Clinical trial results:
IMMUNOGENICITY AND SAFETY OF THE JAPANESE ENCEPHALITIS VACCINE IC51 (IXIARO®, JESPECT®) IN A PEDIATRIC POPULATION IN NONENDEMIC COUNTRIES. UNCONTROLLED, OPENLABEL PHASE 3 STUDY.

Summary

EudraCT number	2009-015595-10
Trial protocol	DE SE DK
Global end of trial date	09 August 2013

Results information

Result version number	v1 (current)
This version publication date	31 January 2016
First version publication date	31 January 2016

Trial information

Trial identification

Sponsor protocol code	IC51-322

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01047839
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Valneva Austria GmbH
Sponsor organisation address	Campus Vienna Biocenter 3, Vienna, Austria, 1030
Public contact	Clinical Operations, Valneva Austria GmbH, 0043 1206200, info@valneva.com
Scientific contact	Clinical Operations, Valneva Austria GmbH, 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	10 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assessment of the safety profile of IC51 vaccine in a pediatric population from regions where Japanese Encephalitis is not endemic.

Protection of trial subjects:

An independent Data Safety Monitoring Board (DSMB) reviewed safety data after 44 subjects had received their first vaccination. 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	24 February 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	United States: 40
Worldwide total number of subjects	100
EEA total number of subjects	41

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)	7
Children (2-11 years)	34

Adolescents (12-17 years)	59
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited in 11 study centers located in Australia, EU (Germany, Denmark, Sweden) and the United States. Recruitment started on 24-Feb-2010 and was completed on 24-Jan-2013.

Pre-assignment

Screening details:

Uncontrolled, open-label Phase 3 study in children aged ≥ 2 months to < 18 years planning to travel to countries where JE is endemic and JE vaccination would be recommended.

Period 1

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

Arms

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

Arm description:

Safety and Immunogenicity follow-up to M7

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 interval of 4 weeks (Day 0 and 28).

Arm title	IC51 0.5 ml group

Arm description:

Safety and Immunogenicity follow-up to M7

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 interval of 4 weeks (Day 0 and 28).

Number of subjects in period 1	IC51 0.25 ml group	IC51 0.5 ml group
Started	12	88
Completed	10	82
Not completed	2	6
Consent withdrawn by subject	-	1
Reason unknown	-	2
Lost to follow-up	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	100	100	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	7	7	
Children (2-11 years)	34	34	
Adolescents (12-17 years)	59	59	
Age continuous			
Age in years at Screening.			
Units: years			
arithmetic mean	11.62		
full range (min-max)	0.9 to 18	-	
Gender categorical Units: Subjects			
Female	53	53	
Male	47	47	

End points

End points reporting groups

Reporting group title	IC51 0.25 ml group
Reporting group description:	
Safety and Immunogenicity follow-up to M7	
Reporting group title	IC51 0.5 ml group
Reporting group description:	
Safety and Immunogenicity follow-up to M7	

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.[1]
End point description:	
End point type	Primary
End point timeframe:	
56 Days after the first IC51 vaccination.	

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: Analysis of the primary endpoint was descriptive, i.e. no statistical hypothesis test was performed.

End point values	IC51 0.25 ml group	IC51 0.5 ml group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	88		
Units: % of subjects				
number (confidence interval 95%)	33.3 (9.9 to 65.1)	9.1 (4 to 17.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of subjects with SAEs and medically attended AEs up to Month 7 after the first vaccination.

End point title	Rate of subjects with SAEs and medically attended AEs up to Month 7 after the first vaccination.
End point description:	
End point type	Secondary
End point timeframe:	
7 Months after the first IC51 vaccination.	

End point values	IC51 0.25 ml group	IC51 0.5 ml group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	88		
Units: % of subjects				
number (confidence interval 95%)	33.3 (9.9 to 65.1)	18.2 (10.8 to 27.8)		

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 Month 7.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Safety population

Reporting group description:

All subjects who were enrolled in the study.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 100 (3.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Dizziness, Giddiness			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression resulting in self harm			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes Mellitus I			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 100 (81.00%)		
Nervous system disorders			
Headache	Additional description: Systemic symptom typically associated with vaccinations which occurred within 7 days after a IC51 vaccination.		
subjects affected / exposed	7 / 100 (7.00%)		
occurrences (all)	13		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 100 (6.00%)		
occurrences (all)	9		
Injection site pain	Additional description: Local symptom at injection site typically associated with vaccinations which occurred within 7 days after a IC51 vaccination.		
subjects affected / exposed	22 / 100 (22.00%)		
occurrences (all)	28		
Injection site tenderness	Additional description: Local symptom at injection site typically associated with vaccinations which occurred within 7 days after a IC51 vaccination.		
subjects affected / exposed	45 / 100 (45.00%)		
occurrences (all)	62		
Injection site hardening	Additional description: Local symptom at injection site typically associated with vaccinations which occurred within 7 days after a IC51 vaccination.		
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	6		
Injection site redness	Additional description: Local symptom at injection site typically associated with vaccinations which occurred within 7 days after a IC51 vaccination.		
subjects affected / exposed	7 / 100 (7.00%)		
occurrences (all)	7		
Irritability	Additional description: Systemic symptom typically associated with vaccinations which occurred within 7 days after a IC51 vaccination.		
subjects affected / exposed	6 / 100 (6.00%)		
occurrences (all)	8		
Excessive fatigue	Additional description: Systemic symptom typically associated with vaccinations which occurred within 7 days after a IC51 vaccination.		
subjects affected / exposed	10 / 100 (10.00%)		
occurrences (all)	10		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	6		
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	6 / 100 (6.00%)		
occurrences (all)	6		
Nausea	Additional description: Systemic symptom typically associated with vaccinations which occurred within 7 days after a IC51 vaccination.		
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	9		
Diarrhoea	Additional description: Systemic symptom typically associated with vaccinations which occurred within 7 days after a IC51 vaccination.		
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 100 (6.00%)		
occurrences (all)	6		
Musculoskeletal and connective tissue disorders			
Muscle pain	Additional description: Systemic symptom typically associated with vaccinations which occurred within 7 days after a IC51 vaccination.		
subjects affected / exposed	27 / 100 (27.00%)		
occurrences (all)	34		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 100 (8.00%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2010	Amendment 1/Amendment 2: Age limit for subjects was lowered from 6 months to 2 months. Minimum recruitment numbers for each age group were stipulated. Exclusion criterion 3 was amended to ease inclusion of children less than 6 months old with dense childhood immunization schedules (all Amendment 1). Timing of Visit 0 (Screening) and Visit 1 were amended to allow for a combined visit. Exclusion criteria 1 and 3 were amended to include history of any Flavivirus disease and to harmonize forbidden concomitant active or passive vaccination during the treatment period for all age groups. Relevant protocol deviations which might be noticed after the first vaccination were specified in more detail. Number of subjects in each age group was further clarified (all Amendment 2).
16 December 2010	Amendment 3: Consolidation of local amendments in Australia and Sweden. Results of the dose finding run-in phase from Study IC51-323 were added to the Introduction and the appropriate dose for subjects aged ≥ 3 to < 12 years added throughout the protocol. In case of a combined visit (Visit 0 and Visit 1) the pregnancy testing was amended.
20 May 2011	Amendment 4: Removal of age-stratification for an enrollment of 100 children aged ≥ 2 months to < 18 years. Initial planned suspension of enrollment during the DSMB review was amended to allow enrollment during the review.
05 August 2011	Amendment 5: Non-substantial amendment. Details of an interim analysis were added, which was to be performed on data from all subjects enrolled up to approximately the beginning of July 2011. Details were added on a review of the data by an independent DSMB and the subsequent recommendation. Description of the assay for the assessment of immunogenicity was updated.
31 October 2011	Amendment 6: Primary objective and primary endpoint were changed from immunogenicity to safety, with immunogenicity assessments limited to children enrolled under previous protocol versions (up to Protocol Version 9.0). Statistical analysis details and prespecified subgroup analysis were adjusted to accommodate the changes to the objectives and endpoints, minimum number of subjects with immunogenicity data evaluable was set to 50. Time window for performing the first followup visit, Visit 3, was widened to a minimum of 7 days to a maximum of 2 months after Visit 2 (Day 28). Details of Visit 3 were amended to allow the visit to be conducted face-to-face or as a telephone call and, if the latter, to permit the subject diary to be mailed to the site. Inclusion criterion specifying the timing of travel was amended to accommodate the change to Visit 3. Interim safety results of the DSMB review were included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

As the number of subjects in the 0.25 mL dose group was low, a meaningful comparison between the 2 dose groups is not possible.

Notes: