



Clinical trial results:

SAFETY AND IMMUNOGENICITY OF THE JAPANESE ENCEPHALITIS VACCINE IC51 (IXIARO®) IN A PEDIATRIC POPULATION. OPEN-LABEL, RANDOMIZED, ACTIVE CONTROLLED, PHASE 3 STUDY.

Summary

EudraCT number	2009-015588-15
Trial protocol	Outside EU/EEA
Global end of trial date	12 July 2011

Results information

Result version number	v1 (current)
This version publication date	15 April 2016
First version publication date	15 April 2016

Trial information

Trial identification

Sponsor protocol code	IC51-323
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01041573
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Valneva Austria GmbH (formerly Intercell AG)
Sponsor organisation address	Campus Vienna Biocenter 3, Vienna, Austria, 1030
Public contact	Clinical Operations, Valneva Austria GmbH (formerly Intercell AG), 0043 1206200, info@valneva.com
Scientific contact	Clinical Operations, Valneva Austria GmbH (formerly Intercell AG), 0043 1206200, info@valneva.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000559-PIP01-09
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 November 2011
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 July 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assessment of the systemic and local safety profile of IC51 vaccine in a pediatric population from regions where Japanese Encephalitis is endemic. Assessment of the immunogenicity of IC51 using Geometric Mean Titers (GMTs) and Seroconversion Rates (SCRs) at Day 56. Establishment of the appropriate IC51 dose (0.25 ml or 0.5 ml) for subjects aged ≥ 3 to < 12 years.

Protection of trial subjects:

An independent Data Safety Monitoring Board (DSMB) analyzed safety of vaccination with the 0.25 ml and 0.5 ml dose after the dose finding runin phase in children aged ≥ 3 to < 12 years. The subject's legal representative or the subject, as applicable, was asked to report all symptoms (solicited and unsolicited AEs) after vaccination with IC51.

Background therapy: -

Evidence for comparator:

Control vaccines were Prevnar® for children below 12 months of age and inactivated HAVRIX®720 for children aged 12 months and above at randomization. The control group allowed for comparison of adverse event rates with background incidences.

Subjects aged ≥ 2 months to < 1 year were randomized in a 2:1 ratio to receive IC51 (0.25 ml) or Prevnar®. Children aged ≥ 1 to < 3 years and ≥ 12 to < 18 years were randomized in a 3:1 ratio to receive IC51 (0.25 ml < 3 years or 0.5 ml ≥ 12 years) or HAVRIX®720. For subjects aged ≥ 3 to < 12 years, a dose finding runin phase was performed, in which subjects were randomized 1:1 to receive either the 0.25 ml or the 0.5 ml dose of IC51. The appropriate dose was then determined based on an interim analysis.

Subjects randomized into one of the control groups were offered vaccination with the other safety comparator vaccine (i.e. either HAVRIX®720 or Prevnar® or another licensed Pneumococcal Conjugate Vaccine) after concluding the study. Additionally, subjects were offered other vaccination (e.g. Varicella vaccine, Meningococcal vaccine, MMR vaccine) after concluding the study. The selection of which was based on the medical need of the subject.

Subjects randomized into the IC51 group were offered vaccination with both HAVRIX®720 and Prevnar®/another licensed Pneumococcal Conjugate Vaccine after concluding the study.

Actual start date of recruitment	17 March 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	7 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Philippines: 1869
Worldwide total number of subjects	1869
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	620
Children (2-11 years)	929
Adolescents (12-17 years)	320
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited at 3 study centers in the Philippines. Recruitment started on 17-Mar-2010 and was completed on 10-Dec-2010.

Pre-assignment

Screening details:

Open-label, randomized, active-controlled Phase 3 study in children aged ≥ 2 months to < 18 years.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	IC51 0.25 ml group

Arm description: -

Arm type	Experimental
Investigational medicinal product name	IC51
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects aged ≥ 2 months to < 3 years received 2 vaccinations of 0.25 ml IC51 at an intervals of 4 weeks (Day 0 and 28).

Arm title	IC51 0.5 ml group
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	IC51
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects aged ≥ 12 to < 18 years received 2 vaccinations of 0.5 ml IC51 at an intervals of 4 weeks (Day 0 and 28).

Arm title	Pprevnar® group
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Pprevnar®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects aged ≥ 2 to < 6 months received 4 vaccinations on Days 0, 28, 56 and Month 713 (subjects aged ≥ 2 to < 6 months were to receive the 4th vaccination when 1215 months old, i.e., the vaccination was to be performed outside the study, depending on the subject's age at day of first

vaccination).

Subjects aged ≥ 6 months to < 1 year received 3 vaccinations on Days 0, 56 and Month 7.

Arm title	Havrix®720 group
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Havrix®720
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects aged ≥ 1 to < 18 years received 2 vaccinations on Day 0 and Month 7.

Number of subjects in period 1	IC51 0.25 ml group	IC51 0.5 ml group	Prevnar® group
Started	871	540	64
Completed	858	535	62
Not completed	13	5	2
Relocation	4	1	1
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	5	2	-
Positive for anti-HCV	-	1	-
Adverse event, non-fatal	2	-	-
Further blood extraction	1	-	-
Lost to follow-up	1	-	1

Number of subjects in period 1	Havrix®720 group
Started	394
Completed	387
Not completed	7
Relocation	3
Adverse event, serious fatal	-
Consent withdrawn by subject	2
Positive for anti-HCV	-
Adverse event, non-fatal	-
Further blood extraction	-
Lost to follow-up	2

Baseline characteristics

Reporting groups

Reporting group title	IC51 0.25 ml group
Reporting group description: -	
Reporting group title	IC51 0.5 ml group
Reporting group description: -	
Reporting group title	Prevnar® group
Reporting group description: -	
Reporting group title	Havrix®720 group
Reporting group description: -	

Reporting group values	IC51 0.25 ml group	IC51 0.5 ml group	Prevnar® group
Number of subjects	871	540	64
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Age continuous Units: years			
arithmetic mean	2.41	10.64	0.67
full range (min-max)	0.2 to 11.9	3.1 to 17.8	0.2 to 1
Gender categorical Units: Subjects			
Female	449	249	30
Male	422	291	34

Reporting group values	Havrix®720 group	Total	
Number of subjects	394	1869	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Age continuous Units: years			
arithmetic mean	5.98		
full range (min-max)	1 to 17.9	-	
Gender categorical Units: Subjects			
Female	197	925	
Male	197	944	

End points

End points reporting groups

Reporting group title	IC51 0.25 ml group
Reporting group description: -	
Reporting group title	IC51 0.5 ml group
Reporting group description: -	
Reporting group title	Pprevnar® group
Reporting group description: -	
Reporting group title	Havrix®720 group
Reporting group description: -	
Subject analysis set title	Ixiaro®, subjects aged ≥ 2 months to < 1 year
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects aged ≥ 2 months to < 1 year at Visit 1 who received IC51 0.25 ml	
Subject analysis set title	Pprevnar®, subjects aged ≥ 2 months to < 1 year
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects aged ≥ 2 months to < 1 year at Visit 1 who received control, i.e. Pprevnar®	
Subject analysis set title	Ixiaro®, subjects aged ≥ 1 year
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects aged ≥ 1 year at Visit 1 who received any Ixiaro® dose, i.e. IC51 0.25 ml or IC51 0.5 ml	
Subject analysis set title	Havrix®720, subjects aged ≥ 1 year
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects aged ≥ 1 year at Visit 1 who received control, i.e. Havrix®720	

Primary: Rate of subjects with SAEs and medically attended AEs up to Day 56 after the first vaccination.

End point title	Rate of subjects with SAEs and medically attended AEs up to Day 56 after the first vaccination.
End point description:	
End point type	Primary
End point timeframe:	
56 Days after the first IC51 vaccination.	

End point values	Ixiaro®, subjects aged ≥ 2 months to < 1 year	Pprevnar®, subjects aged ≥ 2 months to < 1 year	Ixiaro®, subjects aged ≥ 1 year	Havrix®720, subjects aged ≥ 1 year
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	131	64	1280	394
Units: % of subjects				
number (confidence interval 95%)	38.2 (29.8 to 47.1)	42.2 (29.9 to 55.2)	16.1 (14.1 to 18.2)	14.2 (10.9 to 18.1)

Statistical analyses

Statistical analysis title	D56 comparison in subjects < 1 year
Statistical analysis description: Comparison of the number of subjects with the event across the treatment groups.	
Comparison groups	Ixiaro®, subjects aged ≥ 2 months to < 1 year v Prevnar®, subjects aged ≥ 2 months to < 1 year
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.641
Method	Fisher exact

Statistical analysis title	D56 comparison in subjects > 1 year
Statistical analysis description: Comparison of the number of subjects with the event across the treatment groups	
Comparison groups	Havrix®720, subjects aged ≥ 1 year v Ixiaro®, subjects aged ≥ 1 year
Number of subjects included in analysis	1674
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were recorded at all study visits until Month 7.

Adverse event reporting additional description:

Certain events were captured systemically (use of diary); events such as injection site pain might not have been assessable in the very young study participants.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.0
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Reporting groups

Reporting group title	IC51 0.5 ml
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Reporting group description: -

Reporting group title	IC51 0.25 ml
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Reporting group description: -

Reporting group title	Havrix®720
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Reporting group description: -

Reporting group title	Prevnam®
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Reporting group description: -

Serious adverse events	IC51 0.5 ml	IC51 0.25 ml	Havrix®720
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 540 (1.30%)	16 / 871 (1.84%)	10 / 394 (2.54%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 540 (0.19%)	0 / 871 (0.00%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 540 (0.00%)	1 / 871 (0.11%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kawasaki's disease			

subjects affected / exposed	1 / 540 (0.19%)	0 / 871 (0.00%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Familial periodic paralysis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 540 (0.00%)	0 / 871 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Febrile convulsion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 540 (0.00%)	5 / 871 (0.57%)	3 / 394 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Stillbirth			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 540 (0.19%)	0 / 871 (0.00%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 540 (0.19%)	0 / 871 (0.00%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Eye disorders			
Strabismus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 540 (0.19%)	0 / 871 (0.00%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 540 (0.00%)	0 / 871 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 540 (0.19%)	3 / 871 (0.34%)	2 / 394 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 540 (0.00%)	2 / 871 (0.23%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 540 (0.19%)	1 / 871 (0.11%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 540 (0.00%)	2 / 871 (0.23%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 540 (0.00%)	1 / 871 (0.11%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis A			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 540 (0.00%)	1 / 871 (0.11%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis bacterial			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 540 (0.19%)	0 / 871 (0.00%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngotonsillitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 540 (0.19%)	0 / 871 (0.00%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Typhoid fever			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 540 (0.19%)	0 / 871 (0.00%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 540 (0.19%)	0 / 871 (0.00%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 540 (0.00%)	1 / 871 (0.11%)	0 / 394 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 540 (0.00%)	0 / 871 (0.00%)	1 / 394 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Prevnar®		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 64 (1.56%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haematoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Kawasaki's disease			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Familial periodic paralysis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Febrile convulsion			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Stillbirth			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Strabismus			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Bronchopneumonia				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 64 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dengue fever				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 64 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 64 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 64 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis A				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 64 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningitis bacterial				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 64 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pharyngotonsillitis				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Typhoid fever			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	IC51 0.5 ml	IC51 0.25 ml	Havrix®720
Total subjects affected by non-serious adverse events			
subjects affected / exposed	300 / 540 (55.56%)	691 / 871 (79.33%)	252 / 394 (63.96%)
Nervous system disorders			
Headache			
subjects affected / exposed	31 / 540 (5.74%)	10 / 871 (1.15%)	10 / 394 (2.54%)
occurrences (all)	37	10	10

General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	35 / 540 (6.48%)	122 / 871 (14.01%)	36 / 394 (9.14%)
occurrences (all)	36	127	40
Injection site pain			
subjects affected / exposed	65 / 540 (12.04%)	15 / 871 (1.72%)	20 / 394 (5.08%)
occurrences (all)	74	17	20
Tenderness	Additional description: = pain upon touching at vaccination site		
subjects affected / exposed	48 / 540 (8.89%)	38 / 871 (4.36%)	27 / 394 (6.85%)
occurrences (all)	55	40	27
Hardening	Additional description: Hardening at vaccination site		
subjects affected / exposed	8 / 540 (1.48%)	10 / 871 (1.15%)	2 / 394 (0.51%)
occurrences (all)	8	10	2
Swelling	Additional description: Swelling at vaccination site		
subjects affected / exposed	14 / 540 (2.59%)	34 / 871 (3.90%)	12 / 394 (3.05%)
occurrences (all)	15	35	15
Redness	Additional description: at injection site		
subjects affected / exposed	22 / 540 (4.07%)	81 / 871 (9.30%)	25 / 394 (6.35%)
occurrences (all)	22	93	25
Flu-like symptoms			
subjects affected / exposed	16 / 540 (2.96%)	21 / 871 (2.41%)	16 / 394 (4.06%)
occurrences (all)	17	23	16
Fever			
subjects affected / exposed	61 / 540 (11.30%)	244 / 871 (28.01%)	49 / 394 (12.44%)
occurrences (all)	76	316	53
Irritability			
subjects affected / exposed	6 / 540 (1.11%)	87 / 871 (9.99%)	16 / 394 (4.06%)
occurrences (all)	9	111	17
Excessive fatigue			
subjects affected / exposed	12 / 540 (2.22%)	28 / 871 (3.21%)	5 / 394 (1.27%)
occurrences (all)	14	32	5
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	3 / 540 (0.56%) 3	30 / 871 (3.44%) 32	10 / 394 (2.54%) 10
Vomiting subjects affected / exposed occurrences (all)	10 / 540 (1.85%) 11	58 / 871 (6.66%) 69	13 / 394 (3.30%) 14
Diarrhea subjects affected / exposed occurrences (all)	6 / 540 (1.11%) 6	94 / 871 (10.79%) 113	13 / 394 (3.30%) 13
Skin and subcutaneous tissue disorders Heat rash alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	4 / 540 (0.74%) 4	9 / 871 (1.03%) 10	4 / 394 (1.02%) 4
Rash subjects affected / exposed occurrences (all)	5 / 540 (0.93%) 5	49 / 871 (5.63%) 57	6 / 394 (1.52%) 6
Infections and infestations Upper respiratory tract infection alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	67 / 540 (12.41%) 72	326 / 871 (37.43%) 414	97 / 394 (24.62%) 115
Gastroenteritis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 540 (0.56%) 3	58 / 871 (6.66%) 61	14 / 394 (3.55%) 14
Nasopharyngitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	14 / 540 (2.59%) 16	77 / 871 (8.84%) 89	27 / 394 (6.85%) 27
Rhinitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	8 / 540 (1.48%) 8	45 / 871 (5.17%) 48	17 / 394 (4.31%) 19
Metabolism and nutrition disorders			

Loss of appetite subjects affected / exposed occurrences (all)	11 / 540 (2.04%) 14	65 / 871 (7.46%) 78	13 / 394 (3.30%) 16
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Non-serious adverse events	Prevnar®		
Total subjects affected by non-serious adverse events subjects affected / exposed	57 / 64 (89.06%)		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0		
General disorders and administration site conditions Pyrexia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Injection site pain subjects affected / exposed occurrences (all)	8 / 64 (12.50%) 10 0 / 64 (0.00%) 0		
Tenderness subjects affected / exposed occurrences (all)	Additional description: = pain upon touching at vaccination site 8 / 64 (12.50%) 10		
Hardening subjects affected / exposed occurrences (all)	Additional description: Hardening at vaccination site 5 / 64 (7.81%) 6		
Swelling subjects affected / exposed occurrences (all)	Additional description: Swelling at vaccination site 5 / 64 (7.81%) 6		
Redness subjects affected / exposed occurrences (all)	Additional description: at injection site 23 / 64 (35.94%) 30		
Flu-like symptoms subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0		
Fever			

subjects affected / exposed occurrences (all) Irritability subjects affected / exposed occurrences (all) Excessive fatigue subjects affected / exposed occurrences (all)	24 / 64 (37.50%) 31 9 / 64 (14.06%) 16 5 / 64 (7.81%) 7		
Gastrointestinal disorders Diarrhoea alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Diarrhea subjects affected / exposed occurrences (all)	5 / 64 (7.81%) 5 5 / 64 (7.81%) 5 6 / 64 (9.38%) 7		
Skin and subcutaneous tissue disorders Heat rash alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 5 9 / 64 (14.06%) 9		
Infections and infestations Upper respiratory tract infection alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Gastroenteritis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	33 / 64 (51.56%) 50 9 / 64 (14.06%) 12		

Nasopharyngitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	5 / 64 (7.81%) 6		
Rhinitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 64 (4.69%) 5		
Metabolism and nutrition disorders Loss of appetite subjects affected / exposed occurrences (all)	6 / 64 (9.38%) 12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2010	- Lower age limit for the youngest age group lowered from 6 to 2 months. Visit schedule for subjects aged ≥ 2 to < 6 months receiving Prevnar® adapted to allow vaccination at Day 28. - For IC51 treatment arm subject numbers were amended: 130 subjects aged ≥ 2 months to < 1 year incl. 30 subjects for immunogenicity subgroup; 639 subjects aged ≥ 1 to < 3 years; 240 subjects aged ≥ 12 to < 18 years; total number of subjects treated with IC51 = 1409 subjects incl. 495 subjects from immunogenicity subgroup. Total sample size = 1867. - Details on introduction of enrolment cap for subjects recruited into the ≥ 6 to < 12 months age group to warrant enrolment of at least 45 subjects aged ≥ 2 to < 6 months following approval of the amendment. - Vaccination history of Prevnar® (Excl. Crit. #3) is an excl. crit. applicable for subjects < 1 year only. - Excl. Crit. #4 amended: children < 6 months of age are excluded from the study if they receive active or passive immunizations within one week before and one week after each IC51 vaccination. - Safety laboratory testing restricted to subjects aged ≥ 6 months. - Study hypothesis described in more detail. - Evaluation of riskbenefit ratio broadened by additional identified benefits. - Relevant protocol deviations which might be noticed after 1st vaccination leading to either subject withdrawal from further vaccination/study participation specified in more detail. - Clarifications on definition of solicited/unsolicited AEs, capturing of solicited/unsolicited AEs in the eCRF and on the causality assessment of solicited AEs added. - Details on statistical methods applied during Interim Analysis added. - Reporting of concomitant symptoms during a SAE clarified. - Approval status of IXIARO®/JESPECT® added. - Implementation dates for protocol version 1.0 and 2.0 amended/added. - Contact details updated. - Details on Data Safety Monitoring Board added. - Error re frequency of AEs following JE-VAX vaccination corrected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported