Clinical trial results:
LONG TERM IMMUNITY AND SAFETY WITH OR WITHOUT A BOOSTER DOSE FOLLOWING PRIMARY VACCINATION WITH THE JAPANESE ENCEPHALITIS VACCINE IC51 (IXIARO®) IN A PEDIATRIC POPULATION IN A JEV-ENDEMIC COUNTRY. OPEN-LABEL, RANDOMIZED, PHASE 3 STUDY.

Summary

EudraCT number	2010-022265-10
Trial protocol	Outside EU/EEA
Global end of trial date	14 October 2013

Results information

Result version number	v1 (current)
This version publication date	14 April 2016
First version publication date	14 April 2016

Trial information

Trial identification

Sponsor protocol code	IC51-325

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01296360
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)	EMEA-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	26 February 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assessment of the immune response (geometric mean titers [GMTs] and seroconversion rates [SCRs]) 28 days after one single booster vaccination with the purified inactivated Japanese Encephalitis (JE) vaccine Ixiaro® administered at 12 months after primary immunization in a pediatric population from JEV endemic regions.

Protection of trial subjects:

In the booster group, 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: -

Actual start date of recruitment	08 December 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Philippines: 300
Worldwide total number of subjects	300
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)	62
Children (2-11 years)	178
Adolescents (12-17 years)	60
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 08-Dec-2010 and was completed on 29-Apr-2011. All subjects had participated in parent study IC51-323.

Pre-assignment

Screening details:

Open-label, randomized, Phase 3 study in children aged ≥ 9 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	Booster group

Arm description:

Group received a booster dose of IC51 (Ixiaro®) at 12 months after the first vaccination with IC51 in study IC51-323 and was followed for another 24 months.

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 ≥ 14 months to < 3 years at Visit 2 received 1 vaccination of 0.25 ml IC51. Subjects aged ≥ 3 years to < 18 years at Visit 2 received 1 vaccination of 0.5 ml IC51.

Arm title	Non-Booster group

Arm description:

Group was followed for 36 months after the first vaccination with IC51 (Ixiaro®) in study IC51-323.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Booster group	Non-Booster group
Started	150	150
Completed	144	142
Not completed	6	8
Consent withdrawn by subject	1	-
Developed exclusion criteria	2	1
Non-compliance	2	4
Lost to follow-up	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	300	300	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	62	62	
Children (2-11 years)	178	178	
Adolescents (12-17 years)	60	60	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	5.3		
full range (min-max)	1.2 to 17.3	-	
Gender categorical Units: Subjects			
Female	151	151	
Male	149	149	

End points

End points reporting groups

Reporting group title	Booster group
Reporting group description:	
Group received a booster dose of IC51 (Ixiaro®) at 12 months after the first vaccination with IC51 in study IC51-323 and was followed for another 24 months.	
Reporting group title	Non-Booster group
Reporting group description:	
Group was followed for 36 months after the first vaccination with IC51 (Ixiaro®) in study IC51-323.	
Subject analysis set title	Booster 0.25 ml
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects aged ≥ 14 months to < 3 years at Visit 2 who had received 1 vaccination of 0.25 ml IC51.	
Subject analysis set title	Booster 0.5 ml
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects aged ≥ 3 years to < 18 years at Visit 2 who had received 1 vaccination of 0.5 ml IC51.	

Primary: SCRs as defined by percentage of subjects with plaque reduction neutralization test (PRNT50) titers of ≥1:10 at 1 month after the booster dose.

End point title	SCRs as defined by percentage of subjects with plaque reduction neutralization test (PRNT50) titers of ≥1:10 at 1 month after the booster dose.[1][2]
End point description:	
End point type	Primary
End point timeframe:	
1 Month after the IC51 booster dose.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Non-Booster group did not receive treatment. Endpoint concerns Booster group only.

End point values	Booster group	Booster 0.25 ml	Booster 0.5 ml	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	148	81	67	
Units: % of subjects				
number (confidence interval 95%)	100 (97.5 to 100)	100 (95.5 to 100)	100 (94.6 to 100)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were recorded at all study visits until 36 months after the first IC51 vaccination in study IC51-323.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Booster group

Reporting group description:

Group received a booster dose of IC51 (Ixiaro®) at 12 months after the first vaccination with IC51 in study IC51-323 and was followed for another 24 months.

Reporting group title	Non-Booster group

Reporting group description:

Group was followed for 36 months after the first vaccination with IC51 (Ixiaro®) in study IC51-323.

Serious adverse events	Booster group	Non-Booster group	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 150 (4.67%)	3 / 150 (2.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Concussion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Finger amputation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Paralysis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amoebic dysentery			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Booster group	Non-Booster group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	99 / 150 (66.00%)	100 / 150 (66.67%)	
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 150 (6.67%)	8 / 150 (5.33%)	
occurrences (all)	10	8	
Fever			
subjects affected / exposed	12 / 150 (8.00%)	0 / 150 (0.00%)	
occurrences (all)	12	0	
Infections and infestations			
Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	37 / 150 (24.67%)	34 / 150 (22.67%)	
occurrences (all)	53	43	
Rhinitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	17 / 150 (11.33%)	16 / 150 (10.67%)	
occurrences (all)	20	17	
Nasopharyngitis			
subjects affected / exposed	16 / 150 (10.67%)	15 / 150 (10.00%)	
occurrences (all)	22	17	
Varicella			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 150 (6.00%)	14 / 150 (9.33%)	
occurrences (all)	9	14	
Gastroenteritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 150 (4.67%)	8 / 150 (5.33%)	
occurrences (all)	7	9	
Bronchitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 150 (4.00%)	8 / 150 (5.33%)	
occurrences (all)	7	11	
Impetigo			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 150 (6.67%)	4 / 150 (2.67%)	
occurrences (all)	10	4	
Viral infection			
subjects affected / exposed	9 / 150 (6.00%)	5 / 150 (3.33%)	
occurrences (all)	11	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2013	1) A change in provision of subsequent therapy (free vaccination after study end) has been made: Subjects randomized into the Non-booster group were supposed to receive another locally available vaccine against JEV after study end. Instead, another licensed pediatric vaccine (Measles, Mumps, Rubella vaccine) will now be offered at no cost to all study participants, according to approved prescribing information. 2) An update on the description of the method regarding JE neutralization tests for assessment of immunogenicity is given and a change in the Department name of Valneva´s laboratory is reflected. 3) The actual study start was reflected. The planned implementation date for the amended protocol (final version 2.0, Q2 2013) has been added. 4) Administrative changes have been made regarding change of Valneva study responsible personnel and revision of responsible Monitoring office. 5) A typographical error in the protocol title on the signature page has been corrected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported