not result in an overestimation of the response in children in non-endemic settings as pre-existing Flavivirus immunity appears to lead to lower titers.

In addition, findings from adults that the immune response to IXIARO is not influenced by ethnicity may be extrapolated to the pediatric population.

- o Interaction between IXIARO and other travel vaccines has not been studied in children. As more than one travel vaccine is often administered, the presence or absence of interactions should be known. The absence of data on interaction in children should be justified. Further vaccine interaction studies in the appropriate age groups, especially in young children should be considered.

The MAH responded that the interaction between IXIARO and other travel vaccines was and is being studied in adults. One trial found that there was no interference with the immune response to either vaccine when IXIARO was given with Hepatitis A vaccine (HAVRIX). Two further studies are ongoing which investigate whether there are any interactions of IXIARO when administered with Meningococcal conjugate vaccine and Rabies vaccine. A further study which will study concomitant or consecutive administration of IXIARO with Hepatitis A and B vaccine and injectable Typhoid vaccine is planned. The MAH asserts that results from these trials in adults can be extrapolated to the paediatric population, as underlying immunological mechanisms of interference – if any - would probably not differ substantially between children (at least for those with matured immune system e.g. approximately from ages above 1 year on) and adults. It is acknowledged that extrapolation of data from adults to the very young age groups (infants, toddlers below 1 year) should be applied with lower confidence as for older children; on the other hand interference between vaccine components of pediatric combination vaccines have been studied extensively in this age group. While differences in the magnitude of antibody responses were found for some antigens (n.b., comparing administration of combined product with concomitant administrations of single components) those were not clinically significant due to generally high seroresponse rates or titers in infants (e.g., Guerra et al, 2009).

It is acknowledged that more than one travel vaccine may be given to children, as is the case for adults. However, the feasibility of conducting interference studies that are adequately sized to obtain meaningful data in that particular very young age group is considered virtually impossible as recruitment experience from study IC51-322 has shown - reflecting very low projected use of IXIARO (and consequently any co-vaccination with IXIARO even lower) in the very young age group.

With respect to possible combinations, Rabies vaccine is considered the most important concomitantly administered vaccine, because the profile of travelers who are recommended JE and Rabies pre-exposure prophylaxis overlap in many aspects (e.g. prolonged rural exposure, hiking, farming, hunting, camping etc.). Interference between IXIARO and Rabipur (Rabies vaccine) is currently under investigation in adults.

Other vaccines that may be important to travelers are Hepatitis A and B Virus vaccines. For adults, it has been demonstrated that Hepatitis A vaccine does not interfere with the response to IXIARO or vice versa. A study investigating interference between Hepatitis B vaccine and IXIARO in adults is in planning stage. Intercell expects that concomitant administration with Hepatitis B vaccine will be of limited relevance for medical care of pediatric travelers, since by 2004 the majority of European member states had introduced Hepatitis B vaccination the routine childhood vaccination programs.

Routine pediatric vaccines would be the only vaccines for which interaction data could not be derived from adults. These vaccines however are given at very young ages, making it unlikely that concomitant administration with IXIARO will be common, as travel itineraries for which JEV vaccine is recommended are very unlikely to be undertaken with infants.

The CHMP concluded that the MAH provided information about ongoing or planned studies on concomitant use with other travelers' vaccines. It is acknowledged that any concomitant use study in very young children is most likely not feasible.

- The current indication is restricted to adults. There is no discussion on the relevance of the recommendations for a booster dose to children that received a primary vaccination from the age of two months. The MAH should discuss the need for a booster dose to children of different age categories, especially the youngest ones, and plans to establish recommendations for a booster vaccine.

As with other inactivated viral vaccines and as in adults, the MAH expects a booster dose in children to become necessary for IXIARO. However, the optimal timing of a booster may not be the same for children as for adults, especially when considering that the initial immune response to the primary schedule is considerably higher in children, especially in the younger age groups. These initially higher titers might result in a longer interval until titers decline below the protective threshold in a relevant fraction of vaccinees, so potentially a booster dose may be required at a later time point for certain age groups.

While the limited currently available data show that the antibody titers decline considerably in all age groups (as expected), the protection rates observed in studies IC51-323 and -322 at Month 7 still remain substantial, again especially in the youngest age groups (< 1 of age); pointing to a good persistence of immunity in children (see Table 20). However, in the absence of long-term follow-up data from JEV non-endemic regions it would be premature to conclude on a booster recommendation.

Table 20 Persistence of neutralizing antibodies against IXIARO: Adult and Pediatric Clinical studies

Study Code / Age and Dose	Day 56 SCR / GMT	Month 6 / 7 SCR /GMT	Month 12 / 15 SCR /GMT	Month 24 SCR /GMT	Month 36 SCR /GMT
ADULTS					
IC51-303 N = 181	99% / 311	95% / 84	83% / 41	82% / 44	85% / 44
IC51-305 N = 116	97% / 219	83% / 47	58% / 18	48.3 %/ 16	
IC51-311 N = 198	97% / 171	n.d.	69% / 23 (Month 15)	n.d. (not done)	n.d.
PEDIATRIC					
IC51-322					
0.25 ml < 3 yrs N = 5	100% / 216	100% / 48 *	n.d. (IC51-324)	n.d. (IC51-324)	n.d. (IC51-324)
0.5 ml / ≥ 3 yrs N = 46	100% / 332	100% / 84 **	n.d. (IC51-324)	n.d. (IC51-324)	n.d. (IC51-324)
IC51-323					
0.25 ml < 1 yrs N = 28	100% / 458	100% / 89	n.d. (IC51-325)	n.d. (IC51-325)	n.d. (IC51-325)
0.25 ml 1 - < 3 yrs N = 124	99.2% / 259	85.5% / 39	n.d. (IC51-325)	n.d. (IC51-325)	n.d. (IC51-325)
0.5 ml 3 - < 12 yrs N = 100	100% / 214	91.0% / 44	n.d. (IC51-325)	n.d. (IC51-325)	n.d. (IC51-325)
0.5 ml 12 - < 18 yrs N = 137	100% / 176	97.1% / 87	n.d. (IC51-325)	n.d. (IC51-325)	n.d. (IC51-325)

The MAH and PDCO have agreed on study plans to establish a booster recommendation for IXIARO in children during the PIP procedure. Specifically, two trials were agreed on and are proceeding; both are follow-up studies of children enrolled in the pivotal studies IC51-323 / Philippines and IC51-322 / Non-endemic countries. Brief outlines of these studies are provided below:

Clinical Studies on Antibody Persistence and Booster in Children:

IC51-324:

This is an uncontrolled, open-label Phase 3 study including subjects aged ≥ 9 months to < 21 years who have completed study IC51-322 in the immunogenicity subgroup. Safety and immunogenicity follow-up visits will take place at 12, 24, and 36 months after first vaccination in study IC51-322. Subjects will be withdrawn from the study as soon as their neutralizing antibody titers are known to be negative. No formal hypothesis testing will be performed. Study IC51-324 is currently ongoing. Recruitment has been completed and a total of 23 subjects could be enrolled into this study. This study will provide information on the duration of protection after primary vaccination with IXIARO in children, in a JEV non-endemic setting. As the children in this study are not at risk of JEV infection after their initial travel, no booster doses were administered.

IC51-325:

This is a randomized, open-label Phase 3 study including children aged ≥9 months to <17 years and 7 months (at the time of enrolment into IC51-325) who have been vaccinated with IXIARO (two vaccinations) in study IC51-323. Only subjects receiving the confirmed dose in the dose-finding run-in phase of study IC51-323 will be included in IC51-325. A total of 300 children will be recruited stratified by age and randomized 1:1 into two groups. One group will be followed for 36 months after the first IXIARO vaccination in study IC51-323 (Non-booster Group) to evaluate the long-term immunity and safety. The second group will receive a booster dose of IXIARO at 12 months after the first IXIARO vaccination (Booster Group) and will be followed for another 24 months to evaluate the booster response and long-term immunity and the safety profile of a booster dose.

The IXIARO dose administered for boosting depends on the age of the subject at the visit at which the booster dose is given. Subjects aged ≥14 months to <3 years (at the respective study visit) will receive a 0.25 ml dose; subjects aged ≥3 years to ≤18 years will receive a dose of 0.5 ml. Study IC51-325 is currently ongoing, recruitment has been completed. The final study report from an interim analysis carried out 1 month after the booster will become available over the next months.

Plans to Establish A Pediatric Booster Recommendation:

To determine the appropriate timing for a booster dose in children, a review of results from multiple clinical trials, focusing on duration of protection after priming in JEV endemic settings (potential of natural boosting) and non-endemic settings and on the immunogenicity and safety of a booster dose will be required:

- Immunogenicity and safety of a booster dose in children: These data will be provided by Study IC51-325
- Antibody persistence in children after primary immunization: A small cohort of children from JEV non-endemic regions is being followed-up in study IC51-324; a larger cohort of children is being followed in study IC51-325 but these are children from JEV endemic areas.
- Further supportive data on antibody persistence for 6 months after the completed primary schedule, in JEV non-endemic settings, will become available with the final study report of study IC51-322. The presently submitted Interim Analysis only includes data from a total of 18 children followed up to Month 7.

The CHMP commented that it is noted that antibody persistence and booster studies are performed in children and adolescents as agreed with PDCO. Two follow-up studies are currently ongoing. The MAH will provide the antibody persistence/booster data of both studies and plans to update the product

information afterwards This is deemed to be acceptable. Nonetheless the MAH is asked to provide the interim report for study IC51-325 as soon as this is available (1Q2013).

- The MAH should discuss if the immune response in infants and the youngest children is expected to cover a broad range of strains from different genotypes as demonstrated in adults. Potentially, there could be a difference in cross-reactivity in response between naïve subjects and exposed subjects. The MAH should justify the lack of data on cross-reactivity with other JEV strains in the youngest children.

Based on the responses provided by the MAH, the CHMP remarked that indeed following marketing authorization, the MAH presented data on cross-neutralization experiments using different genotypes (Genotype 1-4) and recent isolates (Genotype 1 and 3). In these experiments it was confirmed that sera from adult vaccinees having received two doses of Ixiaro were capable to neutralize all six JEV strains tested regardless of the genotype of the strain or whether the strain was recently isolated (Ref. FUM017, March 2010). Indeed, there is no indication or reason to assume that the neutralizing antibody response elicited by Ixiaro differs in adult subjects and children. Current available data does not suggest that other inactivated JEV vaccines induce diverging neutralizing antibody responses in different age categories.

- There is little information submitted on the use of other inactivated JEV vaccines in children from 2 months of age on a global basis. As there is no JEV vaccine used as a comparator to the youngest children (< 1 year) in the studies, information on recommendations for dosing and booster doses to the youngest children for other licensed vaccines would be supportive and should be provided.

The MAH asserts that vaccination against JEV is not routinely performed at ages below 12 months in South-East Asia. WHO even recommends to not vaccinate children less than 6 months of age, on the one hand because the incidence of JE is very low in infants, and on the other hand because interference with maternal antibodies was a theoretical concern by WHO.

Based on review of available information, relatively little information from the current use of JE vaccines in Asia may be directly applicable to IXIARO used as a paediatric traveller's vaccine, due to the different routes of administration, schedules and vaccine technologies (no adjuvants in the inactivated vaccines used widely in Asia to date). However, it appears that both the use of a half antigen dose in children below the age of 3 years and a schedule of two initial doses followed by a third dose after approximately one year, similar to the primary schedule and booster dose of IXIARO in adults, are basic concepts in the prevention of JE through inactivated vaccines in the JEV endemic regions.

CHMP concludes that the MAH's review shows that JEV vaccines are not approved in children below 6 months of age in countries endemic for JEV and most countries recommend it from the age of 1 year onwards.

2.3.2. Discussion on immunogenicity /clinical efficacy

Results of three clinical trials conducted in children and adolescents were submitted to support approval of the paediatric indication of Ixiaro; two studies were performed in endemic regions (IC51-221 and IC51-323) and one study is performed in non-endemic countries (IC51-322). The study in non-endemic countries is still ongoing but an interim report was available.

Study IC51-221 was a phase 2 study designed to identify and establish the optimal dose in healthy children aged 1 to 3 years in comparison to the licensed inactivated vaccine JEV vaccine JenceVac. This study was performed in India, where JEV is endemic. The immunogenicity results demonstrated that the SCRs and GMTs obtained with the two dose levels of Ixiaro (0.25ml/3µg and 0.5ml/6µg) were similar and that both dose levels of Ixiaro induced antibody responses comparable to the active comparator JenceVac. In conclusion the 0.25ml vaccine dose was found to elicit high SCRs and acceptable GMT levels post dose 2 in children aged 1 to 3 years. Based on these study data the PDCO agreed that no further dose finding study was needed in children <3 years of age.

The second study conducted in JEV endemic regions IC51-323 was designed to assess the safety of Ixiaro in children aged ≥ 2 months to < 18 years in comparison to two licensed vaccines, Havrix 720 and Prevnar. Additional objective of this study was to evaluate two different dosages of Ixiaro (0.25ml or 0.5ml) in children aged ≥ 3 to <12 years, in order to define appropriate dosing regimens with respect to safety and immunogenicity. The study was conducted only in study centres in the Philippines, although it was initially planned to include centres in Malaysia as well. Conduct of the study in Malaysia was however not initiated as the request of the national authorities to use another inactivated JEV vaccine as comparator seemed not feasible. According to the study report, no JEV vaccine is licensed in the Philippines. Although, JEV is endemic in that country, the MAH provided satisfactory justification for the lack of JEV vaccine as a comparator included in study IC51-323.

The determination of anti JEV and DENV antibody titers at baseline prior vaccination shows that pre-existing maternal antibodies against JEV and DENV are present in a high proportion of small children below 6 months (anti-JEV: 30% and anti-DENV: 60%), while in children aged 6 months to <1year no JEV antibodies and in only 10% DENV antibodies were found. In contrast from the age of 1 year onwards the number of baseline seropositive subjects increases due to natural infection with JEV or DENV. The seropositivity rates for JEV for children aged 1 to <3 years were comparable to the rates observed in study IC51-221 (3.2% vs 4.2%). The baseline seropositivity rates for children 3 to <12 years of age were generally comparable in the two vaccination groups (0.25ml and 0.5ml) and 12-17% of subjects were found seropositive for JEV prior vaccination and 50-52% were seropositive for DENV. In the age group of the 12 to <18 years old approx. 46% were seropositive for JEV and 74% for DENV.

The immunogenicity results of study IC51-323 demonstrate high immune response rates post dose 2 for both treatment groups with SCRs of 98-100% and GMTs of 190-199. This results must be cautiously interpreted since the outcome of the immunogenicity analysis by treatment group is impacted by the fact that the study design allows overlapping age categories, i.e. the age group of the 3 to <12 year olds received either 0.5ml or 0.25ml. Therefore further immunogenicity analyses stratified by treatment group and age were provided. Moreover a significant difference in the antibody levels was observed following administration of either 0.25ml or 0.5ml vaccine. Children receiving the half dose (0.25ml) had lower GMTs post dose 2 and at month 7 (113.89 and 28.76) compared to children receiving the full vaccine dose (213.67 and 43.60). At Month 7 only 77.1% of children in the half dose group had neutralizing antibody titers ≥1:10, while a SCR of 91.0% was reported in children in the ‘full dose’ group. Since the baseline characteristics, especially as regards JEV and DENV seropositivity, were comparable for both vaccination

groups, the difference in the magnitude of the immune response is deemed to result from the higher antigen dose and is not due to cross-reactive factors.

In conclusion for the age group of 3 to <12 years old the immunogenicity data clearly demonstrate that the 'full dose' regimen elicits higher neutralising antibody responses than the 'half dose' regimen and thus the full-dose regimen is recommended for this age category.

In the age group of the 1 to <3 years old a SCR of 99.2% and a GMT of 258.9 was reported at day 56, which confirms the results of the phase II study IC51-221 for the 0.25ml vaccine dose. At month 7, the neutralising antibody titres declined and a SCR of 85.5% and GMT of 38.91 were determined. With respect to persistence of neutralising antibodies, it is currently uncertain whether this age group might benefit from a higher vaccine dose as no 6-month antibody persistence data are available for the 0.5ml dose group.

All infants aged 2 months to <1 year had neutralising antibody titres of ≥1:10 post dose 2 and at Month 7. The GMTs declined from 457.93 at day 56 to 88.6 at month 7. A high proportion of these children, especially the 2 to 6 months old had pre-existing immunity against JEV and DENV most likely due to persisting maternal antibodies, which might impact the magnitude of the immune response post dose 2.

Since no information on a booster vaccination is available, the robustness of the immune responses in children and adolescents cannot be finally assessed. Results from booster vaccinations in adult subjects indicate however that the immune response can be "boostered" in subjects with low or no detectable antibody levels up to 24 month following the primary vaccination series. The MAH discussed the need for a booster dose to children of different age categories.

The analysis stratified by baseline JEV antibody status shows, that all seronegative children and adolescents from 3 to <18 years receiving the full vaccine dose regimen (IC51 2x0.5ml) seroconverted post dose 2. The GMT observed at day 56 was 203 for baseline seronegative subjects, which is in the same range as previously reported for adults from non-endemic countries. At Month 7 a SCR of 92.4% and a GMT of 52.8 were measured for subjects without pre-existing JEV immunity. Baseline DENV seropositivity seems to negatively impact the antibody responses post dose 2 but not at Month 7.

In order to assess the combined impact of JEV and DENV baseline seropositivity on the immune response to the different doses of Ixiaro the MAH was asked to provide further analyses stratified by JEV+DENV baseline immunity as well as stratified by JEV+DENV baseline immunity and stratified in age categories of 2 months to 1 year, 1-<3 years, 3-<12 years and 12 -<18 years.

Although limited, the available immunogenicity data indicate that Ixiaro is highly immunogenic in children and adolescents. Immunogenicity analysis stratified by baseline serostatus and age revealed that post dose 2 all JEV/DENV naïve subjects except one in the age group of the 1-3 years old seroconverted. The GMTs were highest in the youngest age group of the 2-<12 months old naïve subjects although only data from 19 subjects are available. In the group of the 1-<3 years a lower GMT of 273 was achieved than in the group below 1 year of age. This GMT is comparable to the GMT of 332.1 reported in study IC51-322 for the ITT population and well above the accepted seroprotective titer of 1:10.

Following marketing authorization the MAH presented data on cross-neutralization experiments using different genotypes (Genotype 1-4) and recent isolates (Genotype 1 and 3). In these experiments it was confirmed that sera from adult vaccinees having received two doses of Ixiaro were capable to neutralize all six JEV strains tested regardless of the genotype of the strain or whether the strain was recently isolated (Ref. FUM017, March 2010). Indeed there is no indication or reason to assume that the neutralizing antibody response elicited by Ixiaro differs in adult subjects and children. Currently available data do not suggest that other inactivated JEV vaccines induce diverging neutralizing antibody responses in different age categories.

Antibody persistence data up to 6 months after the last dose further indicate that in JEV/DENV naïve subjects the neutralizing response declines slightly faster than in JEV seropositive subjects. As stated, studies to evaluate antibody persistence and booster doses are currently ongoing and an interim report on IC51-325 is available during 1Q2013.

Further information was provided on studies investigating concomitant use with Ixiaro.

2.4. Clinical Safety aspects

2.4.1. Methods – analysis of data submitted

IC51-221

A seven-day follow-up (day 0 to day 6) of solicited local and general adverse events was performed by the subject's parents / legal representative/guardian post 60 minutes after vaccination. Data concerning the following adverse experiences were solicited using subject diary and case report form (Table 21).

Table 21: Solicited adverse events IC51-221

Local Tolerability (injection site)	Systemic Tolerability
Local Pain	Fever
Itching	Sleep disturbance
Tenderness	Unusual crying
Hardening	Unusual drowsiness
Swelling	Loss of appetite
Redness	Diarrhoea
	Vomiting
	Rash

Any other unsolicited adverse event reported at any time till the study completion was recorded.

IC51-322

Subject Diary Symptoms (solicited AEs) Day 0- Day 6:

- Injection site reactions: injection site pain, itching, tenderness, hardening, swelling, redness
- Systemic tolerability: headache, muscle pain, flu-like symptoms, excessive fatigue, rash, fever (measured), nausea, vomiting, diarrhea, irritability, loss of appetite

Additionally, the following information was collected: symptoms present after Day 6 (yes/no), last day of symptoms (date). There was the possibility to add other unsolicited symptoms of local and/or systemic AEs as free text.

IC51-323

The primary endpoint was the rate of subjects with SAEs and medically-attended AEs up to Day 56 in the treatment groups Ixiaro (IC51), HAVRIX 720 and Prevnar, i.e., 4 weeks after the completed primary immunization. For evaluating the secondary endpoints of the study the following safety data were collected:

- Rate of subjects with SAEs and medically-attended AEs up to Month 7 after the first vaccination.
- Rate of subjects with solicited local and systemic AEs assessed with a subject diary for 7 consecutive days after each vaccination (except for Month 7).
- Rate of subjects with unsolicited AEs up to Day 56 and up to Month 7 after the first vaccination.
- Rate of subjects with abnormal laboratory parameters (hematology, biochemistry, urinalysis) up to Day 56 and up to Month 7 after the first vaccination.

Subjects had to be children and adolescents of good general health aged ≥ 2 months to < 18 years at the time of the first vaccination. If female, the subject was to have either no childbearing potential or, if after menarche, a negative pregnancy test and willingness to practice a reliable method of contraception. Subjects must not have been vaccinated against JEV, yellow fever, West Nile virus or DENV at any time before the study.

2.4.2. Results

IC51-221

All 60 subjects randomised received at least one dose. Thereof, 58 subjects received all doses of study vaccine as per protocol. i.e., 24 subjects in IC51 – 3µg dose group, 22 subjects in IC51 – 6µg dose group and 12 subjects in JenceVac group received all doses of study vaccine. No subjects were withdrawn from the study.

Table 22 summarizes all adverse events, which were observed during the study.

Table 22: Overview of adverse events in children aged 1-<3 years of age in study IC51-221

	IC51 3mcg N=24 n (%)	IC51 6mcg N=24 n (%)	JenceVac™ N=12 n (%)	All N=60 n (%)	p-Value*
Number of Adverse Events (% against total events)	**3 (23.1)**	**5 (38.5)**	**5 (38.5)**	**13 (100)**	
Number of Subjects with at least one Adverse Event	**3 (12.5)**	**5 (20.8)**	**4 (33.3)**	**12 (20.0)**	**0.2850**
Fever	0 (0.0)	1 (4.2)	1 (8.3)	2 (3.3)	
Injection Site Tenderness	2 (8.2)	3 (12.5)	3 (25)	8 (13.3)	
Skin Lesion	1 (4.2)	0 (0.0)	0 (0.0)	1 (1.7)	
Skin Rash	0 (0.0)	1 (4.2)	0 (0.0)	1 (1.7)	

In total 13 AEs were reported by 12 subjects, all AEs were mild in nature. Injection site tenderness was most frequently reported from all three vaccination groups. Overall more adverse events were reported from subjects, who received JenceVac compared to both dose groups of Ixiaro. No differences in reporting frequencies of adverse events were observed between the two dose groups of Ixiaro. No serious adverse events were reported during the study.

Laboratory Values Over Time

During the course of the entire study, there were no clinically significant abnormal laboratory parameters or for urinalysis for any enrolled subject. No abnormalities were observed for vital signs within the course of the study.

IC51-322 (Interim Analysis)

At the time of data cut-off, 60 subjects (100.0%) had been administered 1 vaccination and 56 of those subjects (93.3%) had been administered a second vaccination. 53 subjects (88.3 %) had completed Visit 3 (Day 56) and 22 subjects (36.7%) had completed the study at Visit 4 (Month7). Verified diary data for the 7 days after the first vaccination were available for analysis for 59 subjects (98.3%) and for the 7 days after the second vaccination for 52 subjects (92.9%).

Only treatment-emergent AEs are presented, i.e., those AEs that started on or after Day 0.

In the safety results, 'Day 56' refers to data collected at Visit 3 rather than a strict cut-off of 56 days after dosing; likewise 'Month 7' refers to data collected at Visit 4. Table 23 shows the disposition of subjects by dose group.

Table 23: Subject disposition by dose group

	IC51 0.25 mL n (%)	IC51 0.5 mL n (%)	Total n (%)
Enrolled	5	55	60
Safety Population	5 (100.0)	55 (100.0)	60 (100.0)
ITT Population	5 (100.0)	49 (89.1)	54 (90.0)
PP Population	3 (60.0)	22 (40.0)	25 (41.7)
Ongoing in the study (prior to Visit 3)	0	6 (10.9)	6 (10.0)
Completed Visit 3	5 (100.0)	48 (87.3)	53 (88.3)
Completed the study (Visit 4)	3 (60.0)	19 (34.5)	22 (36.7)
Premature discontinuation from the study		1 (1.8)	1 (1.7)
Consent withdrawn		1 (1.8)	1 (1.7)

In total 5 children in the age of two months to <3 years , 14 children in the age of 3 years to <12 years as well as 41 children and adolescents in the age of 12 to <18 years were enrolled.

Mean age of subjects was 12.50 years (median 15.19; range 0.9 to 17.9 years) for the Safety Population and most subjects were Caucasian (83.3%). The proportion of females (56.7%) was greater than males (43.3%). No subject (ITT Population) had PRNT50 titers ≥ 1:10 at baseline.

Solicited adverse events by maximum severity after the first vaccination are shown in Table 24.

Table 24: Solicited adverse events experienced by subjects within 7 days after first vaccination

	IC51 0.25 mL N=5					IC51 0.5 mL N=55					
Severity Grade[a]	1 %	2 %	3 %	All % (n/N)	[95% CI]	1 %	2 %	3 %	All % (n/N)	[95% CI]	p-value
Any Local AE	20.0	0	0	20.0 (1/5)	[0.5, 71.6]	40.0	0	0	40.0 (22/55)	[27.0, 54.1]	0.640
Injection site pain	0	0	0	(0/2)	[0.0, 52.2]	18.2	0	0	18.2 (10/55)	[9.1, 30.9]	0.578
Injection site itching	0	0	0	(0/2)	[0.0, 52.2]	3.6	0	0	3.6 (2/55)	[0.4, 12.5]	1.000
Injection site tenderness	0	0	0	(0/5)	[0.0, 52.2]	30.9	0	0	30.9 (17/55)	[19.1, 44.8]	0.309
Injection site hardening	20.0	0	0	20.0 (1/5)	[0.5, 71.6]	0	0	0	(0/55)	[0.0, 6.5]	0.083
Injection site swelling	0	0	0	(0/5)	[0.0, 52.2]	0	0	0	(0/55)	[0.0, 6.5]	
Injection site redness	20.0	0	0	20.0 (1/5)	[0.5, 71.6]	5.5	0	0	5.5 (3/55)	[1.1, 15.1]	0.301
Any Systemic AE	20.0	0	0	20.0 (1/5)	[0.5, 71.6]	40.0	1.8	0	41.8 (23/55)	[28.7, 55.9]	0.639
Irritability	0	0	0	(0/5)	[0.0, 52.2]	0	0	0	(0/55)	[0.0, 6.5]	
Nausea	0	0	0	(0/2)	[0.0, 52.2]	0	1.8	0	1.8 (1/55)	[0.0, 9.7]	1.000
Vomiting	0	0	0	(0/5)	[0.0, 52.2]	0	0	0	(0/55)	[0.0, 6.5]	
Diarrhea	20.0	0	0	20.0 (1/5)	[0.5, 71.6]	1.8	0	0	1.8 (1/55)	[0.0, 9.7]	0.161
Flu-like symptoms	0	0	0	(0/2)	[0.0, 52.2]	0	0	0	(0/55)	[0.0, 6.5]	
Excessive fatigue	0	0	0	(0/5)	[0.0, 52.2]	10.9	1.8	0	12.7 (7/55)	[5.3, 24.5]	1.000
Muscle pain	0	0	0	(0/2)	[0.0, 52.2]	27.3	0	0	27.3 (15/55)	[16.1, 41.0]	0.318
Rash	0	0	0	(0/5)	[0.0, 52.2]	1.8	0	0	1.8 (1/55)	[0.0, 9.7]	1.000
Headache	0	0	0	(0/2)	[0.0, 52.2]	1.8	0	0	1.8 (1/55)	[0.0, 9.7]	1.000
Loss of appetite	0	0	0	(0/5)	[0.0, 52.2]	1.8	0	0	1.8 (1/55)	[0.0, 9.7]	1.000
Fever	0	0	0	(0/5)	[0.0, 52.2]	3.6	1.8	0	5.5 (3/55)	[1.1, 15.1]	1.000

A total of 34 subjects (56.7%) experienced a solicited local or systemic AE within the 7 days after the first vaccination.

Twenty-three subjects (38.3%) experienced at least 1 solicited local AE. All solicited local AEs were classified as Grade 1. The most frequently reported were injection site tenderness (pain upon touching) (17 subjects [28.3%]) and injection site pain (pain without touching) (10 subjects [17.5%]).

Twenty-four subjects (40.0%) experienced at least 1 solicited systemic AE after the first vaccination (Table 24). Most solicited systemic AEs were of Grade 1 except for the solicited AEs of nausea, excessive fatigue and fever, all of Grade 2 and experienced by 1 subject. These solicited AEs remained at that severity for no more than 1 day. The most frequently reported solicited systemic AEs were muscle pain (15 subjects [26.3%]) and excessive fatigue (7 subjects [11.7%]).

After second vaccination fewer subjects (19 subjects [35.2%] experienced a solicited local or systemic adverse event within 7 days after the first vaccination. Fifteen subjects (27.8%) experienced at least 1 solicited local AE. All AEs were Grade 1.

As after the first vaccination, the most frequently reported solicited local AEs were injection site tenderness (12 subjects [22.2%]) and injection site pain (8 subjects [15.7%]).

Nine subjects (16.7%) experienced at least 1 solicited systemic AE after the second vaccination. The majority of AEs were Grade 1. One subject (1.9%) reported Grade 2 irritability. Another subject (1.9%) reported Grade 3 headache after the second vaccination and Grade 2 nausea, excessive fatigue and fever after the first vaccination. Both AEs of irritability and headache lasted no more than 1 day.

Unlike after the first vaccination, the most frequently reported solicited systemic AEs were irritability (3 subjects [5.6%]) and headache (2 subjects [3.9%]).

The most frequently reported solicited local AEs after both vaccinations combined were injection site tenderness (22 subjects [36.7%]) and injection site pain (14 subjects [24.6%]). The most frequently reported solicited systemic AEs after both vaccinations combined were muscle pain (15 subjects [26.3%]), excessive fatigue (7 subjects [11.7%]) and fever (4 subjects [6.7%]).

The CHMP commented that the number of subjects, who received 0.25 ml of the vaccine, is too limited to draw any final conclusion on the safety of Ixiaro in small children from non-endemic regions. Additionally

for a better overview of solicited adverse events the MAH should provide a summary of all solicited adverse events after both vaccinations to evaluate the frequency or solicited AEs in non-endemic countries.

The MAH provided the requested overview (Table 25) of solicited adverse events after both vaccinations of study IC51-322.

Table 25

Table 26 Solicited Adverse Events Experienced by Subjects within 7 Days after Both Vaccinations Combined by Maximum Severity, Safety Population

	IC51 0.25 mL N=5					IC51 0.5 mL N=55					
Severity Grade[a]	1 %	2 %	3 %	All % (n/N) [95% CI]		1 %	2 %	3 %	All % (n/N) [95% CI]		p-value
Any Local AE	**40.0**	**0**	**0**	**40.0 (2/5)**	**[5.3, 85.3]**	**49.1**	**0**	**0**	**49.1 (27/55)**	**[35.4, 62.9]**	**1.000**
Injection site pain	0	0	0	0 (0/5)	[0.0, 52.2]	25.5	0	0	25.5 (14/55)	[14.7, 39.0]	0.329
Injection site itching	0	0	0	0 (0/5)	[0.0, 52.2]	5.5	0	0	5.5 (3/55)	[1.1, 15.1]	1.000
Injection site tenderness	0	0	0	0 (0/5)	[0.0, 52.2]	40.0	0	0	40.0 (22/55)	[27.0, 54.1]	0.148
Injection site hardening	20.0	0	0	20.0 (1/5)	[0.5, 71.6]	1.8	0	0	1.8 (1/55)	[0.0, 9.7]	0.161
Injection site swelling	0	0	0	0 (0/5)	[0.0, 52.2]	0	0	0	0 (0/55)	[0.0, 6.5]	NC
Injection site redness	40.0	0	0	40.0 (2/5)	[5.3, 85.3]	5.5	0	0	5.5 (3/55)	[1.1, 15.1]	0.051
Any Systemic AE	**20.0**	**0**	**0**	**20.0 (1/5)**	**[0.5, 71.6]**	**41.8**	**1.8**	**1.8**	**45.5 (25/55)**	**[32.0, 59.4]**	**0.377**
Irritability	0	0	0	0 (0/5)	[0.0, 52.2]	3.6	1.8	0	5.5 (3/55)	[1.1, 15.1]	1.000
Nausea	0	0	0	0 (0/5)	[0.0, 52.2]	1.8	1.8	0	3.6 (2/55)	[0.4, 12.5]	1.000
Vomiting	0	0	0	0 (0/5)	[0.0, 52.2]	1.8	0	0	1.8 (1/55)	[0.0, 9.7]	1.000
Diarrhea	20.0	0	0	20.0 (1/5)	[0.5, 71.6]	1.8	0	0	1.8 (1/55)	[0.0, 9.7]	0.161
Flu-like symptoms	0	0	0	0 (0/5)	[0.0, 52.2]	0	0	0	0 (0/55)	[0.0, 6.5]	NC
Excessive fatigue	0	0	0	0 (0/5)	[0.0, 52.2]	10.9	1.8	0	12.7 (7/55)	[5.3, 24.5]	1.000
Muscle pain	0	0	0	0 (0/5)	[0.0, 52.2]	27.3	0	0	27.3 (15/55)	[16.1, 41.0]	0.318
Rash	0	0	0	0 (0/5)	[0.0, 52.2]	3.6	0	0	3.6 (2/55)	[0.4, 12.5]	1.000
Headache	0	0	0	0 (0/5)	[0.0, 52.2]	3.6	0	1.8	5.5 (3/55)	[1.1, 15.1]	1.000
Loss of appetite	0	0	0	0 (0/5)	[0.0, 52.2]	1.8	0	0	1.8 (1/55)	[0.0, 9.7]	1.000
Fever	0	0	0	0 (0/5)	[0.0, 52.2]	5.5	1.8	0	7.3 (4/55)	[2.0, 17.6]	1.000

Furthermore the applicant bridged the safety data from populations in JEV endemic countries Protocol IC51-323 to the western population, because the adverse event rate of the subjects after vaccination is independent on their baseline pre-existing immunity as shown in Table 26. Additionally, the AE rates did not differ substantially for the subjects neither for the 0.25 ml nor for the 0.5 mL dose group (all ages combined).

Table 26

Table 27 Summary of Treatment-Emergent Adverse Events to Study Completion by Pre-Existing JEV Status, Safety Population

JEV Seropositive	IC51 0.25 mL N=39 n (%) [95% CI]	IC51 0.5 mL N=169 n (%) [95% CI]	HAVRIX®720 N=79 n (%) [95% CI]	Prevnar® N=6 n (%) [95% CI]	IC51 N=208 n (%) [95% CI]	Total
Number of subjects with at least one:						
Solicited or unsolicited AE	32 (82.1%) (66.5%, 92.5%)	89 (52.7%) (44.9%, 60.4%)	35 (44.3%) (33.1%, 55.9%)	5 (83.3%) (35.9%, 99.6%)	121 (58.2%) (51.2%, 65.0%)	
Any Related Solicited or Unsolicited AE	18 (46.2%) (30.1%, 62.8%)	57 (33.7%) (26.6%, 41.4%)	19 (24.1%) (15.1%, 35.0%)	5 (83.3%) (35.9%, 99.6%)	75 (36.1%) (29.5%, 43.0%)	

JEV Seronegative	IC51 0.25 mL N=828 n (%) [95% CI]	IC51 0.5 mL N=371 n (%) [95% CI]	HAVRIX®720 N=313 n (%) [95% CI]	Prevnar® N=58 n (%) [95% CI]	IC51 N=1199 n (%) [95% CI]	Total
Number of subjects with at least one:						
Solicited or unsolicited AE	671 (81.0%) (78.2%, 83.7%)	218 (58.8%) (53.6%, 63.8%)	226 (72.2%) (66.9%, 77.1%)	53 (91.4%) (81.0%, 97.1%)	889 (74.1%) (71.6%, 76.6%)	
Any Related Solicited or Unsolicited AE	412 (49.8%) (46.3%, 53.2%)	129 (34.8%) (29.9%, 39.9%)	112 (35.8%) (30.5%, 41.4%)	40 (69.0%) (55.5%, 80.5%)	541 (45.1%) (42.3%, 48.0%)	

In addition to this stratified analysis, covariate analysis were performed to determine the impact of treatment group, age, baseline JEV and baseline DENV immunity on safety, and these support the findings from the stratified analysis.

Within the age group ≥ 2 months to < 1 year the AE rate correlated statistically significant with age (OR: 12.5, p = 0.05, indicating AE rate increasing with age). No such correlation was found for pre-existing JEV-status, pre-existing DENV status and vaccine group.

Table 27

Table 14.3.2.3 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

The CHMP commented that the MAH showed that the safety data generated in JEV endemic countries can be extrapolated to the non-endemic western countries. The analyses presented indicate that the AE rates are independent of the treatment group or pre-existing immunity of JEV and DENV. Age was the only effect significantly associated with the AE rate to Day 56 in subjects aged ≥ 2 months to < 1 year. Higher AE rates were observed in children aged close to 1 year than in the younger children in the age group ≥ 2 months to < 1 year.

Unsolicited adverse events up to day 56 are summarized in Table 28 (IC51-322).

Table 28: Unsolicited adverse events to Day 56

	IC51 0.25 mL N=5 n (%) [95% CI]	IC51 0.5 mL N=55 n (%) [95% CI]
Number of subjects with at least one AE	3 (60.0) [14.7, 94.7]	9 (16.4) [7.8, 28.8]
General disorders and administration site conditions	2 (40.0) [5.3, 85.3]	2 (3.6) [0.4, 12.5]
Influenza-like illness	1 (20.0) [0.5, 71.6]	1 (1.8) [0.0, 9.7]
Pyrexia	2 (40.0) [5.3, 85.3]	0 [0.0, 6.5]
Fatigue	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]
Respiratory, thoracic and mediastinal disorders	0 [0.0, 52.2]	3 (5.5) [1.1, 15.1]
Asthma	0 [0.0, 52.2]	2 (3.6) [0.4, 12.5]
Cough	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]
Oropharyngeal pain	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]
Gastrointestinal disorders	1 (20.0) [0.5, 71.6]	1 (1.8) [0.0, 9.7]
Diarrhea	1 (20.0) [0.5, 71.6]	1 (1.8) [0.0, 9.7]
Nausea	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]
Infections and infestations	0 [0.0, 52.2]	2 (3.6) [0.4, 12.5]
Nasopharyngitis	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]
Otitis media chronic	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]
Tonsillitis	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]
Nervous system disorders	0 [0.0, 52.2]	2 (3.6) [0.4, 12.5]
Headache	0 [0.0, 52.2]	2 (3.6) [0.4, 12.5]
Skin and subcutaneous tissue disorders	1 (20.0) [0.5, 71.6]	1 (1.8) [0.0, 9.7]
Dermatitis contact	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]
Pruritus	1 (20.0) [0.5, 71.6]	0 [0.0, 6.5]
Rash erythematous	1 (20.0) [0.5, 71.6]	0 [0.0, 6.5]
Injury, poisoning and procedural complications	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]
Laceration	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]
Musculoskeletal and connective tissue disorders	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]
Myalgia	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]
Psychiatric disorders	1 (20.0) [0.5, 71.6]	0 [0.0, 6.5]
Initial insomnia	1 (20.0) [0.5, 71.6]	0 [0.0, 6.5]
Reproductive system and breast disorders	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]
Dysmenorrhea	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]

Twelve subjects (20.0%) were reported with unsolicited AEs to Day 56 (Visit 3); all had a maximum intensity of mild (Grade 1; 9 subjects [15.0%]) or moderate (Grade 2; 3 subjects [5.0%]). Influenza-like illness, pyrexia, asthma, diarrhea and headache (2 subjects [3.3%] each) were the most frequently reported AEs.

Two subjects (3.3%) had unsolicited AEs that were considered to be possibly related to study vaccine. Subject 22204001, from the IC51 0.5 mL group, reported cough and oropharyngeal pain (both mild: Grade 1) 2 days after the first vaccination. Subject 22515001, from the IC51 0.25 mL group, was reported with pruritus and erythematous rash, both mild (Grade 1), 8 days after the first vaccination with a duration of 2-3 days.

A total of 19 subjects (31.7%) were reported with unsolicited AEs to Month 7 (Visit 4) at the time of data cut-off.

The majority of AEs to Month 7 were of mild (13 subjects [21.7%]) or moderate (4 subjects [6.7%]) intensity (Grade 1 or 2). One subject (Subject 22413009 from the IC51 0.5 mL group) had a potentially life-threatening (Grade 4) AE of type 1 diabetes mellitus (also classified as serious), which was considered unlikely related to study vaccine by the investigator.

Tables 29 and 30 summarize the percentage of solicited, unsolicited, related events with their severity grades of events as well as specially monitored events in two time periods.

Table 29: Summary of all adverse events to day 56

	IC51 0.25 mL N=5 n (%) [95% CI]	IC51 0.5 mL N=55 n (%) [95% CI]
Number of subjects with at least one:		
AE (solicited or unsolicited)	3 (60.0) [14.7, 94.7]	37 (67.3) [53.3, 79.3]
Related AE (solicited or unsolicited)	3 (60.0) [14.7, 94.7]	35 (63.6) [49.6, 76.2]
Solicited AE	2 (40.0) [5.3, 85.3]	35 (63.6) [49.6, 76.2]
Unsolicited AE	3 (60.0) [14.7, 94.7]	9 (16.4) [7.8, 28.8]
Unsolicited AE that was:		
Probably related	0 [0.0, 52.2]	0 [0.0, 6.5]
Possibly related	1 (20.0) [0.5, 71.6]	1 (1.8) [0.0, 9.7]
Solicited or unsolicited AE with severity grade of:		
Grade 1	3 (60.0) [14.7, 94.7]	33 (60.0) [45.9, 73.0]
Grade 2	0 [0.0, 52.2]	3 (5.5) [1.1, 15.1]
Grade 3	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]
Grade 4	0 [0.0, 52.2]	0 [0.0, 6.5]
SAE	0 [0.0, 52.2]	0 [0.0, 6.5]
Related SAE	0 [0.0, 52.2]	0 [0.0, 6.5]
SAE or medically-attended AE	1 (20.0) [0.5, 71.6]	2 (3.6) [0.4, 12.5]
Medically-attended AE	1 (20.0) [0.5, 71.6]	2 (3.6) [0.4, 12.5]
Related medically-attended AE	0 [0.0, 52.2]	0 [0.0, 6.5]
Unsolicited AE of special interest	1 (20.0) [0.5, 71.6]	3 (5.5) [1.1, 15.1]
Related unsolicited AE of special interest	1 (20.0) [0.5, 71.6]	0 [0.0, 6.5]
Discontinuation due to an AE	0 [0.0, 52.2]	0 [0.0, 6.5]

Table 30: Summary of all adverse events to month 7

	IC51 0.25 mL N=5 n (%) [95% CI]	IC51 0.5 mL N=55 n (%) [95% CI]
Number of subjects with at least one:		
AE (solicited or unsolicited)	4 (80.0) [28.4, 99.5]	40 (72.7) [59.0, 83.9]
Related AE (solicited or unsolicited)	3 (60.0) [14.7, 94.7]	36 (65.5) [51.4, 77.8]
Solicited AE	2 (40.0) [5.3, 85.3]	35 (63.6) [49.6, 76.2]
Unsolicited AE	4 (80.0) [28.4, 99.5]	15 (27.3) [16.1, 41.0]
Unsolicited AE that was:		
Probably related	0 [0.0, 52.2]	0 [0.0, 6.5]
Possibly related	1 (20.0) [0.5, 71.6]	2 (3.6) [0.4, 12.5]
Solicited or unsolicited AE with severity grade of:		
Grade 1	4 (80.0) [28.4, 99.5]	33 (60.0) [45.9, 73.0]
Grade 2	0 [0.0, 52.2]	4 (7.3) [2.0, 17.6]
Grade 3	0 [0.0, 52.2]	2 (3.6) [0.4, 12.5]
Grade 4	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]
SAE	0 [0.0, 52.2]	2 (3.6) [0.4, 12.5]
Related SAE	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]
SAE or medically-attended AE	1 (20.0) [0.5, 71.6]	5 (9.1) [3.0, 20.0]
Medically-attended AE	1 (20.0) [0.5, 71.6]	5 (9.1) [3.0, 20.0]
Related medically-attended AE	0 [0.0, 52.2]	1 (1.8) [0.0, 9.7]
Unsolicited AE of special interest	1 (20.0) [0.5, 71.6]	4 (7.3) [2.0, 17.6]
Related unsolicited AE of special interest	1 (20.0) [0.5, 71.6]	0 [0.0, 6.5]
Discontinuation due to an AE	0 [0.0, 52.2]	0 [0.0, 6.5]

Serious Adverse Events or Medically-attended Adverse Events

There were no SAEs reported up to Day 56. Three subjects (5.0%) reported medically-attended AEs to Day 56: pyrexia, nasopharyngitis, tonsillitis and asthma. None of these medically-attended AEs was considered related to study vaccine by the investigator. All of these AEs were either mild (Grade 1) or moderate (Grade 2).

A total of 6 subjects (10%) reported medically attended AEs and 2 subjects (3.3%) reported SAEs up to Month 7 (Visit 4) at the time of the data cut-off. One subject reported a potentially life-threatening (Grade 4) SAE of type 1 diabetes mellitus, considered unlikely related to study vaccine by the investigator. One subject had an SAE of dizziness, which was moderate in intensity (Grade 2) and considered possibly related to study vaccine by the investigator. One further subject reported severe (Grade 3) AEs of upper abdominal pain, vomiting and dehydration, which were medically-attended and considered not related to study vaccine by the investigator.

Adverse Events of Special Interest

Adverse events of special interest are predefined AEs potentially associated with allergy/hypersensitivity and neurological disorders. Four subjects (6.7%) had AEs of special interest to Day 56 (Visit 3); all were associated with potential allergy/hypersensitivity:

- Two subjects (3.3%) had AEs of asthma: one subject had 2 AEs of asthma, both considered to be not related to study vaccine by the investigator, 1 event starting the day after the first vaccination and resolving the same day and the second starting 6 months after the second vaccination and resolving the same day. One subject had an AE of asthma, considered unlikely related to study vaccine by the investigator, starting 9 days after the first vaccination and resolving 12 days later
- One subject (1.7%), Subject 22204001, had an AE of contact dermatitis, considered unlikely related to study vaccine by the investigator, which started 12 days after the first vaccination and was not noted to resolve.
- One subject (1.7%), Subject 22515001, had 2 AEs of special interest, pruritus and erythematous rash, both considered possibly related to study vaccine by the investigator. Both events started 8 days after the first vaccination and resolved 2 days later.

One additional AE of special interest was reported to Month 7 (Visit 4) at the time of data cut-off. The subject reported mild (Grade 1) paraesthesia, which was considered unlikely to be related to study vaccine by the investigator. The event started more than 4 months after the second vaccination and lasted 27 days.

Laboratory Values Over Time

No data are available in the interim report.

IC51-323

Each subject in the IC51 treatment group was to be vaccinated (two vaccinations) within a period of 28 days (± 4 days). Subjects in the comparator groups were to be vaccinated within a period of 7 months: Havrix 720 group, 2 vaccinations and Prevnar group, 3 vaccinations. Table 31 shows the overall extent of exposure.

Table 31: 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.

Overall, 195 subjects were given study vaccines in the ≥ 2 months to < 1 year age group; 853 subjects in the ≥ 1 year to < 3 years age group; 501 subjects in the ≥ 3 years to < 12 years age group; and 320 subjects in ≥ 12 years to < 18 years age group. Two subjects in the Prevnar group, 5 subjects in the total IC51 group and 7 subjects in the HAVRIX 720 group received only 1 dose of study vaccine.

Adverse events

A summary of AEs reported from Day 0 to Day 56 for the population aged ≥ 2 months to < 1 year is presented in Table 32.

Table 32: Summary of Adverse Events to Day 56 Reported for Subjects Aged ≥ 2 Months to < 1 Year, Safety Population

≥ 2 Months to < 1 Year	IC51 0.25 mL N=131 n (%) [95% CI]	Prevnar® N=64 n (%) [95% CI]	p-value	Total N=195 n (%) [95% CI]
Number of subjects with at least one:				
Solicited or unsolicited AE	110 (84.0) [76.5, 89.8]	56 (87.5) [76.8, 94.4]		166 (85.1) [79.3, 89.8]
Solicited AE	76 (58.0) [49.1, 66.6]	38 (59.4) [46.4, 71.5]		114 (58.5) [51.2, 65.5]
Unsolicited AE	95 (72.5) [64.0, 80.0]	42 (65.6) [52.7, 77.1]	0.323	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)	0.174	5 (2.6) [0.8, 5.9]
Possibly related	5 (3.8) [1.3, 8.7]	2 (3.1) [0.4, 10.8]	1.000	7 (3.6) [1.5, 7.3]
Solicited or unsolicited 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 (23.6) [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, 5.6]		1 (0.5) [0.0, 2.8]
SAE	0 [0.0, 2.8]	1 (1.6) [0.0, 8.4]	0.328	1 (0.5) [0.0, 2.8]
Related SAE	0 [0.0, 2.8]	0 [0.0, 5.6]		0 [0.0, 1.9]
Serious or medically-attended AE	50 (38.2) [29.8, 47.1]	27 (42.2) [29.9, 55.2]	0.641	77 (39.5) [32.6, 46.7]
Medically-attended AE	50 (38.2) [29.8, 47.1]	27 (42.2) [29.9, 55.2]	0.641	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]	0.664	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]	0.732	10 (5.1) [2.5, 9.2]
Related unsolicited AE of special interest	0 [0.0, 2.8]	0 [0.0, 5.6]		0 [0.0, 1.9]
AE that led to discontinuation	0 [0.0, 2.8]	0 [0.0, 5.6]		0 [0.0, 1.9]
AE that led to death	0 [0.0, 2.8]	0 [0.0, 5.6]		0 [0.0, 1.9]

In the ≥ 2 months to < 1 year age group, 76 subjects (58.0%) from the IC51 0.25 mL treatment group and 38 subjects (59.4%) from the Prevnar group were reported with at least 1 solicited AE to Day 56. Within 7 days of the first vaccination, solicited local AEs were reported by 19.1% of subjects in the IC51 0.25 mL group versus 31.7% of subjects in the Prevnar group; most frequently reported reaction was injection site redness.

Solicited systemic AEs after the first vaccination were reported by 35.9% of subjects in the IC51 0.25 mL group versus 39.7% of subjects in the Prevnar group; most frequently reported reactions were fever, irritability and diarrhea. Unsolicited AEs were reported by 95 subjects (72.5%) in the IC51 0.25 mL treatment group and 42 subjects (65.6%) in the Prevnar group.

One subject from the Prevnar treatment group was reported to have a SAE. None was reported in the IC51 group. Overall, 77 (39.5 %) had medically-attended AEs, 50 subjects (38.2 %) in the IC51 0.25 mL group and 27 subjects (42.2 %) in the Prevnar group. Of these, 3 subjects (2.3%) from the IC51 0.25 mL group and 2 subjects (3.1%) from the Prevnar group had medically-attended AEs that were considered by the investigator to be related to study vaccine.

Table 33 summarizes the adverse events to Day 56 for the subjects aged ≥ 1 year to <18 years.

Table 33: Summary of Adverse Events to Day 56 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	530 (71.6) [68.2, 74.8]	264 (48.9) [44.6, 53.2]	235 (59.6) [54.6, 64.5]		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]		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, 0.3]	0 [0.0, 0.2]

In the ≥ 1 year to < 18 years age group, 522 subjects (40.8%) from the total IC51 group and 116 subjects (29.4%) from the HAVRIX 720 group were reported with at least 1 solicited AE to Day 56 (Visit 3). Subjects in the HAVRIX 720 group received only 1 vaccination up to Day 56 compared to subjects in the IC51 groups who received 2 vaccinations.

Within 7 days of the first vaccination, solicited local AEs were reported by 11.4% of subjects in the IC51 0.25 mL group, 16.5% of subjects in the IC51 0.5 mL group and 13.7% of subjects in the HAVRIX 720 group; most frequently reported reactions were injection site pain and tenderness.

Solicited systemic AEs after the first vaccination were reported by 27.8% of subjects in the IC51 0.25 mL group (vaccinees aged 1 to < 12 years), 15.9% of subjects in the IC51 0.5 mL group (vaccinees aged 3 to < 18 years) and 19.3% of subjects in the HAVRIX 720 group (vaccinees aged 1 to < 18 years); most frequently reported reaction was fever. Unsolicited AEs were reported by 595 subjects (46.5%) from the total IC51 group and 183 subjects (46.4%) from the HAVRIX 720 group.

In the ≥ 1 year to < 18 years age group, 10 subjects (0.6%) overall had SAEs, 6 subjects (0.5%) in the total IC51 group and 4 subjects (1.0%) in the HAVRIX 720 group. A total of 262 subjects (15.7%) had medically-attended AEs (total IC51 group 206 subjects [16.1%]; HAVRIX 720 group 56 subjects [14.2%]). Of these, 12 subjects (0.9%) from the total IC51 group and 4 subjects (1.0%) from the HAVRIX 720 group had medically-attended AEs that were considered to be related to study vaccine by the investigator.

Tables 34 and 35 summarize all AEs reported from Day 0 to Month 7 including those AEs reported to Day 56 for both population groups.

Table 34: Summary of Adverse Events to Month 7 Reported for Subjects aged ≥ 2 Months to < 1 Year, Safety Population

≥ 2 Months to < 1 Year	IC51 0.25 mL N=131 n (%) [95% CI]	Prevnar® N=64 n (%) [95% CI]	p-value	Total N=195 n (%) [95% CI]
Number of subjects with at least one:				
Solicited or unsolicited AE	115 (87.8) [80.9, 92.9]	58 (90.6) [80.7, 96.5]		173 (88.7) [83.4, 92.8]
Solicited AE	76 (58.0) [49.1, 66.6]	44 (68.8) [55.9, 79.8]		120 (61.5) [54.3, 68.4]
Unsolicited AE	101 (77.1) [68.9, 84.0]	52 (81.3) [69.5, 89.9]	0.581	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]	0.666	6 (3.1) [1.1, 6.6]
Possibly related	5 (3.8) [1.3, 8.7]	3 (4.7) [1.0, 13.1]	0.719	8 (4.1) [1.8, 7.9]
Solicited or unsolicited 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]	1.000	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]	0.174	102 (52.3) [45.1, 59.5]
Medically-attended AE	64 (48.9) [40.0, 57.7]	38 (59.4) [46.4, 71.5]	0.174	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]	0.664	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]	0.213	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 that led to discontinuation	0 [0.0, 2.8]	0 [0.0, 5.6]		0 [0.0, 1.9]
AE that led to death	0 [0.0, 2.8]	0 [0.0, 5.6]		0 [0.0, 1.9]

In the ≥ 2 months to < 1 year age group, 58.0% of subjects from the IC51 0.25 mL group and 68.8% of subjects from the Prevnar group had at least one solicited AE during the study (i.e., to Month 7). Unsolicited AEs were reported for 77.1% of subjects from the IC51 0.25 mL group and 81.3% of subjects from the Prevnar group.

Until Month 7 (Visit 4), a total of 3 subjects (1.5%) were reported with a SAE, 2 subjects (1.5%) in the IC51 0.25 mL group and 1 subject (1.6%) from the Prevnar group (already reported to Day 56). None of the events were considered to be related to study vaccine by the investigator. A total of 64 subjects (48.9%) from the IC51 0.25 mL group and 38 subjects (59.4%) from the Prevnar group were reported with medically-attended AEs during the study. The number of subjects with medically-attended AEs considered to be related to study vaccine by the investigator remained unchanged from what was reported to Day 56, i.e., 3 subjects (2.3%) from the IC51 0.25 mL group and 2 subjects (3.1%) from the Prevnar group.

Table 35: Summary of Adverse Events to Month 7 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]

In the ≥ 1 year to < 18 years age group, 40.8% of subjects from the total IC51 group and 31.7% of subjects from the HAVRIX 720 group had at least 1 solicited AE during the study (to Month 7). Unsolicited AEs were reported by 58.5% of subjects in the total IC51 group and 57.6% of subjects from the HAVRIX 720 group.

Between Day 56 and study completion (Month 7), 1 fatal SAE of disseminated intravascular coagulation was reported for a 12-year-old subject; the event was considered not related to study vaccine by the investigator.

Until Month 7 (Visit 4), a total of 31 subjects (1.9%) had SAEs (total IC51 group 21 subjects [1.6%]; HAVRIX 720 group 10 subjects [2.5%]). Medically-attended AEs were reported by 337 subjects (26.3%) from the total IC51 group and 101 subjects (25.6%) from the HAVRIX 720 group.

One subject (0.1%) from the total IC51 group had a SAE that was considered to be related to study vaccine by the investigator (no subjects in the HAVRIX 720 group).

Thirteen subjects (1.0%) from the total IC51 group and 4 subjects (1.0%) from the HAVRIX 720 group had medically-attended AEs that were considered to be related to study vaccine by the investigator.

Analysis of adverse events

≥ 2 Months to < 1 Year

Table 36 shows solicited adverse events by maximum severity after the first vaccination for Subjects Aged ≥ 2 Months to < 1 Year.

Table 36: Solicited Adverse Events Experienced by Subjects Aged ≥ 2 Months to < 1 Year within 7 Days after the First Vaccination by Maximum Severity, Safety Population

≥ 2 Months to < 1 Year	IC51 0.25 mL N=131					Prevnar® N=64[a]					
Severity Grade[b]	1 %	2 %	3 %	All % (n/N)	[95% CI]	1 %	2 %	3 %	All % (n/N)	[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

Solicited local adverse events in the population aged ≥ 2 Months to < 1 Year 23.2 % (45 of 194) of subjects had at least 1 solicited local AE within 7 days after the first vaccination. More subjects experienced solicited local AEs in the Prevnar group (31.7 %) compared to the IC51 0.25mL group (19.1 %), especially regarding Tenderness. The majority of subjects experienced Grade 1 local AEs without reporting of Grade 3 or Grade 4 local AEs.

Solicited systemic AEs were experienced by 37.1% (72 of 194) of subjects and the proportions of subjects were similar in the IC51 0.25 mL (35.9% [47 of 131] of subjects) and the Prevnar groups (39.7% [25 of 63] of subjects). The most frequently reported systemic AEs were fever followed by irritability, diarrhoea and rash. Solicited systemic AEs were graded as Grade 1 in the majority of subjects and none as Grade 4 in the time period of seven days after first vaccination. Three subjects had Grade 3 AEs: 1 subject in the IC51 0.25 mL group had Grade 3 diarrhoea and in the Prevnar group 1 subject had Grade 3 fever and 1 subject had Grade 3 irritability.

Solicited AEs after second vaccination

A smaller proportion of subjects experienced solicited local AEs after the second vaccination (10.9% [21 of 192] subjects than after the first (23.2% [45 of 194]). As observed after the first vaccination, a greater proportion of subjects experienced solicited local AEs in the Prevnar group (18.0% [11 of 61] subjects) than in the IC51 0.25 mL group (7.6% [10 of 131] subjects); the difference was statistically significant (p-value 0.045). The most frequently reported solicited local AE after the second vaccination was injection site redness (IC51 0.25 mL, 5.3% [7 of 131]; Prevnar, 16.4% [10 of 61] subjects, the difference was statistically significant [p-value 0.026]). Total subjects experiencing other solicited local AEs ranged from 0 to 3. All solicited local AEs were of Grade 1 or Grade 2.

Solicited systemic AEs were experienced by a smaller proportion of subjects after the second vaccination (25.5% [49 of 192] subjects) than after the first (37.1% [72 of 194]). A greater proportion of subjects experienced solicited systemic AEs in the Prevnar group (31.1% [19 of 61] subjects) than in the IC51 0.25 mL group (22.9% [30 of 131] subjects).

Related unsolicited adverse events

A summary of AEs to Day 56 that were considered to be related (i.e., possibly or probably related) to study vaccine by the investigator is presented in Table 37.

Table 37: Related Unsolicited Adverse Events to Day 56, Subjects Aged ≥ 2 Months to < 1 Year, Safety Population

≥ 2 Months to < 1 Year	IC51 0.25 mL N=131 n (%) [95% CI]	Prevnar® N=64 n (%) [95% CI]	p-value	Total N=195 n (%)[95% CI]
Number of subjects with at least one related AE:	10 (7.6) [3.7, 13.6]	2 (3.1) [0.4, 10.8]	0.343	12 (6.2) [3.2, 10.5]
Infections and infestations	4 (3.1) [0.8, 7.6]	0 [0.0, 5.6]	0.305	4 (2.1) [0.6, 5.2]
Bronchitis	1 (0.8) [0.0, 4.2]	0 [0.0, 5.6]	1.000	1 (0.5) [0.0, 2.8]
Bronchopneumonia	1 (0.8) [0.0, 4.2]	0 [0.0, 5.6]	1.000	1 (0.5) [0.0, 2.8]
Viral infection	1 (0.8) [0.0, 4.2]	0 [0.0, 5.6]	1.000	1 (0.5) [0.0, 2.8]
Viral rash	1 (0.8) [0.0, 4.2]	0 [0.0, 5.6]	1.000	1 (0.5) [0.0, 2.8]
Investigations	2 (1.5) [0.2, 5.4]	1 (1.6) [0.0, 8.4]	1.000	3 (1.5) [0.3, 4.4]
ALT increased	2 (1.5) [0.2, 5.4]	1 (1.6) [0.0, 8.4]	1.000	3 (1.5) [0.3, 4.4]
AST increased	2 (1.5) [0.2, 5.4]	1 (1.6) [0.0, 8.4]	1.000	3 (1.5) [0.3, 4.4]
General disorders and administration site conditions	2 (1.5) [0.2, 5.4]	0 [0.0, 5.6]	1.000	2 (1.0) [0.1, 3.7]
Pyrexia	2 (1.5) [0.2, 5.4]	0 [0.0, 5.6]	1.000	2 (1.0) [0.1, 3.7]
Respiratory, thoracic and mediastinal disorders	2 (1.5) [0.2, 5.4]	0 [0.0, 5.6]	1.000	2 (1.0) [0.1, 3.7]
Cough	2 (1.5) [0.2, 5.4]	0 [0.0, 5.6]	1.000	2 (1.0) [0.1, 3.7]
Vascular disorders	1 (0.8) [0.0, 4.2]	1 (1.6) [0.0, 8.4]	0.550	2 (1.0) [0.1, 3.7]
Hematoma	1 (0.8) [0.0, 4.2]	1 (1.6) [0.0, 8.4]	0.550	2 (1.0) [0.1, 3.7]
Ear and labyrinth disorders	1 (0.8) [0.0, 4.2]	0 [0.0, 5.6]	1.000	1 (0.5) [0.0, 2.8]
Otorrhea	1 (0.8) [0.0, 4.2]	0 [0.0, 5.6]	1.000	1 (0.5) [0.0, 2.8]
Gastrointestinal disorders	1 (0.8) [0.0, 4.2]	0 [0.0, 5.6]	1.000	1 (0.5) [0.0, 2.8]
Stomatitis	1 (0.8) [0.0, 4.2]	0 [0.0, 5.6]	1.000	1 (0.5) [0.0, 2.8]

The overall proportion of subjects with related unsolicited AEs was slightly greater in the IC51 0.25 mL group (7.6% of subjects) than in the Prevnar group (3.1% of subjects). The most frequently reported related AEs overall were ALT and AST increased (2 subjects in the IC51 0.25 mL group and 1 subject in the Prevnar group). All the related AEs were mild (Grade 1) or moderate (Grade 2) in intensity.

Proportions of subjects aged ≥ 2 months to < 1 year with unsolicited AEs (related and unrelated to vaccination) up to Month 7 were similar in both treatment groups (IC51 0.25 mL group: 77.1% [101 of 131] subjects; Prevnar group: 81.3% [52 of 64] subjects).

As seen at Day 56, most of the AEs to Month 7 were infections and infestations. The most frequently reported unsolicited AEs were upper respiratory tract infection (47.7% of subjects) and pyrexia (13.8% of subjects). Proportions were similar across treatment groups.

≥ 1 year to < 18 age group

Solicited adverse events after first vaccination in subjects aged ≥ 1 year to < 18 age group are summarized in Tables 38 and 39.

Table 38: 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

≥ 1 to < 18 Years	IC51 0.25 mL N=740				IC51 0.5 mL N=540				HAVRIX®720 N=394					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]

In the population aged ≥ 1 year to < 18 years solicited local AEs were observed by 13.6 % of subjects (227 of 1674), who had at least one solicited local AE within 7 days after the first vaccination. The percentage of reported local AEs was slightly higher in the higher dose group of IC51 group compared to the lower dose group beside redness, which was reported more often in the lower dose group.

The frequency of reported local AEs was similar between the Havrix group and the total IC51 group. Most frequently was reported injection site pain, injection site tenderness and injection site redness in the range from 4.4 % to 7.8 % in both groups.

Solicited local AEs were classified as Grade 1 in the majority of subjects aged ≥ 1 year to < 18 years; no Grade 4 solicited local AEs were reported. One subject (IC51 0.5 mL treatment group) was reported as having Grade 3 swelling at the injection site.

Proportions of subjects were similar between treatment groups in subjects aged ≥ 1 year to < 3 years and ≥ 12 years to < 18 years. In subjects aged ≥ 3 years to < 12 years, a greater proportion of subjects in the total IC51 group (12.5%) experienced local AEs than in the HAVRIX 720 group (5.9%). The local AEs experienced by considerably greater proportions of subjects in the total IC51 group were injection site pain and tenderness.

Table 39: 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

≥ 1 to < 18 Years	IC51 0.25 mL N=740				IC51 0.5 mL N=540				HAVRIX®720 N=394					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	2.0	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	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	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	2.0	1.1	14.5 (185/1280) [12.6, 16.5]

Solicited systemic AEs were experienced by 22.0% of subjects (368 of 1674) aged ≥ 1 year to < 18 years within 7 days after the first vaccination. The proportions of subjects were similar in the total IC51 (22.8% [292 of 1280] subjects) and the HAVRIX 720 groups (19.3% [76 of 394] subjects). The most frequently reported systemic AEs were fever, irritability and flu-like symptoms in the range from 3.4 % to 14.5 %. More systemic AEs were reported in the lower dose group of IC51 compared to the higher dose group.

Solicited systemic AEs after the first vaccination were classified as Grade 1 in the majority of subjects aged ≥ 1 year to < 18 years and no Grade 4 solicited systemic AEs were reported. A total of 23 of 1674 subjects (1.4%) had Grade 3 solicited systemic AEs. Proportions were similar between groups: total IC51 group 1.3% of subjects and HAVRIX 720 group 1.5% of subjects. The most frequently reported Grade 3 AE was fever (14 subjects [1.1%] in the total IC51 group and 5 subjects [1.3%] in the HAVRIX 720 group). Other Grade 3 solicited systemic AEs across both treatment groups included loss of appetite (3 subjects [0.2%]), diarrhea and vomiting (2 subjects each [0.1%]), and flu-like symptoms, nausea and irritability (1 subject each [0.1%]).

In the individual age groups, proportions were similar between treatment groups except in those subjects aged ≥ 3 years to < 12 years. A slightly greater proportion of subjects in the total IC51 group (16.5%) experienced systemic AEs than in the HAVRIX720 group (10.9%).

Solicited adverse events after the second vaccination

Subjects in the total IC51 group were administered their second vaccination 28 days after the first and subjects in the HAVRIX 720 group, 7 months after their first vaccination, i.e., at study completion. For the HAVRIX 720 group, solicited AE data for only 60 minutes after the second vaccination are available; hence a comparison between the IC51 and HAVRIX 720 treatment groups on the number of subjects with solicited AEs after the second vaccination was not meaningful.

Unsolicited adverse events

A summary of related AEs (i.e., possibly or probably related) to Day 56 (Visit 3) is presented in Table 40.

Table 40: Related Unsolicited Adverse Events to Day 56 (Visit 3), 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 related AE:	43 (5.8) [4.2, 7.7]	7 (1.3) [0.5, 2.7]	15 (3.8) [2.1, 6.2]	<0.001	50 (3.9) [2.9, 5.1]	65 (3.9) [3.0, 4.9
Infections and infestations	20 (2.7) [1.7, 4.1]	2 (0.4) [0.0, 1.3]	7 (1.8) [0.7, 3.6]	0.003	22 (1.7) [1.1, 2.6]	29 (1.7) [1.2, 2.5
Upper respiratory tract infection	7 (0.9) [0.4, 1.9]	0 [0.0, 0.7]	3 (0.8) [0.2, 2.2]	0.050	7 (0.5) [0.2, 1.1]	10 (0.6) [0.3, 1.1
Gastroenteritis	6 (0.8) [0.3, 1.8]	1 (0.2) [0.0, 1.0]	1 (0.3) [0.0, 1.4]	0.310	7 (0.5) [0.2, 1.1]	8 (0.5) [0.2, 0.9]
Nasopharyngitis	4 (0.5) [0.1, 1.4]	1 (0.2) [0.0, 1.0]	2 (0.5) [0.1, 1.8]	0.624	5 (0.4) [0.1, 0.9]	7 (0.4) [0.2, 0.9]
Viral infection	2 (0.3) [0.0, 1.0]	0 [0.0, 0.7]	1 (0.3) [0.0, 1.4]	0.609	2 (0.2) [0.0, 0.6]	3 (0.2) [0.0, 0.5]
Pharyngitis	1 (0.1) [0.0, 0.8]	0 [0.0, 0.7]	0 [0.0, 0.9]	1.000	1 (0.1) [0.0, 0.4]	1 (0.1) [0.0, 0.3]
Rhinitis	1 (0.1) [0.0, 0.8]	0 [0.0, 0.7]	0 [0.0, 0.9]	1.000	1 (0.1) [0.0, 0.4]	1 (0.1) [0.0, 0.3]
General disorders and administration site conditions	14 (1.9) [1.0, 3.2]	4 (0.7) [0.2, 1.9]	5 (1.3) [0.4, 2.9]	0.235	18 (1.4) [0.8, 2.2]	23 (1.4) [0.9, 2.1
Pyrexia	12 (1.6) [0.8, 2.8]	2 (0.4) [0.0, 1.3]	5 (1.3) [0.4, 2.9]	0.087	14 (1.1) [0.6, 1.8]	19 (1.1) [0.7, 1.8
Influenza-like illness	1 (0.1) [0.0, 0.8]	2 (0.4) [0.0, 1.3]	1 (0.3) [0.0, 1.4]	0.822	3 (0.2) [0.0, 0.7]	4 (0.2) [0.1, 0.6]
Vaccination site inflammation	1 (0.1) [0.0, 0.8]	0 [0.0, 0.7]	0 [0.0, 0.9]	1.000	1 (0.1) [0.0, 0.4]	1 (0.1) [0.0, 0.3]
Gastrointestinal disorders	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
Diarrhea	3 (0.4) [0.1, 1.2]	0 [0.0, 0.7]	2 (0.5) [0.1, 1.8]	0.256	3 (0.2) [0.0, 0.7]	5 (0.3) 0.1, 0.7]
Vomiting	1 (0.1) [0.0, 0.8]	0 [0.0, 0.7]	2 (0.5) [0.1, 1.8]	0.173	1 (0.1) [0.0, 0.4]	3 (0.2) [0.0, 0.5]
Abdominal pain	1 (0.1) [0.0, 0.8]	0 [0.0, 0.7]	0 [0.0, 0.9]	1.000	1 (0.1) [0.0, 0.4]	1 (0.1) [0.0, 0.3]
Aphthous stomatitis	0 [0.0, 0.5]	0 [0.0, 0.7]	1 (0.3) [0.0, 1.4]	0.235	0 [0.0, 0.3]	1 (0.1) [0.0, 0.3]
Mucous stools	1 (0.1) [0.0, 0.8]	0 [0.0, 0.7]	0 [0.0, 0.9]	1.000	1 (0.1) [0.0, 0.4]	1 (0.1) [0.0, 0.3]
Respiratory, thoracic and mediastinal disorders	4 (0.5) [0.1, 1.4]	1 (0.2) [0.0, 1.0]	2 (0.5) [0.1, 1.8]	0.624	5 (0.4) [0.1, 0.9]	7 (0.4) [0.2, 0.9]
Cough	3 (0.4) [0.1, 1.2]	1 (0.2) [0.0, 1.0]	1 (0.3) [0.0, 1.4]	0.856	4 (0.3) [0.1, 0.8]	5 (0.3) [0.1, 0.7]
Dyspnea	0 [0.0, 0.5]	0 [0.0, 0.7]	1 (0.3) [0.0, 1.4]	0.235	0 [0.0, 0.3]	1 (0.1) [0.0, 0.3]
Epistaxis	1 (0.1) [0.0, 0.8]	0 [0.0, 0.7]	0 [0.0, 0.9]	1.000	1 (0.1) [0.0, 0.4]	1 (0.1) [0.0, 0.3]
Investigations	2 (0.3) [0.0, 1.0]	1 (0.2) [0.0, 1.0]	1 (0.3) [0.0, 1.4]	1.000	3 (0.2) [0.0, 0.7]	4 (0.2) [0.1, 0.6]
AST increased	2 (0.3) [0.0, 1.0]	1 (0.2) [0.0, 1.0]	0 [0.0, 0.9]	0.798	3 (0.2) [0.0, 0.7]	3 (0.2) [0.0, 0.5]
ALT increased	1 (0.1) [0.0, 0.8]	1 (0.2) [0.0, 1.0]	0 [0.0, 0.9]	1.000	2 (0.2) [0.0, 0.6]	2 (0.1) [0.0, 0.4]
Blood ALP increased	0 [0.0, 0.5]	0 [0.0, 0.7]	1 (0.3) [0.0, 1.4]	0.235	0 [0.0, 0.3]	1 (0.1) [0.0, 0.3]
Skin and subcutaneous tissue disorders	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]
Rash	1 (0.1) [0.0, 0.8]	0 [0.0, 0.7]	1 (0.3) [0.0, 1.4]	0.715	1 (0.1) [0.0, 0.4]	2 (0.1) [0.0, 0.4]
Heat rash	0 [0.0, 0.5]	0 [0.0, 0.7]	1 (0.3) [0.0, 1.4]	0.235	0 [0.0, 0.3]	1 (0.1) [0.0, 0.3]
Rash papular	1 (0.1) [0.0, 0.8]	0 [0.0, 0.7]	0 [0.0, 0.9]	1.000	1 (0.1) [0.0, 0.4]	1 (0.1) [0.0, 0.3]
Blood and lymphatic system disorders	1 (0.1) [0.0, 0.8]	0 [0.0, 0.7]	0 [0.0, 0.9]	1.000	1 (0.1) [0.0, 0.4]	1 (0.1) [0.0, 0.3]
Lymphadenopathy	1 (0.1) [0.0, 0.8]	0 [0.0, 0.7]	0 [0.0, 0.9]	1.000	1 (0.1) [0.0, 0.4]	1 (0.1) [0.0, 0.3]
Metabolism and nutrition disorders	0 [0.0, 0.5]	0 [0.0, 0.7]	1 (0.3) [0.0, 1.4]	0.235	0 [0.0, 0.3]	1 (0.1) [0.0, 0.3]
Decreased appetite	0 [0.0, 0.5]	0 [0.0, 0.7]	1 (0.3) [0.0, 1.4]	0.235	0 [0.0, 0.3]	1 (0.1) [0.0, 0.3]
Musculoskeletal and connective tissue disorders	1 (0.1) [0.0, 0.8]	0 [0.0, 0.7]	0 [0.0, 0.9]	1.000	1 (0.1) [0.0, 0.4]	1 (0.1) [0.0, 0.3]
Muscle hemorrhage	1 (0.1) [0.0, 0.8]	0 [0.0, 0.7]	0 [0.0, 0.9]	1.000	1 (0.1) [0.0, 0.4]	1 (0.1) [0.0, 0.3]
Nervous system disorders	0 [0.0, 0.5]	0 [0.0, 0.7]	1 (0.3) [0.0, 1.4]	0.235	0 [0.0, 0.3]	1 (0.1) [0.0, 0.3]
Headache	0 [0.0, 0.5]	0 [0.0, 0.7]	1 (0.3) [0.0, 1.4]	0.235	0 [0.0, 0.3]	1 (0.1) [0.0, 0.3]

The number of related AEs was higher in the IC51 0.25 mL group compared to the higher dose group and the Havrix 720 group. The overall proportion of subjects with related unsolicited AEs up to Visit 3 was similar in the IC51 and Havrix 720 groups (3.9 % and 3.8 % of subjects, respectively). The most frequently reported related AEs were pyrexia, upper respiratory tract infection and gastroenteritis in both vaccine groups.

The majority of unsolicited AEs (related and unrelated to vaccination) to Month 7 were mild. A total of 59 of 1674 subjects (3.5%) had AEs with a maximum intensity of severe (Grade 3). Proportions were similar in the total IC51 and HAVRIX 720 groups (3.6% [46 of 1280] and 3.3% of subjects [13 of 394], respectively). Severe unsolicited AEs included 34 of 1674 subjects (2.0%) with severe infections or infestations and 16 of 1674 subjects (1.0%) with severe pyrexia.

Four of 1674 subjects (0.2%), all from the total IC51 group, had a total of 6 AEs to Month 7 that were considered potentially life-threatening (Grade 4) in intensity: pneumonia, bronchopneumonia, bacterial meningitis, stillbirth, disseminated intravascular coagulation and Kawasaki's disease. All were classified as serious. Kawasaki's disease was the only SAE considered related to study vaccine by the investigator. Subjects with unsolicited AEs considered related to study vaccine to Month 7 were in the same range as to Visit 3.

Dose confirmation in subjects aged 3 to < 12 years

Within this trial an interim analysis was conducted on 201 children aged 3 to < 12, enrolled in the dose-finding part. The children were randomized 1:1 and received two doses 28 days apart of either 0.25 ml or 0.5 ml.

Safety was assessed using subject diaries covering 7 days after each vaccination, and by collecting unsolicited adverse events (AEs) up to Day 56. There was no significant difference between the two dose groups for safety parameters, neither solicited nor unsolicited AEs. Up to Day 56, solicited local AEs were reported in 22.8% and 16.0%, solicited systemic AE in 20.8% and 25.0% and unsolicited AE in 39.6% and 33.0% of subjects in the 0.5 ml and 0.25 ml dose group, respectively.

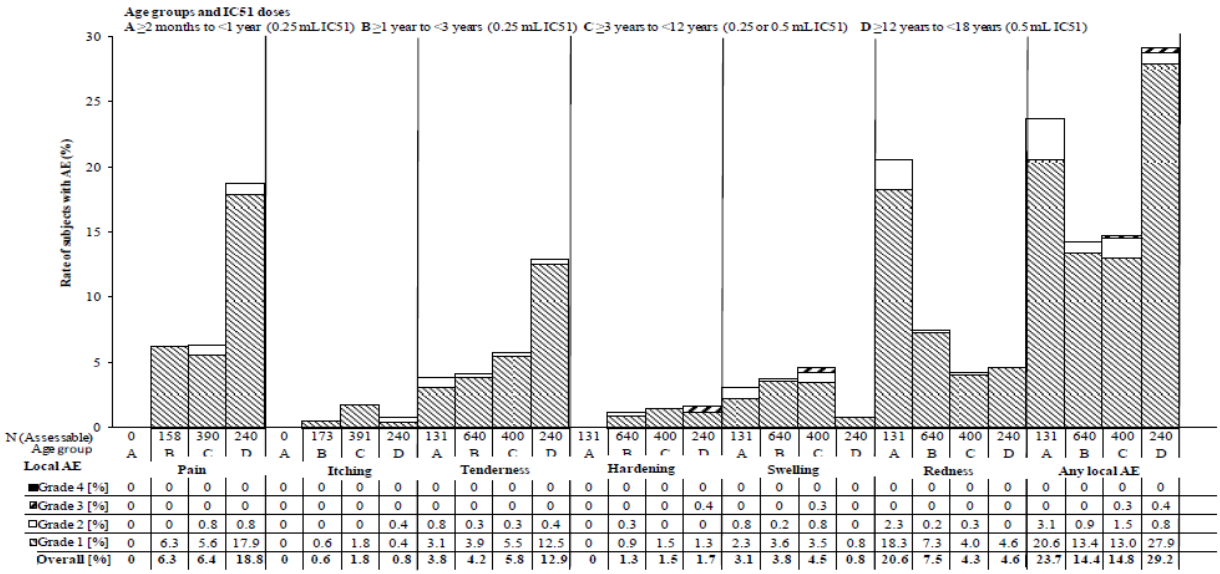
After the first dose, 19% of subjects in the 0.5 ml and 15% of subjects in the 0.25 ml group reported any solicited local symptom. The majority of local reactions were mild (grade 1). Injection site pain, tenderness, swelling and redness occurred in comparable frequencies (between 4% and 9% for each symptom and dose group). There were no significant differences between the two dose groups. The rate of local reactions was lower following the second dose.

After the first dose, 18% of subjects in the 0.5 ml and 17% of subjects in the 0.25 ml group reported any solicited systemic symptom. The majority of systemic symptoms were mild (grade 1). Fever (12% in the 0.5 mL group vs. 15% in the 0.25 mL group) was the dominant symptom, while all other symptoms were reported in ≤5% of subjects. There were no significant differences between the two dose groups. The rate of systemic reactions was lower following the second dose.

Overview of solicited adverse events by age group

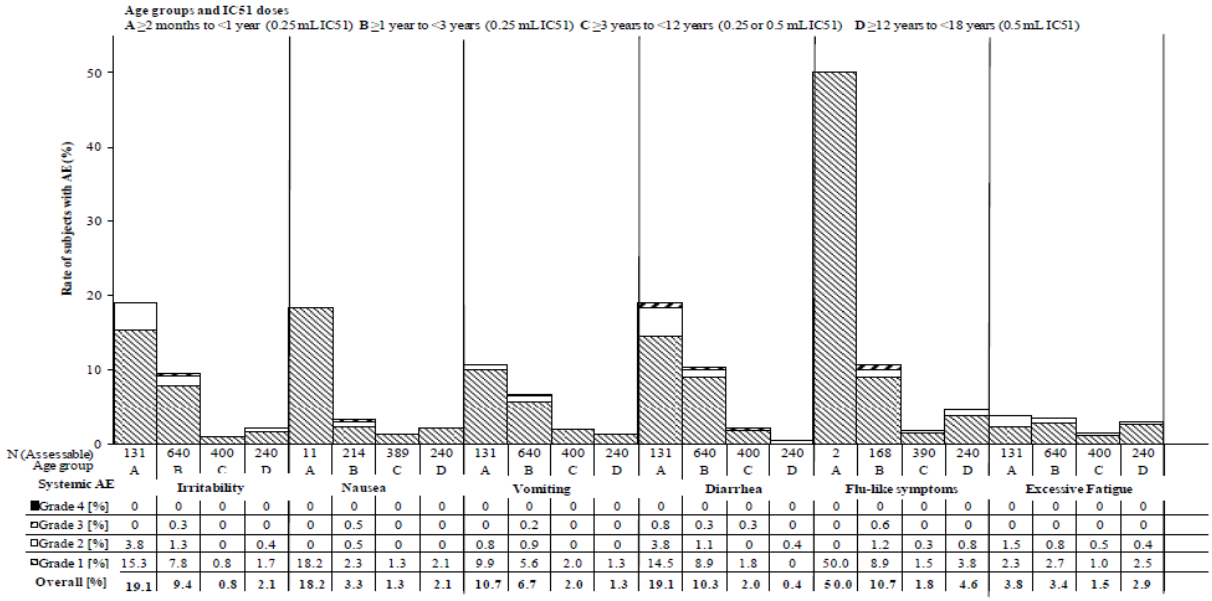
For assessing the AE rates in different dose groups, which are added to the SmPC, the figures 6 to 8 display the rates of subjects with solicited local AEs (1) after both IC51 vaccinations combined by age group as well as for the solicited systemic AEs (2 and 3).

Figure 6: Rate of subjects with solicited local adverse events



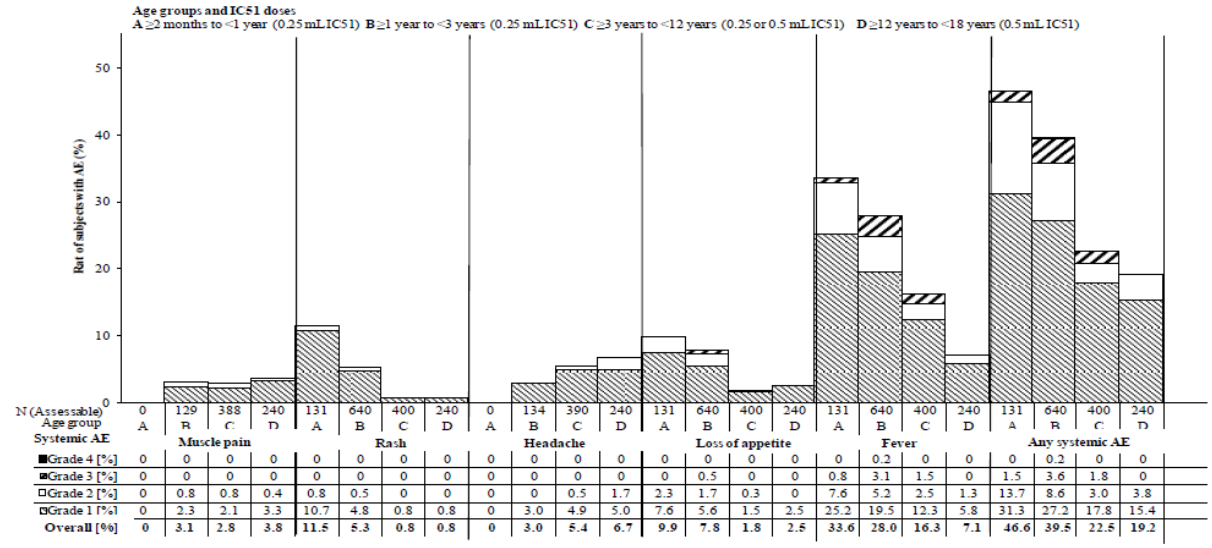
N (Assessable)	0	158	390	240	0	173	391	240	131	640	400	240	131	640	400	240	131	640	400	240	131	640	400	240	131	640	400	240
Age group	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
Local AE	**Pain**				**Itching**				**Tenderness**				**Hardening**				**Swelling**				**Redness**				**Any local AE**			
Grade 4 [%]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 3 [%]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.4	0	0	0.3	0	0	0	0	0	0	0	0.3	0.4
Grade 2 [%]	0	0	0.8	0.8	0	0	0	0.4	0.8	0.3	0.3	0.4	0	0.3	0	0	0.8	0.2	0.8	0	2.3	0.2	0.3	0	3.1	0.9	1.5	0.8
Grade 1 [%]	0	6.3	5.6	17.9	0	0.6	1.8	0.4	3.1	3.9	5.5	12.5	0	0.9	1.5	1.3	2.3	3.6	3.5	0.8	18.3	7.3	4.0	4.6	20.6	13.4	13.0	27.9
Overall [%]	**0**	**6.3**	**6.4**	**18.8**	**0**	**0.6**	**1.8**	**0.8**	**3.8**	**4.2**	**5.8**	**12.9**	**0**	**1.3**	**1.5**	**1.7**	**3.1**	**3.8**	**4.5**	**0.8**	**20.6**	**7.5**	**4.3**	**4.6**	**23.7**	**14.4**	**14.8**	**29.2**

Figure 7: Rate of subjects with solicited systemic adverse events (irritability, nausea, vomiting, diarrhea, flu-like symptoms and excessive fatigue) by age group



N (Assessable)	131	640	400	240	11	214	389	240	131	640	400	240	131	640	400	240	2	168	390	240	131	640	400	240
Age group	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
Systemic AE	Irritability				Nausea				Vomiting				Diarrhea				Flu-like symptoms				Excessive Fatigue			
Grade 4 [%]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 3 [%]	0	0.3	0	0	0	0.5	0	0	0	0.2	0	0	0.8	0.3	0.3	0	0	0.6	0	0	0	0	0	0
Grade 2 [%]	3.8	1.3	0	0.4	0	0.5	0	0	0.8	0.9	0	0	3.8	1.1	0	0.4	0	1.2	0.3	0.8	1.5	0.8	0.5	0.4
Grade 1 [%]	15.3	7.8	0.8	1.7	18.2	2.3	1.3	2.1	9.9	5.6	2.0	1.3	14.5	8.9	1.8	0	50.0	8.9	1.5	3.8	2.3	2.7	1.0	2.5
Overall [%]	19.1	9.4	0.8	2.1	18.2	3.3	1.3	2.1	10.7	6.7	2.0	1.3	19.1	10.3	2.0	0.4	50.0	10.7	1.8	4.6	3.8	3.4	1.5	2.9

Figure 8: Rate of subjects with solicited systemic adverse events (muscle pain, rash, headache, loss of appetite, fever and any systemic AE) by age group



N (Assessable)	0	129	388	240	131	640	400	240	0	134	390	240	131	640	400	240	131	640	400	240	131	640	400	240
Age group	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
Systemic AE	Muscle pain				Rash				Headache				Loss of appetite				Fever				Any systemic AE			
Grade 4 [%]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2	0	0	0	0.2	0	0
Grade 3 [%]	0	0	0	0	0	0	0	0	0	0	0	0	0	0.5	0	0	0.8	3.1	1.5	0	1.5	3.6	1.8	0
Grade 2 [%]	0	0.8	0.8	0.4	0.8	0.5	0	0	0	0	0.5	1.7	2.3	1.7	0.3	0	7.6	5.2	2.5	1.3	13.7	8.6	3.0	3.8
Grade 1 [%]	0	2.3	2.1	3.3	10.7	4.8	0.8	0.8	0	3.0	4.9	5.0	7.6	5.6	1.5	2.5	25.2	19.5	12.3	5.8	31.3	27.2	17.8	15.4
Overall [%]	0	3.1	2.8	3.8	11.5	5.3	0.8	0.8	0	3.0	5.4	6.7	9.9	7.8	1.8	2.5	33.6	28.0	16.3	7.1	46.6	39.5	22.5	19.2

The proportion of subjects experiencing solicited local AEs (i.e., for both doses of IC51 combined) was slightly greater in the oldest age group (≥ 12 years to < 18 years). In the ≥ 2 months to < 1 year age group, injection site redness was the most frequently reported solicited local AE (20.6% of subjects) after both vaccinations of IC51 combined, whereas in the ≥ 12 years to < 18 years age group, injection site pain (18.8% of subjects) was the most frequently reported. Proportions of subjects in the middle age groups were spread more evenly across a number of solicited local AEs. In the ≥ 1 year to < 3 years age group injection site pain (6.3% of subjects) and redness (7.5% of subjects) were the most frequently reported and in the ≥ 3 years to < 12 years age group injection site pain (6.4% of subjects) and tenderness (5.8% of subjects) the most frequently reported.

The proportion of subjects experiencing solicited systemic AEs (i.e., for both doses of IC51 combined) appeared to decrease with age (≥ 2 months to < 1 year, 46.6% of subjects; ≥ 12 years to < 18 years,

19.2% of subjects; Figure 8). Fever was the most frequently reported solicited systemic AE in all age groups (≥ 2 months to < 1 year, 33.6%; ≥ 1 year to < 3 years, 28.0%; ≥ 3 years to < 12 years, 16.3%; ≥ 12 years to < 18 years, 7.1% of subjects).

In the ≥ 2 months to < 1 year age group the following solicited AEs were not assessable:

injection site pain, injection site itching, muscle pain and headache; and only small numbers of subjects had assessable symptoms of nausea and flu-like symptoms. In the age groups ≥ 1 year to < 3 years and ≥ 3 years to < 12 years, not all subjects were old enough to be assessed for AEs of injection site pain, itching, muscle pain, headache, nausea and flu-like symptoms. Consequently, it should be noted that proportions of subjects could be misleadingly high, e.g., flu-like symptoms reported in 1 of only 2 assessable subjects meant a proportion of 50%.

Individual clinically significant abnormalities

Subjects with clinically significant hematology abnormalities where subject proportions are > 0.2 % at any study visit is shown in the Table 41.

Table 41: Clinically significant results in hematology

	IC51 0.25 mL n/N (%)	IC51 0.5 mL n/N (%)	Prevnar® n/N (%)	HAVRIX®720 n/N (%)	Total n/N (%)
Hemoglobin					
Screening (Visit 0)	2/836 (0.2)	0/540	0/49	1/389 (0.3)	3/1814 (0.2)
Day 28 (Visit 2)	1/837 (0.1)	3/539 (0.6)	0/48	0/392	4/1816 (0.2)
Day 56 (Visit 3)	1/831 (0.1)	1/536 (0.2)	0/47	0/391	2/1805 (0.1)
Month 7 (Visit 4)	0/821	2/531 (0.4)	0/47	1/386 (0.3)	3/1785 (0.2)
Hematocrit					
Screening (Visit 0)	1/836 (0.1)	0/540	0/49	1/389 (0.3)	2/1814 (0.1)
Day 28 (Visit 2)	1/837 (0.1)	2/539 (0.4)	0/48	0/392	3/1816 (0.2)
Day 56 (Visit 3)	1/831 (0.1)	2/536 (0.4)	0/47	0/391	3/1805 (0.2)
Month 7 (Visit 4)	0/821	2/531 (0.4)	0/47	0/386	2/1785 (0.1)
White blood cells					
Screening (Visit 0)	10/836 (1.2)	1/540 (0.2)	2/49 (4.1)	3/389 (0.8)	16/1814 (0.9)
Day 28 (Visit 2)	10/837 (1.2)	0/539	2/48 (4.2)	1/392 (0.3)	13/1816 (0.7)
Day 56 (Visit 3)	8/831 (1.0)	0/536	1/47 (2.1)	1/391 (0.3)	10/1805 (0.6)
Month 7 (Visit 4)	1/821 (0.1)	0/531	0/47	1/386 (0.3)	2/1785 (0.1)
Platelets					
Screening (Visit 0)	3/826 (0.4)	0/413	0/49	2/344 (0.6)	5/1632 (0.3)
Day 28 (Visit 2)	6/833 (0.7)	0/539	0/48	2/392 (0.5)	8/1812 (0.4)
Day 56 (Visit 3)	1/831 (0.1)	2/535 (0.4)	0/47	0/391	3/1804 (0.2)
Month 7 (Visit 4)	0/821	0/530	0/47	2/386 (0.5)	2/1784 (0.1)

Concomitant medication

The most frequently reported concomitant medications after the first vaccination in all age groups was paracetamol and ascorbic acid. The proportions of subjects reporting paracetamol use within 7 days after the first vaccination and after the second vaccination of study vaccine are summarized in Table 42.

Table 42: Paracetamol use within 7 Days after each vaccination

	Within 7 Days after First Vaccination n (%)			Within 7 Days after Second Vaccination n (%)		
Age group 2 months to < 1 year	IC51 0.25 mL N=131	IC51 0.5 mL N=0	Prevnar® N=64	IC51 0.25 mL N=131	IC51 0.5 mL N=0	Prevnar® N=64
Paracetamol use	23 (17.6)	-	12 (18.8)	13 (9.9)	-	6 (9.4)
Age group 1 to < 3 years	IC51 0.25 mL N=640	IC51 0.5 mL N=0	HAVRIX® N=213	IC51 0.25 mL N=640	IC51 0.5 mL N=0	HAVRIX® N=213
Paracetamol use	79 (12.3)	-	24 (11.3)	51 (8.0)	-	na.
Age group 3 to < 12 years	IC51 0.25 mL N=100	IC51 0.5 mL N=300	HAVRIX® N=101	IC51 0.25 mL N=100	IC51 0.5 mL N=300	HAVRIX® N=101
Paracetamol use	7 (7.0)	20 (6.7)	7 (6.9)	5 (5.0)	7 (2.3)	na
Age group 12 to < 18 years	IC51 0.25 mL N=0	IC51 0.5 mL N=240	HAVRIX® N=80	IC51 0.25 mL N=0	IC51 0.5 mL N=240	HAVRIX® N=80
Paracetamol use	-	4 (1.7)	2 (2.5)	-	3 (1.3)	na

Based on comments received by CHMP, the AE section has been revised to show adverse event rates separately for adults and in the pediatric population, for those age groups who receive the 0.25 ml dose and those who receive the 0.5ml dose.

Deaths

One death was reported during the study. The subject had a fatal SAE of disseminated intravascular coagulation approximately 4 months after his second vaccination. The event was considered to be not related by the investigator.

Serious and Medically-Attended AEs

The rates of SAEs or medically attended AEs to day 56, the primary endpoint of this study, were similar across treatment groups within each age group:

- ≥ 2 months to < 1 year, IC51 0.25 mL group 38.2% and Prevnar group 42.2%; ≥ 1 year to < 3 years,
- ≥ 1 year to < 3 years , IC51 0.25 mL group 26.7% and HAVRIX 720 group 22.1%;
- ≥ 3 years to < 12 years, IC51 0.25 mL group 7.0%, IC51 0.5 mL group 8.0% and HAVRIX 720 group 5.9%;
- and ≥ 12 years to < 18 years, IC51 0.5 mL group 1.7% and HAVRIX 720 group 3.8%.

A total of 11 subjects (0.6%) had SAEs up to day 56. Medically-attended AEs were experienced by 77 subjects (39.5%) in the ≥ 2 months to < 1 year group and 262 subjects (15.7%) in the ≥ 1 year to < 18 years age group. Rates were similar across the treatment groups within the breakdown of age groups.

The most frequently reported SAE to day 56 was febrile convulsions (4 subjects from the ≥ 1 year to < 3 years age group; 1 subject from the ≥ 2 months to < 1 year age group). None of the SAEs reported to day 56 were considered related to the study vaccine. The most frequently reported medically-attended AEs in populations aged ≥ 2 months to < 1 year and ≥ 1 year to < 18 years were upper respiratory tract infection and gastroenteritis. A total of 21 subjects had medically-attended AEs to day 56 that were considered related to any study vaccine by the investigator.

A total of 34 subjects had SAEs to Month 7 (Visit 4): 1.9% of subjects (31 of 1674) in the ≥ 1 year to < 18 years age group (20 subjects were aged ≥ 1 year to < 3 years) and 1.5% subjects (3 of 195) in the ≥ 2 months to < 1 year age group.

The most frequently reported SAEs to Month 7 were febrile convulsion (8 subjects in the ≥ 1 year to < 18 years age group; 1 subject in ≥ 2 months to < 1 year age group) and pneumonia (4 subjects in the ≥ 1 year to < 18 years age group; 2 subjects in the ≥ 2 months to < 1 year age group). One subject (IC51 0.5 mL group) in the ≥ 3 years to < 12 years age group had an SAE of Kawasaki's disease that was considered possibly related to study vaccine by the investigator, but not within the PSUR#5 assessment. One subject (IC51 0.5 mL group) gave birth to a stillborn child more than 1 year after the second vaccination; the event of stillbirth was considered not related to study vaccine by the investigator.

The CHMP commented that safety results of the comparator controlled clinical trial with IC51 of subjects aged ≥ 2 months to < 18 years showed similar rates of solicited, unsolicited adverse events as well as for SAEs and medically attended AEs in the different age categories. The majority of AEs were mild of intensity. The safety profile of IC51 compared to Prevnar appeared to cause fewer local reactions, specifically less tenderness and hardening in the age group ≥ 2 months to 1 year. All subjects treated with either Havrix 720 or IC51 showed a similar AE profile after vaccination with both 0.25 ml and 0.5 mL Ixiaro or Havrix after the first dose. Less AEs were reported after the second dose of IC51. No marked changes over time were noted in the laboratory data. Regarding vital signs only changes from baseline were observed in increased height and weight, which were acceptable for growing children over a 7-month period. Both doses of IC51 were well tolerated in JEV endemic pediatric population.

However CHMP was concerned with a lack of safety data on the use of the commercial prefilled syringe with a red line as a mark for half a dose to children < 3 years. The average volume delivered by this device is 0.34 ml, while a volume of 0.25 ml was used in the clinical study in children < 1 year. This corresponds to 36% higher dose than used in clinical studies. Also, there is no safety data on a full 0.5 ml dose to children < 1 years, which could be injected by accident.

The MAH asserted that there is currently no indication that higher total amount of the active ingredient changes the safety profile in any significant way (Lyons et al 2007 (15), Dubischar-Kastner et al. 2010 (16), Eder et al.2011 (17)). The somewhat higher total volume of 0.32 to 0.34 ml might in theory be implied to cause more severe local reactions. However, when comparing the local reactogenicity profile of the 0.25 ml doses vs. the 0.5 ml dose used in other age groups, no significant differences emerge. It may therefore be inferred that the local safety profile of the (on average) 0.32 to 0.34 ml dose would be comparable.

Allergic reactions, though rather rare still a concern for vaccines, are not dose dependent. Other reactions known for IXIARO – or other vaccines – also appear to be independent of dosage.

The CHMP accepted the argumentation provided.

Also, the MAH discussed the feasibility of post-marketing follow-up studies in children, especially under 3 years of age. Various difficulties hampering such feasibility were acknowledged by CHMP. In particular, it was agreed that current experience, especially in children below 3 years of age, indicates a very limited use in this age group.

2.4.3. Discussion

In order to support the extension of the age indication to children from 2 months onwards safety results from three clinical trials were submitted. Two studies were conducted in countries, where JEV is endemic and one study was initiated in non-endemic countries.

A Phase II trial was conducted in India with the comparator vaccine JenceVac (IC51-221) and the Phase III trial was conducted in the Philippines with Havrix and Prevenar as control (IC51-323). The majority of data derive from study IC51-323, in which 1869 subjects aged ≥ 2 month to < 18 years were enrolled. Different age groups were vaccinated with two different dosages of IC51. The safety analyses indicate similar rates of solicited, unsolicited adverse events as well as for SAEs and medically attended AEs in the different age categories and a comparable safety profile as the licensed vaccines Havrix and Prevenar.

There was one case of Kawasaki disease which was considered by the investigator to be possibly related to study vaccine, while sponsor considered it unrelated because of no known pathophysiological pathway for an inactivated vaccine. This case was previously discussed in the context of assessment of PSUR#5 and was considered to be not related.

Study IC51-322 is currently ongoing and is conducted in non-endemic countries. Only 60 participants were enrolled in the ongoing Phase III trial in non-endemic environment prior to the interim analysis. The mean age of the participants was 12.5 years at enrolment, which indicates that mostly older adolescents were enrolled. The safety database is currently very limited especially for small children. Overall the safety profile of the data, does not indicate a high reactogenicity of IXIARO with respect to fever rates or other expected adverse reactions. One fatal SAE occurred which was judged to be unrelated to Ixiaro.

On request from CHMP, the MAH discussed the limited safety database and the feasibility of postmarketing studies. The data indicate that the AE rates are independent of the treatment group or pre-existing immunity to flaviviruses. Age was the only effect significantly associated with the AE rate to Day 56 in subjects aged ≥ 2 months to < 1 year. Due to the very limited projected use in children below 3 years postmarketing studies are not feasible.

In conclusion the safety data suggest that Ixiaro is well tolerated and has an acceptable safety profile in children and adolescents.

2.5. Risk management plan

The MAH submitted an updated Risk Management Plan within this variation procedure.

Table 1: Summary of the risk management plan (including the changes related to the application presented highlighted)

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Sensitivity / Allergic Reactions Important identified risks: Dermatitis, dyspnoea, erythema, eye pruritus, flushing, hypersensitivity, pruritus, rash, urticaria Important potential risks:	• Routine pharmacovigilance (ICSRs, PSURs, monitoring safety profile, safety signal generation and detection) • Clinical Studies: Ongoing follow-up studies IC51-324, 325 Ongoing study IC51-322 • Enhanced Surveillance at Sentinel Sites in 20,000 IXIARO recipients IC51-401	• SPC Section 4.3 Contraindications: Hypersensitivity to the active substance or to any of the excipients or to any residuals (e.g. protamin sulphate). Individuals who show hypersensitivity reactions after receiving the first dose of the vaccine should not be given the second dose.

Conjunctivitis, hypotension		
Neurological Adverse Events Important identified risks: Convulsion Important potential risks : Acute disseminated encephalomyelitis, acute encephalitis, acute myelitis, central nervous system inflammation, Guillain-Barré-Syndrome	• Routine pharmacovigilance (ICSRs, PSURs, monitoring safety profile, safety signal generation and detection) • Clinical Studies Ongoing follow-up studies IC51-324, 325 Ongoing study IC51-322 • Enhanced Surveillance at Sentinel Sites in 20,000 IXIARO® recipients IC51-401	• No additional risk minimization measures
Vaccination in pregnant women	• Routine pharmacovigilance (ICSRs, pregnancy questionnaire, PSURs, monitoring safety profile, safety signal generation and detection) • Analysis of clinical trial cases • Enhanced Surveillance at Sentinel Sites in 20,000 IXIARO recipients IC51-401	• SPC Section 4.6 Pregnancy and Lactation: As a precautionary measure, the use of IXIARO® during pregnancy or lactation should be avoided.
Immuno-compromised Individuals	• Routine pharmacovigilance (ICSRs, PSURs, monitoring safety profile, safety signal generation and detection) • Individual case analysis, results reported in PSUR	• SPC Section 4.5 Interaction with other medicinal products and other forms of interaction: In patients receiving immunosuppressive therapy or patients with immunodeficiency an adequate immune response may not be obtained.
Co-vaccinated Individuals	• Routine pharmacovigilance (ICSRs, PSURs, monitoring safety profile, safety signal generation and detection) • New clinical study IC51-316 on influence of concomitant vaccination of IC51 with other traveler's vaccines.	• No additional risk minimization measures

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

2.6. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI):

The SPC is updated with changes associated with the pediatric indication.

Section 4.1 "Therapeutic indications" has been revised to include a pediatric licensure down to 2 months of age: "IXIARO is indicated for active immunization against Japanese encephalitis in adults, adolescents, children and infants aged 2 months and older." This age range is considered justified based on the lower age of children included into the pediatric trials and the fact that both safety and immunogenity data are

very favourable for all ages down to 2 months. With regards to immunogenicity, the very youngest children below 6 months of age, were able to mount the highest titers following immunization.

Section 4.2 Posology and method of administration / Posology has been updated to include the dosing suggested for licensure in the paediatric population:

Children aged 2 months to less than 3 years: 0.25 ml

Children aged 3 years and older: 0.5 ml

This dosing is considered justfied based on pediatric data from the phase 2 trial IC51-221 that demonstrated equal GMTs with an 0.5 ml and an 0.25 ml dose in children below 3 years of age, but a significantly higher GMT with the 0.5 ml dose in children aged 3 - <12 years in the phase 3 trial IC51-323, demonstrating a beneficial effect of a higher dose in this age group. Additionally, for infants and toddlers the anterolateral aspect of the thigh has been added as possible location for vaccination.

The section 4.3 Contraindications has been updated to follow the QRD template format that requires a definitive list of excipients to be named under “hypersensitivity to the active substance or to any of the excipients”, instead of referring to “eg, protamine sulfate”. Hence, several excipients have been added (formaldehyde, bovine serum albumin, host cell DNA, sodium metabisulphite, host cell protein).

Section 4.6 Fertility, pregnancy and lactation has been re-organized to follow the QRD template requirements.

Section 4.7 Effects on ability to drive and use machines has been reworded, based on the QRD template.

Section 4.8 Undesirable effects has been updated to include pediatric safety data. In line with the SPC Guideline (NTA, A Guideline on Summary of Product Characteristics, Rev 2, Sept 2009), this section first describes adverse reactions in adults and the pediatric polulation in general; followed by a display of reactions that are observed in higher frequencies in the pediatric population compared to adults or other pediatric subsets. As the safety profile in adolescents (aged 12-<18 years) resembled the profile in adults, no data are shown separately for this age group. With respect to the classification of ADRs to certain frequency categories, the frequency information from study IC51-323, which provides a much larger subject pool and thus more precise estimate, have been utilized instead of the less precise numbers from study IC51-322.

In detail,

- Nasopharyngits and Rhinitis are suggested to be deleted from the SPC - due to the infectious etiology, a causal association with IXIARO vaccination is not considered reasonable.
- Decreased Appetite has been added as a common reactions because of the frequency in which it was seen in adolescents in study IC51-323.
- Vomiting has been reclassified to common (from uncommon) based on the frequency in adolescents in study IC51-323.
- A combined term for injection site reactions has been introduced, under frequency “common”: injection site reactions e.g. hardening, swelling, itchingThis is planned to be a global term for grouping of local reactions which will include those injection site reactions that are between 1% and <10% in frequency.
- The following ADRs have been selected for display of frequency broken down by age group (<1year, 1-<3 years, 3-<12years) in a separate section on the paediatric population: Vomiting,

Diarrhoea, Rash, Influenza like illness, Hepatic enzymes increased, Irritability, Loss of appetite, Cough, Pyrexia, Injection site redness. These events occurred in higher frequency in at least one of the of the subsets of the pediatric population compared to adults.

Apart from the additions to the SPC ADR section, several AEs judged as related by investigators in the pediatric studies are not proposed to be added to the SPC, for reasons specified below.

The following AEs lack plausibility of a causal association to vaccination, mainly due to their infectious etiology:

- Bronchitis, bronchopneumonia, viral infection, viral rash, oropharyngeal pain, otorrhoea, stomatitis, upper respiratory tract infection, and pharyngitis all have an infectious etiology, hence a causal association with IXIARO vaccination is not considered reasonable.
- For Kawasaki's disease, a causal association with IXIARO vaccination is not considered reasonable as there is no known pathophysiological pathway for an inactivated vaccine to trigger this; additionally the disease is known to occur predominantly in the Asian population in which this study was conducted, and there was a long latency period to vaccination.
- For epistaxis, there is no known pathophysiological pathway for an inactivated vaccine to trigger this.

The following ADRs are considered to be sufficiently covered by other ADR terms already included in the SPC:

- Muscle hemorrhage and vaccination site inflammation are considered covered by injection site reactions.
- Mucous stools is considered covered by diarrhoea.
- Rash papular and rash erythemaous are considered covered by the term rash.

While none of the febrile seizures in the pediatric studies has been considered related to vaccination by the investigators, it is proposed to add information on febrile seizures to the SPC because such reactions may be expected after vaccination of small children, and fever has been observed in a proportion of children.

Section 5.1 has been updated to include pediatric safety and immunogenicity data, in accordance with the SPC guideline.

- Immunogenicity results have been added from both pediatric trials, IC51-322 and IC51-323. Greater detail has been provided for study IC51-323 which contributes the majority of subjects with immunogenicity data. Since this population was from an area where JEV is endemic, there was considerable baseline immunity against JEVespecially in the oldest (12 to <18 years) age group in the study (approximately 40%). To distinguish pre-existing immunity from the vaccine-induced immune response, the proportion of subjects achieving an at least 4-fold increase in neutralizing antibody titers following vaccination is proposed to be displayed along with the seroconversion rates (defined as $PRNT_{50}$ titer ≥1:10) for this study.
- Pediatric safety data have been added from the larger pediatric study IC51-323: Solicited local and systemic AEs are described in tabular form for the major age groups enrolled in this trial. Since the data are from a non-US population, the inclusion of comparative safety data from other licensed vaccines, (Hepatitis A vaccine / Havrix, 7-valent Pneumococcal Conjugate Vaccine /

Prevenar) is considered to be of particular importance and will aid physicians interpretation of the safety data.

Section 6.6 special precautions for disposal and other handling has been updated to provide a description for handling the pre-filled syringe for administration of the 0.25 mL dose.

In the Package Leaflet, the changes described above have also been introduced as appropriate.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) *[e.g. Excipients guideline, storage conditions, Braille, etc…]*, which were reviewed by QRD and accepted by the CHMP.

During the procedure, the CHMP requested additional amendments to the Product Information:

The MAH provided a revised product information and the MAH addressed the issues identified.

The proposal of the MAH to perform a user testing with HCP's, primarily travel physicians, paediatricians and vaccinologists and the outline of such testing are endorsed by CHMP.

3. Overall conclusion and impact on the benefit/risk balance

Benefits

Beneficial effects

JE disease is a potentially debilitating or fatal disease for which there is no drug treatment available. Children are the most vulnerable population for JE. The mortality rates can go as high as 30 % of symptomatic cases and around 50 % of those who survive have permanent neurological sequalae.

Annually over 50,000 cases of JE are reported indicating that it is a considerable public health problem for many Asian countries. Serological surveys conducted in countries such as Malaysia, India, Nepal, Korea, Vietnam, Thailand and Indonesia show that most people living in JE-endemic areas are infected before the age of 15 years. It has also been observed that in hyper-endemic areas, half of the JE cases occur before the age of 4 years and almost all before the age of 10 years.

Vaccination against JE remains the single most important control measure. Immunogenicity data from children from 2 months onwards having received two doses of Ixiaro 4 weeks apart indicate that the vaccine induces high level of neutralizing antibodies in almost all subjects. The highest response is seen in children below 3 years of age following administration of half the adult dose. Antibody persistence data indicate a decline in the neutralizing antibody levels over a 6 month period with over 85% of subjects showing neutralizing antibody titers of 1:10, which is the accepted surrogate marker for protection.

Although only limited data are available for the very small children, the vaccine is expected to induce a high degree of protection against JE disease.

Uncertainty in the knowledge about the beneficial effects

Protection against disease has not been demonstrated. The evaluation of efficacy is based on measuring functional antibodies which is accepted as a surrogate of protection.

The persistence of neutralising antibodies beyond 6 months after the second vaccine dose is not known in children. Antibody persistence and booster studies are ongoing and further results will become available In Q1 2013.

Only limited information is available on the interactions between the immune response of IXIARO and other travel vaccines. These data are derived from adult subjects only. Further studies on the concomitant use of Ixiaro with other travellers' vaccines (e.g. rabies) are ongoing.

Risks

Unfavourable effects

In the main study IC51-323 the safety of IXIARO was compared to Prevnar in children < 1 year and to HAVRIX in children from 1 to 18 years. In general solicited AEs that were recorded the first week after vaccination were similar concerning proportion of subjects experiencing an AE and the intensity when comparing IXIARO with Prevnar and HAVRIX. The Prevnar group had a higher proportion with local reactions than IXIARO, while in the age interval 3-12 years the IXIARO group had a higher proportion of solicited reactions compared to HAVRIX. The most frequent solicited reactions were injection site redness, tenderness and hardening, fever and irritability. In the IXIARO < 1 year group fever of grade 1 (37.7-38.6°C) was observed in 17.6% and fever grade 2 (38.7-39.3°C) in 6.1% of subjects.

SAEs were similarly distributed among IXIARO and control vaccines and none was considered related to study vaccine.

In summary, unfavourable effects are local and systemic reactions during the first week after administration of IXIARO and are according to what is expected for an inactivated viral vaccine.

There is also a risk of individuals that do not respond satisfactorily to vaccination and may therefore be unprotected against disease.

Uncertainty in the knowledge about the unfavourable effects

The limited number of children in clinical studies does not allow the frequency of rare and some uncommon side effects to be calculated. The safety database in infants (< 1 year of age) is small (N=132).

In the clinical study IC51-323 administration of 0.25 ml IXIARO was performed by filling a tuberculin syringe from the commercial prefilled syringe (IXIARO). Thus, the prefilled syringe with a red mark to indicate half a dose has not been tested in clinical trials. The volume injected to children < 1 year in clinical study was probably close to 0.25 ml, while the volume delivered using the prefilled syringe with red mark is 0.34 ml (average). There is a lack of safety data in children < 1 year using a "normal" average dose of 0.34 ml or if the full volume of 0.5-0.6 ml in the syringe is accidently injected.

The main study was performed in the Philippines in an Asian population, while the application relates to use in a European population. There may be some differences in the safety profile according to ethnic group.

Balance

Benefit-risk balance

Japanese encephalitis is a serious and potentially fatal disease for which there is no treatment available. IXIARO induces a high level of neutralising antibodies after a two-dose scheme given 4 weeks apart. Based on the level of neutralising antibodies as a surrogate of protection against disease, more than 99% of children will be protected 4 weeks after the last dose or more than 85% will be protected 6 months after the second dose. As the unfavourable effects are related to mild and moderate local and systemic reactions within the first week after vaccination, the benefit-risk balance is positive for children from 2 months to 18 years.

Conclusions

The overall benefit risk of IXIARO in adolescents and children from 2 months onwards is positive.

The MAH is asked to provide the interim report for study IC51-325 as soon as it becomes available (Q1-2013).

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations requested		**Type**
B.II.e.6.a	B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information	IB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed the extension of indication of Ixiaro to the paediatric segment (2 months of age and older) in line with approved PIP EMEA -000559-PIP01-09-M03. Modification of syringe label to include "half dose mark" for administration of a 0.25 ml nominal dose for the paediatric sub-segment 2 months to below 3 years of age in line with the aforementioned PIP. The latter is grouped with the indication extension as direct result of the proposed extension. The Package Leaflet and Labelling were proposed to be updated accordingly.

Furthermore, the PI is being brought in line with the latest QRD template version 8.2.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.