Clinical trial results:
A phase IV, open-label, multi-center follow-up study to determine the persistence of tick-borne encephalitis (TBE)-specific antibody responses among children and adolescents previously immunized against TBE.

Summary

EudraCT number	2009-010145-31
Trial protocol	DE
Global end of trial date	02 May 2011

Results information

Result version number	v1 (current)
This version publication date	11 May 2016
First version publication date	21 February 2015

Trial information

Trial identification

Sponsor protocol code	M48P3E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01106482
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics
Sponsor organisation address	Via Fiorentina, 1, Siena, Italy, 53100
Public contact	Posting Director, Novartis Vaccines and Diagnostics, RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccines and Diagnostics, RegistryContactVaccinesUS@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	08 June 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 May 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate whether the first booster interval after primary vaccination with Encepur agains Tick borne encephalitis (TBE) can be prolonged from 3 years (current SPC recommendation) to 5 years.

Primary objectives:

1. To determine the proportion of study subjects with a TBE neutralizing titer ≥ 10 at 3, 4 and 5 years after completion of the primary immunization.

2. The kinetics of the TBE antibody response over time (at years 3, then 4, then 5) will also be assessed.

Protection of trial subjects:

This clinical study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations, including the European Directive 2001/20/EC, the US CFR Title 21, and the Japanese Ministry of Health, Labor, and Welfare, Novartis codes on the protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 May 2009
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	Germany: 267
Worldwide total number of subjects	267
EEA total number of subjects	267

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	201
Adolescents (12-17 years)	66
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled from 10 studies center in Germany.

Pre-assignment

Screening details:

All enrolled participants were included in the trial.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1 (TBE_C)

Arm description:

Participants who received Encepur® Children on days 0, 28, and 300 in the parent study M48P3 and had blood collected at approximately 3, 4 and 5 years after last vaccination in the primary immunization series.

Arm type	Experimental
Investigational medicinal product name	Tick-borne encephalitis vaccine (inactivated, adsorbed for pediatric use)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

In this trial no IMP will be administered. This trial consists of 3 blood draws only.

Arm title	Group 2 (TBE_AC)

Arm description:

Participants who received Encepur® Children on days 0, 14, and 300 in the parent study M48P3 and had blood collected at approximately 3, 4 and 5 years after last vaccination in the primary immunization series.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Group 3 (BAX_C)

Arm description:

Participants who received
FSME-Immun® Junior on days 0 and 28 and Encepur® Children on day 300 in the parent study M48P3 and had blood collected at approximately 3 years after last vaccination in the primary immunization series.
After the Year 3 interim analysis the participants were terminated from the study and received a recommendation for a booster injection.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Group 4 (BAX_AC)

Arm description:

Participants who received FSME-Immun® Junior on days 0 and 14 and Encepur® Children on day 300 in the parent study M48P3 and had blood collected at approximately 3 years after last vaccination in the primary immunization series.

After the Year 3 interim analysis the participants were terminated from the study and received a recommendation for a booster injection.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Group 1 (TBE_C)	Group 2 (TBE_AC)	Group 3 (BAX_C)
Started	68	67	65
Completed	60	60	27
Not completed	8	7	38
Consent withdrawn by subject	1	-	-
Unable to classify	-	2	38
Lost to follow-up	3	2	-
Protocol deviation	4	3	-

Number of subjects in period 1	Group 4 (BAX_AC)
Started	67
Completed	31
Not completed	36
Consent withdrawn by subject	-
Unable to classify	36
Lost to follow-up	-
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Group 1 (TBE_C)
Reporting group description:	
Participants who received Encepur® Children on days 0, 28, and 300 in the parent study M48P3 and had blood collected at approximately 3, 4 and 5 years after last vaccination in the primary immunization series.	
Reporting group title	Group 2 (TBE_AC)
Reporting group description:	
Participants who received Encepur® Children on days 0, 14, and 300 in the parent study M48P3 and had blood collected at approximately 3, 4 and 5 years after last vaccination in the primary immunization series.	
Reporting group title	Group 3 (BAX_C)
Reporting group description:	
Participants who received FSME-Immun® Junior on days 0 and 28 and Encepur® Children on day 300 in the parent study M48P3 and had blood collected at approximately 3 years after last vaccination in the primary immunization series. After the Year 3 interim analysis the participants were terminated from the study and received a recommendation for a booster injection.	
Reporting group title	Group 4 (BAX_AC)
Reporting group description:	
Participants who received FSME-Immun® Junior on days 0 and 14 and Encepur® Children on day 300 in the parent study M48P3 and had blood collected at approximately 3 years after last vaccination in the primary immunization series. After the Year 3 interim analysis the participants were terminated from the study and received a recommendation for a booster injection.	

Reporting group values	Group 1 (TBE_C)	Group 2 (TBE_AC)	Group 3 (BAX_C)
Number of subjects	68	67	65
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	9.2	9.2	8.8
standard deviation	± 2.7	± 3.1	± 2.7
Gender categorical Units: Subjects			
Female	29	29	30
Male	39	38	35

Reporting group values	Group 4 (BAX_AC)	Total	
Number of subjects	67	267	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	8.9		
standard deviation	± 2.9	-	
Gender categorical Units: Subjects			
Female	27	115	
Male	40	152	

End points

End points reporting groups

Reporting group title	Group 1 (TBE_C)

Reporting group description:

Participants who received Encepur® Children on days 0, 28, and 300 in the parent study M48P3 and had blood collected at approximately 3, 4 and 5 years after last vaccination in the primary immunization series.

Reporting group title	Group 2 (TBE_AC)

Reporting group description:

Participants who received Encepur® Children on days 0, 14, and 300 in the parent study M48P3 and had blood collected at approximately 3, 4 and 5 years after last vaccination in the primary immunization series.

Reporting group title	Group 3 (BAX_C)

Reporting group description:

Participants who received
FSME-Immun® Junior on days 0 and 28 and Encepur® Children on day 300 in the parent study M48P3 and had blood collected at approximately 3 years after last vaccination in the primary immunization series.
After the Year 3 interim analysis the participants were terminated from the study and received a recommendation for a booster injection.

Reporting group title	Group 4 (BAX_AC)

Reporting group description:

Participants who received FSME-Immun® Junior on days 0 and 14 and Encepur® Children on day 300 in the parent study M48P3 and had blood collected at approximately 3 years after last vaccination in the primary immunization series.
After the Year 3 interim analysis the participants were terminated from the study and received a recommendation for a booster injection.

Subject analysis set title	All Enrolled Set
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who were enrolled irrespective of whether they have provided serum or not.

Subject analysis set title	Per Protocol Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects who were enrolled and who belonged to PPS of study M48P3, and had no major protocol violations as pre-specified in the Analysis Plan.
PPS was categorized in PPS-I and PPS-II:
Per Protocol Set - Version I, subjects boosted since end of study M48P3 excluded.
Per Protocol Set - Version II, subjects boosted since end of study M48P3 included.
Number of subjects reported refers to PPS-I.

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who were enrolled belonged to FAS of M48P3 study and who had at least one evaluable sample for the immunogenicity analysis. Subjects were analyzed according to the vaccines received in study M48P3.
FAS was categorized in FAS-I and FAS-II:
Full Analysis Set - Version I, subjects boosted since end of study M48P3 excluded.
Full Analysis Set - Version II, subjects boosted since end of study M48P3 included.
Number of subjects reported refers to FAS-I.

Primary: 1. Percentages of Subjects with Antibody Titers ≥10 as Measured by NT (year 3)

End point title	1. Percentages of Subjects with Antibody Titers ≥10 as Measured by NT (year 3)[1]

End point description:

The proportion of study subjects with a TBE neutralizing titer (NT) ≥10 at 3 years after completion of the primary immunization were reported as percentages.

End point type	Primary

End point timeframe:

3 years after 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: No statistical analysis were performed for this end point.

End point values	Group 1 (TBE_C)	Group 2 (TBE_AC)	Group 3 (BAX_C)	Group 4 (BAX_AC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	44	60	51
Units: Percentages of subjects				
number (confidence interval 95%)				
PPS-I	100 (93 to 100)	100 (92 to 100)	70 (57 to 81)	65 (50 to 78)
PPS-II	98 (90 to 100)	96 (86 to 100)	68 (55 to 79)	56 (42 to 69)

Statistical analyses

No statistical analyses for this end point

Primary: 2. Percentages of Subjects with Antibody Titers ≥10 as Measured by NT (year 4 and 5)

End point title	2. Percentages of Subjects with Antibody Titers ≥10 as Measured by NT (year 4 and 5)[2][3]

End point description:

The proportion of study subjects with a TBE neutralizing titer (NT) ≥10 at 4 and 5 years after completion of the primary immunization were reported as percentages.

End point type	Primary

End point timeframe:

4 and 5 years after vaccination

Notes:

[2] - 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 were performed for this end point.

[3] - 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: No statistical analysis were performed for this end point.

End point values	Group 1 (TBE_C)	Group 2 (TBE_AC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	44		
Units: Percentages of subjects				
number (confidence interval 95%)				
PPS-I (4 years after primary vacc)	100 (93 to 100)	100 (92 to 100)		
PPS-II (4 years after primary vacc)	94 (85 to 99)	94 (83 to 99)		
PPS-I (5 years after primary vacc)	98 (89 to 100)	98 (88 to 100)		
PPS-II (5 years after primary vacc)	91 (80 to 97)	86 (73 to 94)		

Statistical analyses

No statistical analyses for this end point

Secondary: 3. Percentages of Subjects with Antibody Titers ≥2 as Measured by NT (year 3)

End point title	3. Percentages of Subjects with Antibody Titers ≥2 as Measured by NT (year 3)

End point description:

The proportion of study subjects with a TBE neutralizing titer (NT) ≥2 at 3 years after completion of the primary immunization were reported as percentages.

End point type	Secondary

End point timeframe:

3 years after vaccination

End point values	Group 1 (TBE_C)	Group 2 (TBE_AC)	Group 3 (BAX_C)	Group 4 (BAX_AC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	44	60	51
Units: Percentages of subjects				
number (confidence interval 95%)				
PPS-I	100 (93 to 100)	100 (92 to 100)	97 (88 to 100)	96 (87 to 100)
PPS-II	98 (90 to 100)	96 (86 to 100)	94 (84 to 98)	83 (71 to 92)

Statistical analyses

No statistical analyses for this end point

Secondary: 4. Percentages of Subjects with Antibody Titers ≥2 as Measured by NT (year 4 and 5)

End point title	4. Percentages of Subjects with Antibody Titers ≥2 as Measured by NT (year 4 and 5)[4]

End point description:

The proportion of study subjects with a TBE neutralizing titer (NT) ≥2 at 4 and 5 years after completion of the primary immunization were reported as percentages.

End point type	Secondary

End point timeframe:

4 and 5 years after vaccination

Notes:

[4] - 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: No statistical analysis were performed for this end point.

End point values	Group 1 (TBE_C)	Group 2 (TBE_AC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	44		
Units: Percentages of subjects				
number (confidence interval 95%)				
PPS-I (4 years after primary vacc)	100 (93 to 100)	100 (92 to 100)		
PPS-II (4 years after primary vacc)	94 (85 to 99)	94 (83 to 99)		
PPS-I (5 years after primary vacc)	100 (93 to 100)	100 (92 to 100)		
PPS-II (5 years after primary vacc)	93 (82 to 98)	88 (76 to 95)		

Statistical analyses

No statistical analyses for this end point

Secondary: 5. Geometric Mean Concentration of Antibodies Measured by ELISA (year 3)

End point title	5. Geometric Mean Concentration of Antibodies Measured by ELISA (year 3)

End point description:

The levels of TBE-specific binding antibodies were measured by ELISA 3 years after completion of the primary immunization.

End point type	Secondary

End point timeframe:

3 years after vaccination

End point values	Group 1 (TBE_C)	Group 2 (TBE_AC)	Group 3 (BAX_C)	Group 4 (BAX_AC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	44	60	51
Units: Geometric Mean Concentration of Antibodi				
geometric mean (confidence interval 95%)				
PPS-I	83 (64 to 108)	66 (50 to 87)	35 (26 to 47)	27 (19 to 37)
PPS-II	81 (60 to 110)	57 (41 to 77)	30 (22 to 43)	19 (13 to 26)

Statistical analyses

No statistical analyses for this end point

Secondary: 6. Geometric Mean Concentration of Antibodies Measured by ELISA (year 4 and 5)

End point title	6. Geometric Mean Concentration of Antibodies Measured by ELISA (year 4 and 5)[5]

End point description:

The levels of TBE-specific binding antibodies were measured by ELISA 4 and 5 years after completion of the primary immunization.

End point type	Secondary

End point timeframe:

4 and 5 years after vaccination

Notes:

[5] - 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: No statistical analysis were performed for this end point.

End point values	Group 1 (TBE_C)	Group 2 (TBE_AC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	44		
Units: Geometric Mean Concentration of Antibodi				
geometric mean (confidence interval 95%)				
PPS-I (4 years after primary vacc)	80 (60 to 107)	62 (46 to 83)		
PPS-II (4 years after primary vacc) (N=54,50)	69 (48 to 99)	51 (35 to 74)		
PPS-I (5 years after primary vacc)	81 (58 to 112)	56 (40 to 80)		
PPS-II (5 years after primary vacc) (N=54,50)	66 (43 to 102)	41 (26 to 63)		

Statistical analyses

No statistical analyses for this end point

Secondary: 7. Percentages of Seropositive Subjects as Measured by ELISA (year 3)

End point title	7. Percentages of Seropositive Subjects as Measured by ELISA (year 3)

End point description:

The proportion of study seropositive subjects with a TBE-specific binding antibodies measured by ELISA 3 years after completion of the primary immunization were reported as percentages.

End point type	Secondary

End point timeframe:

3 years after vaccination

End point values	Group 1 (TBE_C)	Group 2 (TBE_AC)	Group 3 (BAX_C)	Group 4 (BAX_AC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	44	60	51
Units: Percentages of subjects				
number (confidence interval 95%)				
PPS-I	100 (93 to 100)	100 (92 to 100)	85 (73 to 93)	90 (79 to 97)
PPS-II	98 (90 to 100)	96 (86 to 100)	82 (70 to 91)	78 (65 to 88)

Statistical analyses

No statistical analyses for this end point

Secondary: 8. Percentages of Seropositive Subjects as Measured by ELISA (year 4 and 5)

End point title	8. Percentages of Seropositive Subjects as Measured by ELISA (year 4 and 5)[6]

End point description:

The proportion of study seropositive subjects with a TBE-specific binding antibodies measured by ELISA 4 and 5 years after completion of the primary immunization were reported as percentages.

End point type	Secondary

End point timeframe:

4 and 5 years after vaccination

Notes:

[6] - 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: No statistical analysis were performed for this end point.

End point values	Group 1 (TBE_C)	Group 2 (TBE_AC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	44		
Units: Percentages of subjects				
number (confidence interval 95%)				
PPS-I (4 years after primary vacc)	98 (89 to 100)	98 (88 to 100)		
PPS-II (4 years after primary vacc) (N=54, 50)	93 (82 to 98)	92 (81 to 98)		
PPS-I (5 years after primary vacc)	96 (86 to 100)	98 (88 to 100)		
PPS-II (5 years after primary vacc) (N=54, 50)	89 (77 to 96)	86 (73 to 94)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

from study start (8 MAY 2009) up to protocol amendment effective (9 FEB 2010)

Adverse event reporting additional description:

First version of the protocol included safety data collection. As no vaccine was administered in the trial, protocol was amended (9 FEB 2010): all paragraphs on AE reporting were removed and safety data were not collected any longer.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Group 1 (TBE_C)

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: As no vaccine was administered in this study the adverse events were not collected.

Serious adverse events	Group 1 (TBE_C)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 68 (1.47%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 68 (1.47%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 68 (1.47%)		
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	Group 1 (TBE_C)		
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 68 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2009	Amendment No. 1 On review of the protocol, ICF and the Assent form, the Ethics Committee of Bavaria, Germany issued comments which were in German. The Regional Physician translated these comments in English. Of the comments, only 2 as outlined below are relevant to the protocol, others will be implemented in the ICF and assent form.
09 February 2010	Amendment No. 2 - As there was no vaccine administered in this study, there is no safety analysis. Therefore, all text referring to adverse events or serious adverse events was removed. - The study protocol was revised to incorporate an analysis for antibody responses to the Neudoerfl antigen included in the FSME-Immun® Junior vaccine, which was one of the two study vaccines administered in the M48P3 parent study. The addition of this analysis broadened the understanding of immune responses in children to two different TBE vaccines over a long-term follow-up period. - It was specified that relevant interim medical history at visit 8 and 9 should include any confirmed or suspected TBE exposure or a tick bite. - The definition for the full analysis set (FAS) and per protocol set (PPS) for immunogenicity was clarified.

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.

The 2 SAEs were collected because the initial version of the protocol included safety data collection. Given that no vaccine was administered in the trial, the protocol was revisited (Feb-2010) and safety data were not collected any longer.

Notes: