

**Clinical trial results:****Open-label Phase IV Study to Investigate the Seropersistence of Tick-borne Encephalitis (TBE) Virus Antibodies After the First Booster and the Response to A Second Booster Vaccination With Fsme-Immun in Children, Adolescents and Young Adults (Follow Up to Study 700401)
Summary**

EudraCT number	2009-009324-36
Trial protocol	AT DE PL
Global end of trial date	10 May 2017

Results information

Result version number	v1 (current)
This version publication date	18 November 2017
First version publication date	18 November 2017

Trial information**Trial identification**

Sponsor protocol code	700802
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00894686
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 011 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.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	16 August 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess tick-borne encephalitis (TBE) antibody persistence at yearly intervals from approximately 3 years (38 months) to 10 years (118 months) after the first booster vaccination (as applicable) with either FSME-IMMUN 0.25 milliliters (mL) Junior or FSME-IMMUN 0.5 mL by means of neutralization test (NT) and enzyme-linked immunosorbent assay (ELISA) [IMMUNOZYM FSME Immunoglobulin G (IgG)].

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 April 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 33
Country: Number of subjects enrolled	Germany: 73
Country: Number of subjects enrolled	Poland: 73
Worldwide total number of subjects	179
EEA total number of subjects	179

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)	0
Children (2-11 years)	40
Adolescents (12-17 years)	80
Adults (18-64 years)	59

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study is a follow-up study of 700401 (NCT00161967) in which subjects received the single booster vaccination.

Period 1

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

Arms

Arm title	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL
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Arm description:

Subjects with low tick-borne encephalitis (TBE) serum antibody levels and received first booster vaccination in Study 700401 (NCT00161967) were administered single intramuscular injection of FSME-IMMUN 0.25 mL Junior (less than 16 years of age) or FSME-IMMUN 0.5 mL (16 years or above of age), as second booster vaccination in this study either at Month 40, 48, 60, 72, 84, 96, 108, or 120. Subjects were followed up to 21-35 days post vaccination in this study.

Arm type	Experimental
Investigational medicinal product name	FSME-IMMUN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects with low tick-borne encephalitis (TBE) serum antibody levels and received first booster vaccination in Study 700401 (NCT00161967) were administered single intramuscular injection of FSME-IMMUN 0.25 mL Junior (less than 16 years of age) or FSME-IMMUN 0.5 mL (16 years or above of age), as second booster vaccination in this study either at Month 40, 48, 60, 72, 84, 96, 108, or 120. Subjects were followed up to 21-35 days post vaccination in this study.

Number of subjects in period 1	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL
Started	179
Completed	123
Not completed	56
Consent withdrawn by subject	50
Physician decision	1
Unspecified	5

Baseline characteristics

Reporting groups

Reporting group title	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL
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Reporting group description:

Subjects with low tick-borne encephalitis (TBE) serum antibody levels and received first booster vaccination in Study 700401 (NCT00161967) were administered single intramuscular injection of FSME-IMMUN 0.25 mL Junior (less than 16 years of age) or FSME-IMMUN 0.5 mL (16 years or above of age), as second booster vaccination in this study either at Month 40, 48, 60, 72, 84, 96, 108, or 120. Subjects were followed up to 21-35 days post vaccination in this study.

Reporting group values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL	Total	
Number of subjects	179	179	
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)	0	0	
Children (2-11 years)	40	40	
Adolescents (12-17 years)	80	80	
Adults (18-64 years)	59	59	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: Years			
arithmetic mean	15.1		
standard deviation	± 4.4	-	
Gender, Male/Female			
Units: Subjects			
Female	88	88	
Male	91	91	

End points

End points reporting groups

Reporting group title	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL
Reporting group description:	
Subjects with low tick-borne encephalitis (TBE) serum antibody levels and received first booster vaccination in Study 700401 (NCT00161967) were administered single intramuscular injection of FSME-IMMUN 0.25 mL Junior (less than 16 years of age) or FSME-IMMUN 0.5 mL (16 years or above of age), as second booster vaccination in this study either at Month 40, 48, 60, 72, 84, 96, 108, or 120. Subjects were followed up to 21-35 days post vaccination in this study.	

Primary: Seropositivity Rate Measured by Neutralization Test (NT) at 21-35 Days After the First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401

End point title	Seropositivity Rate Measured by Neutralization Test (NT) at 21-35 Days After the First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401 ^[1]
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End point description:

Seropositivity rate was reported as percentage of subjects with NT level greater than equal to (\geq) 10 at 21-35 days after the first TBE booster vaccination in Study 700401. Exact 2-sided 95 percent confidence interval (CI) was based upon the observed percentage of subjects. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation. Here, "Number of subjects analyzed" (N) signifies those subjects who were evaluable for this outcome measure.

End point type	Primary
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End point timeframe:

21-35 days after first TBE booster 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: only descriptive data was planned to be analysed for this endpoint

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	171			
Units: Percentage of subjects				
number (confidence interval 95%)	100.0 (97.9 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Seropositivity Rate Measured by Neutralization Test (NT) at 38 Months After the First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401

End point title	Seropositivity Rate Measured by Neutralization Test (NT) at 38 Months After the First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401 ^[2]
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End point description:

Seropositivity rate was reported as percentage of subjects with NT level ≥ 10 at 38 months after the first TBE booster vaccination in Study 700401. Exact 2-sided 95 percent CI was based upon the observed percentage of subjects. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation. Here, "N" signifies those subjects who were evaluable for this outcome measure.

End point type	Primary
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End point timeframe:

38 months after first TBE booster 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: only descriptive data was planned to be analysed for this endpoint

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	167			
Units: Percentage of subjects				
number (confidence interval 95%)	100.0 (97.8 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Seropositivity Rate Measured by Neutralization Test (NT) at 46 Months After the First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401

End point title	Seropositivity Rate Measured by Neutralization Test (NT) at 46 Months After the First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401 ^[3]
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End point description:

Seropositivity rate was reported as percentage of subjects with NT level ≥ 10 at 46 months after the first TBE booster vaccination in Study 700401. Exact 2-sided 95 percent CI was based upon the observed percentage of subjects. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation. Here, "N" signifies those subjects who were evaluable for this outcome measure.

End point type	Primary
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End point timeframe:

46 months after first TBE booster vaccination

Notes:

[3] - 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: only descriptive data was planned to be analysed for this endpoint

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	147			
Units: Percentage of subjects				
number (confidence interval 95%)	100.0 (97.5 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Seropositivity Rate Measured by Neutralization Test (NT) at 58 Months After the First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401

End point title	Seropositivity Rate Measured by Neutralization Test (NT) at 58 Months After the First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401 ^[4]
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End point description:

Seropositivity rate was reported as percentage of subjects with NT level ≥ 10 at 58 months after the first TBE booster vaccination in Study 700401. Exact 2-sided 95 percent CI was based upon the observed percentage of subjects. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation. Here, "N" signifies those subjects who were evaluable for this outcome measure.

End point type	Primary
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End point timeframe:

58 months after first TBE booster vaccination

Notes:

[4] - 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: only descriptive data was planned to be analysed for this endpoint

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	156			
Units: Percentage of subjects				
number (confidence interval 95%)	99.4 (96.5 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Seropositivity Rate Measured by Neutralization Test (NT) at 70 Months After the First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401

End point title	Seropositivity Rate Measured by Neutralization Test (NT) at 70 Months After the First Tick-borne Encephalitis (TBE) Booster
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End point description:

Seropositivity rate was reported as percentage of subjects with NT level ≥ 10 at 70 months after the first TBE booster vaccination in Study 700401. Exact 2-sided 95 percent CI was based upon the observed percentage of subjects. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation. Here, "N" signifies those subjects who were evaluable for this outcome measure.

End point type	Primary
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End point timeframe:

70 months after first TBE booster vaccination

Notes:

[5] - 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: only descriptive data was planned to be analysed for this endpoint

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	157			
Units: Percentage of subjects				
number (confidence interval 95%)	98.1 (94.5 to 99.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Seropositivity Rate Measured by Neutralization Test (NT) at 82 Months After the First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401

End point title	Seropositivity Rate Measured by Neutralization Test (NT) at 82 Months After the First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401 ^[6]
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End point description:

Seropositivity rate was reported as percentage of subjects with NT level ≥ 10 at 82 months after the first TBE booster vaccination in Study 700401. Exact 2-sided 95 percent CI was based upon the observed percentage of subjects. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation. Here, "N" signifies those subjects who were evaluable for this outcome measure.

End point type	Primary
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End point timeframe:

82 months after first TBE booster vaccination

Notes:

[6] - 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: only descriptive data was planned to be analysed for this endpoint

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	156			
Units: Percentage of subjects				
number (confidence interval 95%)	96.8 (92.7 to 99.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Seropositivity Rate Measured by Neutralization Test (NT) at 94 Months After the First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401

End point title	Seropositivity Rate Measured by Neutralization Test (NT) at 94 Months After the First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401 ^[7]
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End point description:

Seropositivity rate was reported as percentage of subjects with NT level ≥ 10 at 94 months after the first TBE booster vaccination in Study 700401. Exact 2-sided 95 percent CI was based upon the observed percentage of subjects. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation. Here, "N" signifies those subjects who were evaluable for this outcome measure.

End point type	Primary
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End point timeframe:

94 months after first TBE booster vaccination

Notes:

[7] - 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: only descriptive data was planned to be analysed for this endpoint

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	156			
Units: Percentage of subjects				
number (confidence interval 95%)	95.5 (91.0 to 98.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Seropositivity Rate Measured by Neutralization Test (NT) at 106 Months After the First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401

End point title	Seropositivity Rate Measured by Neutralization Test (NT) at 106 Months After the First Tick-borne Encephalitis (TBE)
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End point description:

Seropositivity rate was reported as percentage of subjects with NT level ≥ 10 at 106 months after the first TBE booster vaccination in Study 700401. Exact 2-sided 95 percent CI was based upon the observed percentage of subjects. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation. Here, "N" signifies those subjects who were evaluable for this outcome measure.

End point type	Primary
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End point timeframe:

106 months after first TBE booster vaccination

Notes:

[8] - 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: only descriptive data was planned to be analysed for this endpoint

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	156			
Units: Percentage of subjects				
number (confidence interval 95%)	94.9 (90.1 to 97.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Seropositivity Rate Measured by Neutralization Test (NT) at 118 Months After the First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401

End point title	Seropositivity Rate Measured by Neutralization Test (NT) at 118 Months After the First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401 ^[9]
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End point description:

Seropositivity rate was reported as percentage of subjects with NT level ≥ 10 at 118 months after the first TBE booster vaccination in Study 700401. Exact 2-sided 95 percent CI was based upon the observed percentage of subjects. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation. Here, "N" signifies those subjects who were evaluable for this outcome measure.

End point type	Primary
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End point timeframe:

118 months after first TBE booster vaccination

Notes:

[9] - 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: only descriptive data was planned to be analysed for this endpoint

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	155			
Units: Percentage of subjects				
number (confidence interval 95%)	90.3 (84.5 to 94.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Seropositivity Rate Measured by Neutralization Test (NT) at 21-35 Days After the Second Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700802

End point title	Seropositivity Rate Measured by Neutralization Test (NT) at 21-35 Days After the Second Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700802 ^[10]
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End point description:

Seropositivity rate was reported as percentage of subjects with NT level ≥ 10 at 21-35 days after the second TBE booster vaccination. Exact 2-sided 95 percent CI was based upon the observed percentage of subjects. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation.

End point type	Primary
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End point timeframe:

21-35 days after second TBE booster vaccination

Notes:

[10] - 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: only descriptive data was planned to be analysed for this endpoint

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Percentage of subjects				
number (confidence interval 95%)	100.0 (86.8 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Seropositivity Rate Measured by Enzyme-Linked Immunosorbent Assay (ELISA) at Each Available Time Point After First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401

End point title	Seropositivity Rate Measured by Enzyme-Linked Immunosorbent Assay (ELISA) at Each Available Time Point
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End point description:

Seropositivity rate was reported as percentage of subjects with ELISA level greater than (>) 126 vienna units per milliliter (VIE U/mL) at each blood sampling time point after first TBE booster vaccination in Study 700401. Exact 2-sided 95 percent CI was based upon the observed percentage of subjects. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation. Here, "n" signifies number of subjects who were evaluable at specified time points.

End point type Secondary

End point timeframe:

21-35 days and 38, 46, 58, 70, 82, 94, 106, 118 months after first TBE booster vaccination

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	172			
Units: Percentage of subjects				
number (confidence interval 95%)				
After 21-35 days (n =171)	98.8 (95.8 to 99.9)			
After 38 months (n =166)	97.0 (93.1 to 99.0)			
After 46 months (n =146)	100.0 (97.5 to 100.0)			
After 58 months (n =157)	97.5 (93.6 to 99.3)			
After 70 months (n =156)	96.8 (92.7 to 99.0)			
After 82 months (n =156)	96.2 (91.8 to 98.6)			
After 94 months (n =156)	96.2 (91.8 to 98.6)			
After 106 months (n =156)	91.7 (86.2 to 95.5)			
After 118 months (n =155)	87.7 (81.5 to 92.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Seropositivity Rate Measured by Enzyme-Linked Immunosorbent Assay (ELISA) at 21-35 Days After Second Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700802

End point title Seropositivity Rate Measured by Enzyme-Linked Immunosorbent Assay (ELISA) at 21-35 Days After Second Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700802

End point description:

Seropositivity rate was reported as percentage of subjects with ELISA level >126 VIE U/mL at 21-35

days after second TBE booster vaccination. Exact 2-sided 95 percent CI was based upon the observed percentage of subjects. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation.

End point type	Secondary
End point timeframe:	
21-35 days after second TBE booster vaccination	

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Percentage of subjects				
number (confidence interval 95%)	100.0 (86.8 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Concentration Measured by Enzyme-linked Immunosorbent Assay (ELISA) at Each Available Time-Point After First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401

End point title	Geometric Mean Concentration Measured by Enzyme-linked Immunosorbent Assay (ELISA) at Each Available Time-Point After First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401
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End point description:

Antibody against TBE booster vaccination was measured as geometric mean concentration (GMC) by ELISA level at different time points after first booster vaccination. CIs were computed by back transforming the CIs based on the Student t distribution for the mean logarithm of the concentrations. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation. Here, "n" signifies number of subjects who were evaluable at specified time points.

End point type	Secondary
End point timeframe:	
21-35 days and 38, 46, 58, 70, 82, 94, 106, 118 months after first TBE booster vaccination	

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	172			
Units: VIE U/mL				
geometric mean (confidence interval 95%)				

After 21-35 days (n =171)	4368.2 (3605.22 to 5292.63)			
After 38 months (n =166)	1081.5 (933.04 to 1253.51)			
After 46 months (n =146)	1212.1 (1055.77 to 1391.65)			
After 58 months (n =157)	1005.1 (876.16 to 1153.08)			
After 70 months (n =156)	883.4 (767.09 to 1017.25)			
After 82 months (n =156)	728.6 (626.66 to 847.12)			
After 94 months (n =156)	636.8 (541.70 to 748.55)			
After 106 months (n =156)	561.0 (469.95 to 669.58)			
After 118 months (n =155)	506.4 (414.96 to 618.10)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Concentration Measured by Enzyme-linked Immunosorbent Assay (ELISA) at 21-35 Days After Second Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700802

End point title	Geometric Mean Concentration Measured by Enzyme-linked Immunosorbent Assay (ELISA) at 21-35 Days After Second Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700802
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End point description:

Antibody against TBE booster vaccination was measured as GMC by ELISA level after the second booster vaccination. CIs were computed by back transforming the CIs based on the Student t distribution for the mean logarithm of the concentrations. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation.

End point type	Secondary
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End point timeframe:

21-35 days after second TBE booster vaccination

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: VIE U/mL				
geometric mean (confidence interval 95%)	1844.1 (1305.54 to 2604.91)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titer Measured by Neutralization Test (NT) Each Available Time-Point Blood Draw After First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401

End point title	Geometric Mean Titer Measured by Neutralization Test (NT) Each Available Time-Point Blood Draw After First Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700401
End point description:	Antibody against TBE booster vaccination was measured as geometric mean titer (GMT) by NT level at different time points after first booster vaccination. CIs were computed by back transforming the CIs based on the Student t distribution for the mean logarithm of the titers. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation. Here, "n" signifies number of subjects who were evaluable at specified time points.
End point type	Secondary
End point timeframe:	21-35 days and 38, 46, 58, 70, 82, 94, 106, 118 months after first TBE booster vaccination

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	172			
Units: Titers				
geometric mean (confidence interval 95%)				
After 21-35 days (n =171)	380.7 (336.73 to 430.31)			
After 38 months (n =167)	162.1 (139.29 to 188.58)			
After 46 months (n =147)	108.1 (92.41 to 126.34)			
After 58 months (n =156)	111.3 (96.10 to 128.84)			
After 70 months (n =157)	123.4 (105.31 to 144.59)			
After 82 months (n =156)	122.3 (102.33 to 146.28)			
After 94 months (n =156)	82.8 (68.88 to 99.57)			
After 106 months (n =156)	56.0 (46.42 to 67.57)			
After 118 months (n =155)	53.9 (43.40 to 66.87)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titer Measured by Neutralization Test (NT) After Second Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700802

End point title	Geometric Mean Titer Measured by Neutralization Test (NT) After Second Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700802
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End point description:

Antibody against TBE booster vaccination was measured as GMT by NT level after second booster vaccination. CIs were computed by back transforming the CIs based on the Student t distribution for the mean logarithm of the titers. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation.

End point type	Secondary
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End point timeframe:

21-35 days after second TBE booster vaccination

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Titers				
geometric mean (confidence interval 95%)	126.8 (94.76 to 169.64)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Fold Rise (GMFR) in Antibody Concentrations After Second Tick-borne Encephalitis (TBE) Booster Vaccination as Compared to Before the Booster Vaccination as Measured by Enzyme-Linked Immunosorbent Assay (ELISA)

End point title	Geometric Mean Fold Rise (GMFR) in Antibody Concentrations After Second Tick-borne Encephalitis (TBE) Booster Vaccination as Compared to Before the Booster Vaccination as Measured by Enzyme-Linked Immunosorbent Assay (ELISA)
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End point description:

GMFR in antibody concentration from pre-booster (before second booster vaccination) to post-booster (21-35 days after TBE vaccination) was measured by ELISA. CIs were computed by back transforming the CIs based on the Student t distribution for the mean logarithm of the titers, concentrations or the

fold rises. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation.

End point type	Secondary
End point timeframe:	
Before second booster vaccination (pre-vaccination), 21-35 days after second booster vaccination	

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Fold rise				
geometric mean (confidence interval 95%)	8.6 (6.69 to 11.10)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Fold Rise (GMFR) in Antibody Titer After Second Tick-borne Encephalitis (TBE) Booster Vaccination as Compared to Before the Booster Vaccination as Measured by Neutralization Test (NT)

End point title	Geometric Mean Fold Rise (GMFR) in Antibody Titer After Second Tick-borne Encephalitis (TBE) Booster Vaccination as Compared to Before the Booster Vaccination as Measured by Neutralization Test (NT)
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End point description:

GMFR in antibody titers from pre-booster (before second booster vaccination) to post-booster (21-35 days after TBE vaccination) was measured by ELISA. CIs were computed by back transforming the CIs based on the Student t distribution for the mean logarithm of the titers, concentrations or the fold rises. Per-protocol population included subjects who had been enrolled and meet all inclusion/exclusion criteria at all visits, had available assay results at any blood sampling visit and had no other major protocol deviation.

End point type	Secondary
End point timeframe:	
Before second booster vaccination (pre-vaccination), 21-35 days after second booster vaccination	

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Fold rise				
geometric mean (confidence interval 95%)	5.2 (2.78 to 9.67)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Injection Site Reactions and Systemic Reactions After Second Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700802

End point title	Number of Subjects With Injection Site Reactions and Systemic Reactions After Second Tick-borne Encephalitis (TBE) Booster Vaccination in Study 700802
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End point description:

Injection site reactions included swelling, induration, redness, injection site pain, tenderness, ecchymosis and hematoma. Systemic reaction included headache, nausea, vomiting, muscle pain, joint pain, swelling of the lymph nodes, malaise and fatigue. Subjects with any injection site reaction and systemic reaction after second TBE booster vaccination in Study 700802 were reported in this outcome measure. The safety population included any subject who had received the second booster dose.

End point type	Secondary
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End point timeframe:

From second booster vaccination up to 21-35 days after the vaccination

End point values	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Subjects				
Injection site reactions	1			
Systemic reactions	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From second booster vaccination up to 21-35 days after the vaccination

Adverse event reporting additional description:

The safety population included any subject who had received the second booster dose.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL
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Reporting group description:

Subjects with low tick-borne encephalitis (TBE) serum antibody levels and received first booster vaccination in Study 700401 (NCT00161967) were administered single intramuscular injection of FSME-IMMUN 0.25 mL Junior (less than 16 years of age) or FSME-IMMUN 0.5 mL (16 years or above of age), as second booster vaccination in this study either at Month 40, 48, 60, 72, 84, 96, 108, or 120. Subjects were followed up to 21-35 days post vaccination in this study.

Serious adverse events	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	FSME-IMMUN 0.25 milliliters (mL) Junior/0.5 mL		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 26 (3.85%)		
Infections and infestations			
Tenderness			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 September 2011	Additional blood draw visits at yearly intervals up to 10 years (118 months) after the first booster vaccination (as applicable) was introduced.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported