Clinical trial results:
Open-label follow-up study to investigate the seropersistence of TBE antibodies and the booster response to a tick-borne encephalitis vaccine in children and adolescents aged 3 - 18 years.

Summary

EudraCT number	2005-000767-26
Trial protocol	AT DE
Global end of trial date	25 July 2008

Results information

Result version number	v1 (current)
This version publication date	29 June 2016
First version publication date	30 July 2015

Trial information

Trial identification

Sponsor protocol code	700401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00161967
WHO universal trial number (UTN)	-
Other trial identifiers	Alias: B9371020

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., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, 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?	Yes
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 July 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 July 2008
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 24 months and 34 months after the third TBE vaccination with FSME-IMMUN 0.25 milliliter (mL), by means of Enzyme-Linked immunosorbent Assay (ELISA) (IMMUNOZYM FSME immunoglobulin G [IgG]) and neutralization test (NT).

To assess TBE antibody response to a booster vaccination with FSME-IMMUN 0.25 mL or FSME-IMMUN 0.5 mL administered 36 months after the third vaccination, by means of ELISA and NT.

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 Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 May 2005
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	Germany: 160
Country: Number of subjects enrolled	Austria: 79
Country: Number of subjects enrolled	Poland: 119
Worldwide total number of subjects	358
EEA total number of subjects	358

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)	59
Children (2-11 years)	220
Adolescents (12-17 years)	79

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was carried out at 4 study sites in 3 European countries (Austria, Germany and Poland). It started on 09 May 2005 and completed on 25 Jul 2008.

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	3 or 4 Doses FSME-IMMUN

Arm description:

Subjects received primary immunization (3 vaccinations at 0, 1 and 6 Month with FSME-IMMUN 0.25 milliliter [mL]) in study 209 [NCT00161863] were offered a booster dose (4th dose) 3-, 4-, or 5-year after the third vaccination, depending on their TBE titers. Subjects with high TBE antibody levels (ELISA greater than [>] 1000 Vienna Units per milliliter [VIE U/ml] and positive NT result) at 24, 34, 46, and/or 58 months after the third vaccination were not to receive the 4th dose.

Arm type	Experimental
Investigational medicinal product name	FSME-IMMUN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received a booster dose (4th dose) of FSME-IMMUN 0.25 mL (age less than [<] 16 years) or 0.5 mL (age greater than or equal to [>=] 16 years old) 3-, 4-, or 5-years after the third vaccination in study 209 if the TBE antibody level was ELISA <= 1000 VIE U/mL or negative NT results at 24, 34, 46, and/or 58 months after the third vaccination from study 209.

Number of subjects in period 1	3 or 4 Doses FSME-IMMUN
Started	358
36-Month Booster Dose	175 [1]
48-Month Booster Dose	29 [2]
60-Month Booster Dose	1 [3]
Completed	324
Not completed	34
Consent withdrawn by subject	4
Not possible to withdraw blood from the volunteer	1
'Remove of wire of the ulna and radius in hospital '	1
'Already vaccinated by mistake '	2

No return	4
Subject dropped out due to desensitization	1
Lost to follow-up	1
Decision of Medical Director	8
Refused the blood draw	5
Not given study vaccination	5
Subject changed to/went to family doctor	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Not all subjects who enrolled in this study, received a booster vaccination. Subjects with high TBE antibody levels (ELISA >1000 VIE U/ml and positive NT result) at 24, 34, 46, and/or 58 months after the third vaccination did not received the 4th dose.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Not all subjects who enrolled in this study, received a booster vaccination. Subjects with high TBE antibody levels (ELISA >1000 VIE U/ml and positive NT result) at 24, 34, 46, and/or 58 months after the third vaccination did not received the 4th dose.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Not all subjects who enrolled in this study, received a booster vaccination. Subjects with high TBE antibody levels (ELISA >1000 VIE U/ml and positive NT result) at 24, 34, 46, and/or 58 months after the third vaccination did not received the 4th dose.

Baseline characteristics

Reporting groups	
Reporting group title	3 or 4 Doses FSME-IMMUN

Reporting group description:

Subjects received primary immunization (3 vaccinations at 0, 1 and 6 Month with FSME-IMMUN 0.25 milliliter [mL]) in study 209 [NCT00161863] were offered a booster dose (4th dose) 3-, 4-, or 5-year after the third vaccination, depending on their TBE titers. Subjects with high TBE antibody levels (ELISA greater than [>] 1000 Vienna Units per milliliter [VIE U/ml] and positive NT result) at 24, 34, 46, and/or 58 months after the third vaccination were not to receive the 4th dose.

Reporting group values	3 or 4 Doses FSME-IMMUN	Total	
Number of subjects	358	358	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	7.519553		
standard deviation	± 4.391666	-	
Gender categorical Units: Subjects			
Female	178	178	
Male	180	180	

End points

End points reporting groups

Reporting group title	3 or 4 Doses FSME-IMMUN

Reporting group description:

Subjects received primary immunization (3 vaccinations at 0, 1 and 6 Month with FSME-IMMUN 0.25 milliliter [mL]) in study 209 [NCT00161863] were offered a booster dose (4th dose) 3-, 4-, or 5-year after the third vaccination, depending on their TBE titers. Subjects with high TBE antibody levels (ELISA greater than [>] 1000 Vienna Units per milliliter [VIE U/ml] and positive NT result) at 24, 34, 46, and/or 58 months after the third vaccination were not to receive the 4th dose.

Primary: Seropositivity Rate Measured by ELISA and/or NT According to Adner et al., 2001 at 1 Month After the Third Vaccination in Study 209 by First Dose Age Group

End point title	Seropositivity Rate Measured by ELISA and/or NT According to Adner et al., 2001 at 1 Month After the Third Vaccination in Study 209 by First Dose Age Group[1]

End point description:

Proportion of subjects with ELISA >126 VIE U/mL or NT >=10. Here, 'N' signifies those subjects who were evaluable within the specified age group in study 209.

End point type	Primary

End point timeframe:

1 month after the third vaccination in study 209

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 statistics (95% CI) were planned, no formal hypothesis testing analysis performed.

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	358			
Units: Percentage of Subjects				
number (confidence interval 95%)				
1-2 years (N= 75)	100 (95.2 to 100)			
3-6 years (N= 70)	100 (94.9 to 100)			
7-15 years (N= 213)	100 (98.3 to 100)			
12-15 years (N= 79)	100 (95.4 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: Seropositivity Rate Measured by ELISA and/or NT According to Adner et al., 2001 at 24 Months After the Third Vaccination in Study 209 by First Dose Age Group

End point title	Seropositivity Rate Measured by ELISA and/or NT According to Adner et al., 2001 at 24 Months After the Third Vaccination in Study 209 by First Dose Age Group[2]

End point description:

Proportion of subjects with ELISA >126 VIE U/mL or NT >=10. Here, 'N' signifies those subjects who were evaluable within the specified age group in study 209.

End point type	Primary

End point timeframe:

24 months after the third vaccination in study 209

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 statistics (95% CI) were planned, no formal hypothesis testing analysis performed.

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	358			
Units: Percentage of Subjects				
number (confidence interval 95%)				
1-2 years (N= 75)	100 (95.2 to 100)			
3-6 years (N= 70)	98.6 (92.3 to 100)			
7-15 years (N= 213)	97.7 (94.6 to 99.2)			
12-15 years (N= 79)	98.7 (93.1 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: Seropositivity Rate Measured by ELISA and/or NT According to Adner et al., 2001 at 34 Months After the Third Vaccination in Study 209 by First Dose Age Group

End point title	Seropositivity Rate Measured by ELISA and/or NT According to Adner et al., 2001 at 34 Months After the Third Vaccination in Study 209 by First Dose Age Group[3]

End point description:

Proportion of subjects with ELISA >126 VIE U/mL or NT >=10. Here, 'N' signifies those subjects who evaluable within the specified age group in study 209.

End point type	Primary

End point timeframe:

34 months after the third vaccination in study 209

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 statistics (95% CI) were planned, no formal hypothesis testing analysis performed.

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	358			
Units: Percentage of Subjects				
number (confidence interval 95%)				
1-2 years (N= 73)	100 (95.1 to 100)			
3-6 years (N= 68)	98.5 (92.1 to 100)			
7-15 years (N= 212)	97.2 (93.9 to 99)			
12-15 years (N= 78)	97.4 (91 to 99.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Seropositivity Rate Measured by ELISA and/or NT According to Adner et al., 2001 at 46 Months After the Third Vaccination in Study 209 by First Dose Age Group

End point title	Seropositivity Rate Measured by ELISA and/or NT According to Adner et al., 2001 at 46 Months After the Third Vaccination in Study 209 by First Dose Age Group[4]

End point description:

Proportion of subjects with ELISA >126 VIE U/mL or NT >=10. Here, 'N' signifies those subjects who were evaluable within the specified age group in study 209.

End point type	Primary

End point timeframe:

46 months after the third vaccination in study 209

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 statistics (95% CI) were planned, no formal hypothesis testing analysis performed.

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	358			
Units: Percentage of Subjects				
number (confidence interval 95%)				
1-2 years (N= 73)	98.6 (92.6 to 100)			
3-6 years (N= 68)	97.1 (89.8 to 99.6)			
7-15 years (N= 212)	92.9 (88.6 to 96)			
12-15 years (N= 78)	91 (82.4 to 96.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Seropositivity Rate Measured by ELISA and/or NT According to Adner et al., 2001 at 58 Months After the Third Vaccination in Study 209 by First Dose Age Group

End point title	Seropositivity Rate Measured by ELISA and/or NT According to Adner et al., 2001 at 58 Months After the Third Vaccination in Study 209 by First Dose Age Group[5]

End point description:

Proportion of subjects with ELISA >126 VIE U/mL or NT >=10. Here, 'N' signifies those subjects who were evaluable within the specified age group in study 209.

End point type	Primary

End point timeframe:

58 months after the third vaccination in study 209

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 statistics (95% CI) were planned, no formal hypothesis testing analysis performed.

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	358			
Units: Percentage of Subjects				
number (confidence interval 95%)				
1-2 years (N= 73)	87.7 (77.9 to 94.2)			
3-6 years (N= 68)	95.6 (87.6 to 99.1)			
7-15 years (N= 212)	84 (78.3 to 88.6)			
12-15 years (N= 78)	79.5 (68.8 to 87.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Seropositivity Rate Measured by ELISA and/or NT According to Adner et al., 2001 After the 36 Month Booster Vaccination in this Study by First Dose Age Group

End point title	Seropositivity Rate Measured by ELISA and/or NT According to Adner et al., 2001 After the 36 Month Booster Vaccination in this Study by First Dose Age Group[6]

End point description:

Proportion of subjects with ELISA >126 VIE U/mL or with NT >=10 among subjects who received Booster Vaccination at Month 36. Full analysis dataset included subjects who received a booster vaccination at 36 Month after the third vaccination in the study 209, and with assay results 21-35 days after the booster vaccination. Here, 'N' signifies those subjects who received the corresponding booster vaccination at Month 36 and were evaluable within the specified age group in study 209.

End point type	Primary

End point timeframe:

21-35 days after 36-month booster dose

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 statistics (95% CI) were planned, no formal hypothesis testing analysis performed.

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	174			
Units: Percentage of Subjects				
number (confidence interval 95%)				
FSME-IMMUN 0.25mL: 1-2 years (N= 25)	100 (86.3 to 100)			
FSME-IMMUN 0.25mL: 3-6 years (N= 24)	100 (85.8 to 100)			
FSME-IMMUN 0.25mL: 7-15 years (N= 89)	100 (95.9 to 100)			
FSME-IMMUN 0.5mL: 7-15 years (N= 36)	100 (90.3 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: Seropositivity Rate Measured by ELISA and/or NT According to Adner et al., 2001 After the 48 Month Booster Vaccination in this Study by First Dose Age Group

End point title	Seropositivity Rate Measured by ELISA and/or NT According to Adner et al., 2001 After the 48 Month Booster Vaccination in this Study by First Dose Age Group[7]

End point description:

Proportion of subjects with ELISA >126 VIE U/mL or with NT >=10 among subjects who received Booster Vaccination at Month 48. Full analysis dataset included subjects who received a booster vaccination at 48 Month after the third vaccination in the study 209, and with assay results 21-35 days after the booster vaccination. Here, 'N' signifies those subjects who received the corresponding booster vaccination at Month 48 and were evaluable within the specified age group in study 209.

End point type	Primary

End point timeframe:

21-35 days after 48-month booster dose

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 statistics (95% CI) were planned, no formal hypothesis testing analysis performed.

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Percentage of Subjects				
number (confidence interval 95%)				

FSME-IMMUN 0.25mL: 1-2 years (N= 6)	100 (54.1 to 100)			
FSME-IMMUN 0.25mL: 3-6 years (N= 6)	100 (54.1 to 100)			
FSME-IMMUN 0.25mL: 7-15 years (N= 6)	100 (54.1 to 100)			
FSME-IMMUN 0.5mL: 7-15 years (N= 11)	100 (71.5 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: Seropositivity Rate Measured by ELISA and/or NT According to Adner et al., 2001 After the 60 Month Booster Vaccination in this Study by First Dose Age Group

End point title	Seropositivity Rate Measured by ELISA and/or NT According to Adner et al., 2001 After the 60 Month Booster Vaccination in this Study by First Dose Age Group[8]

End point description:

Proportion of subjects with ELISA >126 VIE U/mL or with NT >=10 among subjects who received Booster Vaccination at Month 60. Full analysis dataset included subjects who received a booster vaccination at 60 Month after the third vaccination in the study 209, and with assay results 21-35 days after the booster vaccination. Here, 'N' signifies the subjects who received the corresponding booster vaccination at Month 60 and were evaluable within the specified age group in study 209.

End point type	Primary

End point timeframe:

21-35 days after 60-month booster dose

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 statistics (95% CI) were planned, no formal hypothesis testing analysis performed.

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Percentage of Subjects				
number (confidence interval 95%)				
FSME-IMMUN 0.5mL: 7-15 years	100 (2.5 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Seropositivity Rate Measured by ELISA at Each Available Time Point After the Third Vaccination in the Study 209 by First Dose Age Group

End point title	Seropositivity Rate Measured by ELISA at Each Available Time Point After the Third Vaccination in the Study 209 by First Dose Age Group

End point description:

Proportion of subjects with ELISA concentrations >126 VIE U/mL and 95% confidence interval (CI) were presented. Results were summarized for the applicable categories based on the time point of assessment, dose of FSME-IMMUN received in current study (0.25 mL and 0.5 mL) and age of the subject at first vaccination in study 209: 1-2 years, 3-6 years, 7-15 years, and 12-15 years. Here, 'N' signifies subjects of the mentioned combination of timepoint/age group in study 209/booster dose.

End point type	Secondary

End point timeframe:

1, 24, 34, 46, 58 months after the third vaccination in study 209; 21-35 days after 36-, 48- or 60-month booster dose

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	358			
Units: Percentage of Subjects				
number (confidence interval 95%)				
1 month after third dose:1-2years (N= 75)	100 (95.2 to 100)			
1 month after third dose:3-6years (N= 70)	100 (94.9 to 100)			
1 month after third dose:7-15years (N= 213)	99.5 (97.4 to 100)			
1 month after third dose:12-15years (N= 79)	98.7 (93.1 to 100)			
24 months after third dose:1-2years (N= 75)	100 (95.2 to 100)			
24 months after third dose:3-6years (N= 70)	98.6 (92.3 to 100)			
24 months after third dose:7-15years (N= 213)	93 (88.7 to 96)			
24 months after third dose:12-15years(N= 79)	92.4 (84.2 to 97.2)			
34 months after third dose:1-2years (N= 73)	100 (95.1 to 100)			
34 months after third dose:3-6years (N= 68)	98.5 (92.1 to 100)			
34 months after third dose:7-15years (N= 212)	94.8 (90.9 to 97.4)			
34 months after third dose:12-15years(N= 78)	93.6 (85.7 to 97.9)			
46 month after third dose:1-2years (N= 73)	97.3 (90.5 to 99.7)			
46 months after third dose:3-6years (N= 68)	95.6 (87.6 to 99.1)			
46 months after third dose:7-15years (N= 210)	86.2 (80.8 to 90.6)			
46 months after third dose:12-15years (N= 78)	83.3 (73.2 to 90.8)			
58 months after third dose:1-2years (N= 73)	75.3 (63.9 to 84.7)			
58 months after third dose:3-6years (N= 68)	83.8 (72.9 to 91.6)			
58 months after third dose:7-15years (N= 210)	69.5 (62.8 to 75.7)			
58 months after third dose:12-15years(N= 78)	69.2 (57.8 to 79.2)			

After 36 month booster dose 0.25mL:1-2years(N=25)	100 (86.3 to 100)			
After 36 month booster dose 0.25mL:3-6years(N=24)	95.8 (78.9 to 99.9)			
After 36 month booster dose 0.25mL:7-15years(N=89)	97.8 (92.1 to 99.7)			
After 36 month booster dose 0.5mL:7-15years(N=36)	100 (90.3 to 100)			
After 48 month booster dose 0.25mL:1-2years(N=6)	100 (54.1 to 100)			
After 48 month booster dose 0.25mL:3-6years(N=6)	100 (54.1 to 100)			
After 48 month booster dose 0.25mL:7-15years(N=6)	100 (54.1 to 100)			
After 48 month booster dose 0.5mL:7-15years(N=11)	100 (71.5 to 100)			
After 60 month booster dose 0.5mL:7-15years(N=1)	100 (2.5 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Seropositivity Rate Measured by NT According to Adner et al., 2001 at Each Available Time Point After the Third Vaccination in the Study 209 by First Dose Age Group

End point title	Seropositivity Rate Measured by NT According to Adner et al., 2001 at Each Available Time Point After the Third Vaccination in the Study 209 by First Dose Age Group

End point description:

Proportion of subjects with NT titer >=10 and 95% CI were presented. Results were summarized for the applicable categories based on the time point of assessment, dose of FSME-IMMUN received in current study (0.25 mL and 0.5 mL) and age of the subject at first vaccination in study 209: 1-2 years, 3-6 years, 7-15 years, and 12-15 years. Here, 'N' signifies subjects of the mentioned combination of timepoint/age group in study 209/booster dose.

End point type	Secondary

End point timeframe:

1, 24, 34, 46, 58 months after the third vaccination in study 209; 21-35 days after 36-, 48- or 60-month booster dose

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	358			
Units: Percentage of Subjects				
number (confidence interval 95%)				
1 month after third dose:1-2years (N=75)	100 (95.2 to 100)			
1 month after third dose:3-6years (N=70)	98.6 (92.3 to 100)			
1 month after third dose:7-15years (N=213)	99.5 (97.4 to 100)			

1 month after third dose:12-15years (N= 79)	98.7 (93.1 to 100)			
24 months after third dose:1-2years (N= 75)	100 (95.2 to 100)			
24 months after third dose:3-6years (N= 70)	98.6 (92.3 to 100)			
24 months after third dose:7-15years (N= 213)	97.7 (94.6 to 99.2)			
24 months after third dose:12-15years(N= 79)	98.7 (93.1 to 100)			
34 months after third dose:1-2years (N= 73)	100 (95.1 to 100)			
34 months after third dose:3-6years (N= 68)	98.5 (92.1 to 100)			
34 months after third dose:7-15years (N= 212)	97.2 (93.9 to 99)			
34 months after third dose:12-15years(N= 78)	97.4 (91 to 99.7)			
46 month after third dose:1-2years (N= 73)	94.5 (86.6 to 98.5)			
46 months after third dose:3-6years (N= 68)	97.1 (89.8 to 99.6)			
46 months after third dose:7-15years (N= 211)	91.9 (87.4 to 95.2)			
46 months after third dose:12-15years(N= 77)	88.3 (79 to 94.5)			
58 months after third dose:1-2years (N= 73)	86.3 (76.2 to 93.2)			
58 months after third dose:3-6years (N= 68)	95.6 (87.6 to 99.1)			
58 months after third dose:7-15years (N= 210)	81.9 (76 to 86.9)			
58 months after third dose:12-15years(N= 76)	75 (63.7 to 84.2)			
After 36 month booster dose 0.25mL:1-2years(N=25)	100 (86.3 to 100)			
After 36 month booster dose 0.25mL:3-6years(N=24)	100 (85.8 to 100)			
After 36 month booster dose 0.25mL:7-15years(N=88)	100 (95.9 to 100)			
After 36 month booster dose 0.5mL:7-15years(N=36)	100 (90.3 to 100)			
After 48 month booster dose 0.25mL:1-2years(N=6)	100 (54.1 to 100)			
After 48 month booster dose 0.25mL:3-6years(N=6)	100 (54.1 to 100)			
After 48 month booster dose 0.25mL:7-15years(N=6)	100 (54.1 to 100)			
After 48 month booster dose 0.5mL:7-15years(N=11)	100 (71.5 to 100)			
After 60 month booster dose 0.5mL:7-15years(N=1)	100 (2.5 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Antibody Concentration (GMC) as Measured by ELISA at

Each Available Time Point After the Third Vaccination in the Study 209 by First Dose Age Group

End point title	Geometric Mean Antibody Concentration (GMC) as Measured by ELISA at Each Available Time Point After the Third Vaccination in the Study 209 by First Dose Age Group

End point description:

Antibody GMC for TBE as measured by ELISA for subjects presented. GMC and corresponding 2-sided 95% CIs were evaluated. Results were summarized for the applicable categories based on the time point of assessment, dose of FSME-IMMUN received in current study (0.25 mL and 0.5 mL) and age of the subject at first vaccination in study 209: 1-2 years, 3-6 years, 7-15 years, and 12-15 years. Here -99999 and 99999 indicates lower and upper limit of CI. CI was not estimable as number of subjects evaluable for 60-Month booster dose was 1. Here, 'N' signifies subjects of the mentioned combination of timepoint/age group in study 209/booster dose.

End point type	Secondary

End point timeframe:

1, 24, 34, 46, 58 months after the third vaccination in study 209; 21-35 days after 36-, 48- or 60-month booster dose

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	358			
Units: Vienna Units per milliliter(VIE U/mL)				
geometric mean (confidence interval 95%)				
1 month after third dose:1-2years (N= 75)	9320.9 (8137 to 10677.1)			
1 month after third dose:3-6years (N= 70)	7999.5 (6614.2 to 9674.9)			
1 month after third dose:7-15years (N= 213)	4159.9 (3665.3 to 4721.2)			
1 month after third dose:12-15years (N= 79)	2908.9 (2308 to 3666.4)			
24 months after third dose:1-2years (N= 75)	1836 (1526.7 to 2207.8)			
24 months after third dose:3-6years (N= 70)	1626.1 (1332.8 to 1984)			
24 months after third dose:7-15years (N= 213)	838.2 (731.4 to 960.7)			
24 months after third dose:12-15years(N= 79)	697.3 (559.8 to 868.5)			
34 months after third dose:1-2years (N= 73)	1420.5 (1187.6 to 1699.2)			
34 months after third dose:3-6years (N= 68)	1388.5 (1135 to 1698.6)			
34 months after third dose:7-15years (N= 212)	793.9 (694 to 908.2)			
34 months after third dose:12-15years(N= 78)	688.7 (538.6 to 880.7)			
46 month after third dose:1-2years (N= 73)	863 (666.9 to 1116.9)			
46 months after third dose:3-6years (N= 68)	858.7 (662.5 to 1113)			

46 months after third dose:7-15years (N= 210)	404.3 (340.2 to 480.4)			
46 months after third dose:12-15years(N= 78)	367.3 (273.3 to 493.7)			
58 month after third dose:1-2years (N= 73)	568.9 (401.6 to 805.7)			
58 months after third dose:3-6years (N= 68)	631.6 (443.2 to 900.1)			
58 months after third dose:7-15years (N= 210)	245.6 (195.6 to 308.4)			
58 months after third dose:12-15years(N= 78)	219.5 (150.7 to 319.6)			
After 36 month booster dose 0.25mL:1-2years(N=25)	8686.5 (6077.6 to 12415.4)			
After 36 month booster dose 0.25mL:3-6years(N=24)	5867.5 (3195.4 to 10774.2)			
After 36 month booster dose 0.25mL:7-15years(N=89	3805 (2837.3 to 5102.6)			
After 36 month booster dose 0.5mL:7-15years(N=36)	2737.6 (1886.4 to 3972.9)			
After 48 month booster dose 0.25mL:1-2years(N=6)	7636.3 (6165.7 to 9457.6)			
After 48 month booster dose 0.25mL:3-6years(N=6)	5373.8 (2600.9 to 11103.2)			
After 48 month booster dose 0.25mL:7-15years(N=6)	8400.8 (3862.1 to 18273.3)			
After 48 month booster dose 0.5mL:7-15years(N=11)	5483.4 (3389.6 to 8870.7)			
After 60 month booster dose 0.5mL:7-15years(N=1)	1001 (-99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Antibody Titer (GMT) as Measured by NT According to Adner et al., 2001 at Each Available Time Point After the Third Vaccination in the Study 209 by First Dose Age Group

End point title	Geometric Mean Antibody Titer (GMT) as Measured by NT According to Adner et al., 2001 at Each Available Time Point After the Third Vaccination in the Study 209 by First Dose Age Group

End point description:

GMT for NT and corresponding 2-sided 95% CIs were evaluated. Results were summarized for the applicable categories based on the time point of assessment, dose of FSME-IMMUN received in current study (0.25 mL and 0.5 mL) and age of the subject at first vaccination in study 209: 1-2 years, 3-6 years, 7-15 years, and 12-15 years. Here, -99999 and 99999 indicates lower and upper limit of CI. CI was not estimable as number of subjects evaluable for 60-Month booster dose was 1. Here, 'N' signifies subjects of the mentioned combination of timepoint/age group in study 209/booster dose.

End point type	Secondary

End point timeframe:

1, 24, 34, 46, 58 months after the third vaccination in study 209; 21-35 days after 36-, 48- or 60-

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	358			
Units: Titer				
geometric mean (confidence interval 95%)				
1 month after third dose:1-2years (N= 75)	567.6 (526.6 to 611.8)			
1 month after third dose:3-6years (N= 70)	461.5 (387.4 to 549.8)			
1 month after third dose:7-15years (N= 213)	303.1 (267.5 to 343.3)			
1 month after third dose:12-15years (N= 79)	227.8 (182 to 285.1)			
24 months after third dose:1-2years (N= 75)	153.5 (124.9 to 188.7)			
24 months after third dose:3-6years (N= 70)	204 (165.1 to 252.1)			
24 months after third dose:7-15years (N= 213)	110.8 (95.3 to 128.7)			
24 months after third dose:12-15years(N= 79)	94 (73.2 to 120.7)			
34 months after third dose:1-2years (N= 73)	166.3 (134.9 to 204.9)			
34 months after third dose:3-6years (N= 68)	188.4 (150.2 to 236.3)			
34 months after third dose:7-15years (N= 212)	97.1 (83.2 to 113.3)			
34 months after third dose:12-15years(N= 78)	74.6 (57.1 to 97.5)			
46 months after third dose:1-2years (N= 73)	74.1 (58.1 to 94.5)			
46 months after third dose:3-6years (N= 68)	95.1 (76.5 to 118.2)			
46 months after third dose:7-15years (N= 211)	50.6 (43 to 59.6)			
46 months after third dose:12-15years(N= 77)	42.5 (31.8 to 56.9)			
58 month after third dose:1-2years (N= 73)	57.1 (41.2 to 79.1)			
58 months after third dose:3-6years (N= 68)	81.9 (62.5 to 107.3)			
58 months after third dose:7-15years (N= 210)	36.4 (29.5 to 44.9)			
58 months after third dose:12-15years(N= 76)	29.3 (20.3 to 42.1)			
After 36 month booster dose 0.25mL:1-2years(N=25)	564.9 (490.7 to 650.4)			
After 36 month booster dose 0.25mL:3-6years(N=24)	349.1 (234.5 to 519.8)			
After 36 month booster dose 0.25mL:7-15years(N=88)	330.3 (272.9 to 399.8)			
After 36 month booster dose 0.5mL:7-15years(N=36)	332.8 (245.4 to 451.2)			

After 48 month booster dose 0.25mL:1-2years(N=6)	570.2 (423.7 to 767.3)			
After 48 month booster dose 0.25mL:3-6years(N=6)	522.7 (310.7 to 879.5)			
After 48 month booster dose 0.25mL:7-15years(N=6)	553.9 (382.1 to 803)			
After 48 month booster dose 0.5mL:7-15years(N=11)	489.6 (337.1 to 711.1)			
After 60 month booster dose 0.5mL:7-15years(N=1)	80 (-99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean of Fold Increase in Antibody Concentrations After the Booster Vaccination as Compared to Before the Booster Vaccination as Measured by ELISA by First Dose Age Group

End point title	Geometric Mean of Fold Increase in Antibody Concentrations After the Booster Vaccination as Compared to Before the Booster Vaccination as Measured by ELISA by First Dose Age Group

End point description:

Geometric mean of fold increase in TBE antibody concentrations as measured by ELISA and 95% CIs were evaluated. Results were summarized for the applicable categories based on the dose and timepoint of FSME-IMMUN received and age of the subject at first vaccination: 1-2 years, 3-6 years, 7-15 years. Here, -99999 and 99999 indicates lower and upper limit of CI. It was not estimable as the number of subjects evaluable for 60 Month booster dose was 1. Full analysis dataset included subjects who received a booster vaccination at 36-, 48- or 60-Month after the third vaccination in the study 209, and with assay results 21-35 days after the booster vaccination. Here, 'N' signifies subjects of the mentioned combination of timepoint/age group in study 209/booster dose.

End point type	Secondary

End point timeframe:

From before booster dose to 21-35 days after 36-, 48- or 60-month booster dose

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	204			
Units: Fold Increase				
geometric mean (confidence interval 95%)				
After 36 month booster dose 0.25mL:1-2years(N=25)	13.5 (9.8 to 18.5)			
After 36 month booster dose 0.25mL:3-6years(N=24)	8.2 (5.3 to 12.6)			
After 36 month booster dose 0.25mL:7-15years(N=89)	7.7 (6.2 to 9.5)			
After 36 month booster dose 0.5mL:7-15years(N=36)	7.4 (5.5 to 10)			
After 48 month booster dose 0.25mL:1-2years(N=6)	9.1 (6.7 to 12.3)			
After 48 month booster dose 0.25mL:3-6years(N=6)	7.1 (3.1 to 16.1)			

After 48 month booster dose 0.25mL:7-15years(N=6)	12.6 (7.4 to 21.2)			
After 48 month booster dose 0.5mL:7-15years(N=11)	7 (4 to 12.1)			
After 60 month booster dose 0.5mL:7-15years(N=1)	3.7 (-99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean of Fold Increase in Antibody Titer After the Booster Vaccination as Compared to Before the Booster Vaccination Measured by NT According to Adner et al., 2001 by First Dose Age Group

End point title	Geometric Mean of Fold Increase in Antibody Titer After the Booster Vaccination as Compared to Before the Booster Vaccination Measured by NT According to Adner et al., 2001 by First Dose Age Group

End point description:

Geometric mean of fold increase in TBE antibody titer as measured by NT and 95% CIs were evaluated. Results were summarized for the applicable categories based on the dose and timepoint of FSME-IMMUN received and age of the subject at first vaccination: 1-2 years, 3-6 years, 7-15 years. Here, -99999 and 99999 indicates lower and upper limit of CI. It was not estimable as the number of subjects evaluable for 60-Month booster dose was 1. Full analysis dataset included subjects who received a booster vaccination at 36-, 48- or 60-Month after the third vaccination in the study 209, and with assay results 21-35 days after the booster vaccination. Here, 'N' signifies subjects of the mentioned combination of timepoint/age group in study 209/booster dose.

End point type	Secondary

End point timeframe:

From before booster dose to 21-35 days after 36-, 48- or 60-month booster dose

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	204			
Units: Fold Increase				
geometric mean (confidence interval 95%)				
After 36 month booster dose 0.25mL:1-2years(N=25)	8.2 (6.2 to 10.7)			
After 36 month booster dose 0.25mL:3-6years(N=24)	3.8 (2.5 to 5.9)			
After 36 month booster dose 0.25mL:7-15years(N=88)	5.7 (4.8 to 6.7)			
After 36 month booster dose 0.5mL:7-15years(N=36)	8.2 (6.3 to 10.8)			
After 48 month booster dose 0.25mL:1-2years(N=6)	10.1 (7 to 14.4)			
After 48 month booster dose 0.25mL:3-6years(N=6)	7.3 (3.2 to 16.9)			
After 48 month booster dose 0.25mL:7-15years(N=6)	11 (6 to 20.2)			
After 48 month booster dose 0.5mL:7-15years(N=11)	9.8 (5.2 to 18.4)			

After 60 month booster dose 0.5mL:7-15years(N=1)	11.4 (-99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Seropositivity Rate Measured by NT according to Holzmann et al., 1996 at Each Available Time Point After the Third Vaccination in the Study 209 by First Dose Age Group

End point title	Seropositivity Rate Measured by NT according to Holzmann et al., 1996 at Each Available Time Point After the Third Vaccination in the Study 209 by First Dose Age Group

End point description:

Proportion of subjects with NT100 titers >=10 and NT50 titers >10 and 95% CIs were presented. Results were summarized for the applicable categories based on the time point of assessment, dose of FSME-IMMUN received in current study (0.25 mL and 0.5 mL) and age of the subject at first vaccination in study 209: 1-2 years, 3-6 years, 7-15 years, and 12-15 years. Here, 'N' signifies subjects of the mentioned combination of timepoint/age group in study 209/booster dose.

End point type	Secondary

End point timeframe:

24, 34 month after the third vaccination in study 209; 21-35 days after the 36-, 48- or 60-month booster dose

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	358			
Units: Percentage of Subjects				
number (confidence interval 95%)				
NT50:24 months after third dose:1-2years (N= 75)	84 (73.7 to 91.4)			
NT100:24 months after third dose:1-2years (N= 75)	72 (60.4 to 81.8)			
NT50:24 months after third dose:3-6years (N= 70)	91.4 (82.3 to 96.8)			
NT100:24 months after third dose:3-6years (N= 70)	81.4 (70.3 to 89.7)			
NT50:24 months after third dose:7-15years (N= 212)	73.6 (67.1 to 79.4)			
NT100:24 months after third dose:7-15years(N= 212)	57.1 (50.1 to 63.8)			
NT50:24 months after third dose:12-15years(N= 79)	62 (50.4 to 72.7)			
NT100:24 months after third dose:12-15years(N= 79)	46.8 (35.5 to 58.4)			
NT50:34 months after third dose:1-2years(N= 73)	86.3 (76.2 to 93.2)			
NT100:34 months after third dose:1-2years(N= 73)	75.3 (63.9 to 84.7)			
NT50:34 months after third dose:3-6years(N= 68)	80.9 (69.5 to 89.4)			

NT100:34 months after third dose:3-6years(N= 68)	64.7 (52.2 to 75.9)			
NT50:34 months after third dose:7-15years(N= 211)	55.5 (48.5 to 62.3)			
NT100:34 months after third dose:7-15years(N= 211)	38.9 (32.2 to 45.8)			
NT50:34 months after third dose:12-15years(N= 79)	53.8 (42.2 to 65.2)			
NT100:34 months after third dose:12-15years(N= 79)	30.8 (20.8 to 42.2)			
NT50:36 month booster dose 0.25mL:1-2years(N=25)	100 (86.3 to 100)			
NT100:36 month booster dose 0.25mL:1-2years(N=25)	100 (86.3 to 100)			
NT50:36 month booster dose 0.25mL:3-6years(N=24)	91.7 (73 to 99)			
NT100:36 month booster dose 0.25mL:3-6years(N=24)	91.7 (73 to 99)			
NT50:36 month booster dose 0.25mL:7-15years(N=88)	90.9 (82.9 to 96)			
NT100:36 month booster dose 0.25mL:7-15years(N=88)	87.5 (78.7 to 93.6)			
NT50:36 month booster dose 0.5mL:7-15years(N=36)	88.9 (73.9 to 96.9)			
NT100:36 month booster dose 0.5mL:7-15years(N=36)	86.1 (70.5 to 95.3)			
NT50:48 month booster dose 0.25mL:1-2years(N=6)	100 (54.1 to 100)			
NT100:48 month booster dose 0.25mL:1-2years(N=6)	100 (54.1 to 100)			
NT50:48 month booster dose 0.25mL:3-6years(N=6)	100 (54.1 to 100)			
NT100:48 month booster dose 0.25mL:3-6years(N=6)	100 (54.1 to 100)			
NT50:48 month booster dose 0.25mL:7-15years(N=6)	100 (54.1 to 100)			
NT100:48 month booster dose 0.25mL:7-15years(N=6)	100 (54.1 to 100)			
NT50:48 month booster dose 0.5mL:7-15years(N=11)	100 (71.5 to 100)			
NT100:48 month booster dose 0.5mL:7-15years(N=11)	100 (71.5 to 100)			
NT50:60 month booster dose 0.5mL:7-15years(N=1)	100 (2.5 to 100)			
NT100:60 month booster dose 0.5mL:7-15years(N=1)	0 (0 to 97.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Antibody Titer (GMT) as Measured by NT According to Holzmann et al., 1996 at Each Available Time Point After the Third Vaccination in the Study 209 by First Dose Age Group

End point title	Geometric Mean Antibody Titer (GMT) as Measured by NT According to Holzmann et al., 1996 at Each Available Time Point After the Third Vaccination in the Study 209 by First Dose Age Group

End point description:

GMT for NT and corresponding 2-sided 95% CIs were evaluated. NT100 titers and NT50 titers were presented. Results were summarized for the applicable categories based on the dose and timepoint of FSME-IMMUN received and age of the subject at first vaccination: 1-2 years, 3-6 years, 7-15 years and 12-15 years. Here, -99999 and 99999 indicates lower and upper limit of CI. It was not estimable as number of subjects evaluable for 60-Month booster dose was 1. Here, 'N' signifies subjects of the mentioned combination of timepoint/age group in study 209/booster dose.

End point type	Secondary

End point timeframe:

24, 34 months after the third vaccination in study 209; 21-35 days after 36-, 48- or 60-month booster dose

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	358			
Units: Titer				
geometric mean (confidence interval 95%)				
NT50:24 month after third dose:1-2years (N= 75)	21.7 (17.5 to 26.8)			
NT100:24 months after third dose:1-2years (N= 75)	14 (11.6 to 16.9)			
NT50:24 months after third dose:3-6years (N= 70)	33.4 (27.2 to 41.1)			
NT100:24 months after third dose:3-6years (N= 70)	17.7 (14.7 to 21.3)			
NT50:24 months after third dose:7-15years(N= 212)	18.7 (16.3 to 21.5)			
NT100:24 months after third dose:7-15years(N=212)	11 (9.9 to 12.2)			
NT50:24 months after third dose:12-15years(N= 79)	14.2 (11.4 to 17.7)			
NT100:24 months after third dose:12-15years(N=79)	9.5 (8 to 11.3)			
NT50:34 months after third dose:1-2years (N= 73)	30.7 (24.3 to 38.8)			
NT100:34 months after third dose:1-2years (N= 73)	14.1 (11.7 to 17)			
NT50:34 months after third dose:3-6years (N= 68)	23.8 (18.1 to 31.3)			
NT100:34 months after third dose:3-6years (N= 68)	12.6 (10.3 to 15.5)			
NT50:34 months after third dose:7-15years(N=211)	13.2 (11.5 to 15.3)			
NT100:34 months after third dose:7-15years(N=211)	8.4 (7.5 to 9.3)			
NT50:34 months after third dose:12-15years(N=78)	12.4 (9.8 to 15.6)			
NT100:34 months after third dose:12-15years(N=78)	7.6 (6.5 to 9)			
NT50:36 month booster dose 0.25mL:1-2years(N=25)	103.6 (76.2 to 141)			
NT100:36month booster dose 0.25mL:1-2years(N=25)	65.9 (48.4 to 89.9)			
NT50:36month booster dose 0.25mL:3-6years(N=24)	70.6 (42.6 to 117.1)			

NT100:36month booster dose 0.25mL:3-6years(N=24)	44.7 (27.4 to 73)			
NT50:36month booster dose 0.25mL:7-15years(N=88)	53.2 (42 to 67.4)			
NT100:36month booster dose 0.25mL:7-15years(N=88)	32.3 (25.9 to 40.4)			
NT50:36month booster dose 0.5mL:7-15years(N=36)	39.8 (27.5 to 57.5)			
NT100:36month booster dose 0.5mL:7-15years(N=36)	25 (18.5 to 33.9)			
NT50:48month booster dose 0.25mL:1-2years(N=6)	209.7 (116.3 to 378.1)			
NT100:48month booster dose 0.25mL:1-2years(N=6)	115.4 (83.2 to 160)			
NT50:48month booster dose 0.25mL:3-6years(N=6)	166.4 (80.3 to 344.7)			
NT100:48month booster dose 0.25mL:3-6years(N=6)	64.8 (25.9 to 162.1)			
NT50:48month booster dose 0.25mL:7-15years(N=6)	163.2 (84 to 317.1)			
NT100:48month booster dose 0.25mL:7-15years(N=6)	55 (27 to 111.8)			
NT50:48month booster dose 0.5mL:7-15years(N=11)	140.4 (81.5 to 241.8)			
NT100:48month booster dose 0.5mL:7-15years(N=11)	46.4 (27.5 to 78.1)			
NT50:60month booster dose 0.5mL:7-15years(N=1)	30 (-99999 to 99999)			
NT100:60month booster dose 0.5mL:7-15years(N=1)	5 (-99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean of Fold Increase in Antibody Titer After the Booster Vaccination as Compared to Before the Booster Vaccination Measured by NT According to Holzmann et al., 1996 by First Dose Age Group

End point title	Geometric Mean of Fold Increase in Antibody Titer After the Booster Vaccination as Compared to Before the Booster Vaccination Measured by NT According to Holzmann et al., 1996 by First Dose Age Group

End point description:

Geometric mean of fold increase in TBE antibody titer after the booster vaccination as compared to before the booster vaccination as measured by NT according to Holzmann et al., 1996 and 95% CIs were evaluated. Results were summarized for the applicable categories based on the dose and timepoint of FSME-IMMUN received and age of the subject at first vaccination: 1-2 years, 3-6 years, 7-15 years. Here, -99999 and 99999 indicates lower and upper limit of CI. It was not estimable as the number of subjects evaluable for 60-Month booster dose was 1. Full analysis dataset included subjects who received a booster vaccination at 36-, 48- or 60-Month after the third vaccination in the study 209, and with assay results 21-35 days after the booster vaccination. Here, 'N' signifies subjects of the mentioned combination of timepoint/age group in study 209/booster dose.

End point type	Secondary

End point timeframe:

From before booster dose to 21-35 days after 36-, 48- or 60-month booster dose

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	204			
Units: Fold Increase				
geometric mean (confidence interval 95%)				
NT50:36 month booster dose 0.25mL:1-2years(N=25)	8.7 (5.6 to 13.3)			
NT100:36month booster dose 0.25mL:1-2years(N=25)	10.2 (7.5 to 13.9)			
NT50:36month booster dose 0.25mL:3-6years(N=24)	5.6 (3.1 to 10.2)			
NT100:36month booster dose 0.25mL:3-6years(N=24)	6 (3.9 to 9.5)			
NT50:36month booster dose 0.25mL:7-15years(N=88)	6.7 (5.3 to 8.4)			
NT100:36month booster dose 0.25mL:7-15years(N=88)	5.5 (4.4 to 6.8)			
NT50:36month booster dose 0.5mL:7-15years(N=36)	4.7 (3.1 to 7.2)			
NT100:36month booster dose 0.5mL:7-15years(N=36)	4.6 (3.3 to 6.3)			
NT50:48month booster dose 0.25mL:1-2years(N=6)	13 (4.3 to 39.2)			
NT100:48month booster dose 0.25mL:1-2years(N=6)	13.6 (9.1 to 20.3)			
NT50:48month booster dose 0.25mL:3-6years(N=6)	6.8 (1.9 to 24.1)			
NT100:48month booster dose 0.25mL:3-6years(N=6)	5.1 (1.8 to 14.4)			
NT50:48month booster dose 0.25mL:7-15years(N=6)	17.1 (5.5 to 53.5)			
NT100:48month booster dose 0.25mL:7-15years(N=6)	7.8 (2.6 to 23.4)			
NT50:48month booster dose 0.5mL:7-15years(N=11)	13.9 (6.9 to 27.9)			
NT100:48month booster dose 0.5mL:7-15years(N=11)	6.7 (3.2 to 13.8)			
NT50:60month booster dose 0.5mL:7-15years(N=1)	6 (-99999 to 99999)			
NT100:60month booster dose 0.5mL:7-15years(N=1)	1 (-99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Fever After 36 Month, 48 Month and 60 Month Booster Vaccination

End point title	Percentage of Subjects with Fever After 36 Month, 48 Month and 60 Month Booster Vaccination

End point description:

Proportion of subjects with fever >=38.0 degrees Celsius (C) and their 95% CIs were presented according to the booster dose. Subject his/her parent/legal guardian were asked to carefully monitor for fever and therefore, to measure the body temperature orally or rectally (optional for small children) in the evening of the vaccination day, on the following morning, and in the evening each day for 3 days following the booster vaccination (altogether 4 days). All measured temperatures, including the first day without fever and the method used (oral or rectal), were to be documented in the subject diary. Full analysis dataset included subjects who received a booster vaccination at 36-, 48- or 60-Month after the third vaccination in study 209. Here, 'N' signifies subjects of the mentioned combination of timepoint and booster dose in this study.

End point type	Secondary

End point timeframe:

Within 4 days after 36-, 48- or 60-month booster dose

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	205			
Units: Percentage of Subjects				
number (confidence interval 95%)				
After 36 month booster dose 0.25mL (N=136)	0 (0 to 2.7)			
After 36 month booster dose 0.5mL (N=37)	0 (0 to 9.5)			
After 48 month booster dose 0.25mL (N=18)	0 (0 to 18.5)			
After 48 month booster dose 0.5mL (N=11)	0 (0 to 28.5)			
After 60 month booster dose 0.5mL (N=1)	0 (0 to 97.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Local and Systemic Reactions After 36 Month, 48 Month and 60 Month Booster Vaccination

End point title	Percentage of Subjects with Local and Systemic Reactions After 36 Month, 48 Month and 60 Month Booster Vaccination

End point description:

Proportion of subjects with local reactions (LR) and systemic reactions (SR) (other than fever) after the 36 Month, 48 Month or 60 Month booster dose and 95% CIs were presented according to the booster dose. Local reactions included: swelling, induration, redness, injection site pain and tenderness, ecchymosis and hematoma. Systemic symptoms including headache, nausea, vomiting, muscle pain, joint pain, swelling of the lymph nodes, loss of appetite, changes in sleeping behavior, fatigue and malaise were to be monitored and documented in the subject diary. Full analysis dataset included subjects who received a booster vaccination at 36 Month, 48 Month, or 60 Month after the third vaccination in study 209. Here, 'N' signifies subjects of the mentioned combination of 4th vaccination dose level, timepoint, and endpoints.

End point type	Secondary

End point timeframe:

Within 4 days after 36-, 48- or 60-month booster dose

End point values	3 or 4 Doses FSME-IMMUN			
Subject group type	Reporting group			
Number of subjects analysed	205			
Units: Percentage of Subjects				
number (confidence interval 95%)				
LR: After 36 month booster dose 0.25mL (N=138)	17.4 (11.5 to 24.8)			
LR: After 36 month booster dose 0.5mL (N=37)	18.9 (8 to 35.2)			
SR: After 36 month booster dose 0.25mL (N=138)	5.8 (2.5 to 11.1)			
SR: After 36 month booster dose 0.5mL (N=37)	2.7 (0.1 to 14.2)			
LR: After 48 month booster dose 0.25mL (N=18)	22.2 (6.4 to 47.6)			
LR: After 48 month booster dose 0.5mL (N=11)	9.1 (0.2 to 41.3)			
SR: After 48 month booster dose 0.25mL (N=18)	16.7 (3.6 to 41.4)			
SR: After 48 month booster dose 0.5mL (N=11)	0 (0 to 28.5)			
LR: After 60 month booster dose 0.5mL (N=1)	0 (0 to 97.5)			
SR: After 60 month booster dose 0.5mL (N=1)	0 (0 to 97.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs)/serious AEs recorded through 21 to 35 days after the booster dose. LR and SR were recorded within 4 days after the booster vaccination in a subject diary.

Adverse event reporting additional description:

SAEs and AEs were grouped by system organ class and summarized. AEs included AEs collected in subject diary (local and systemic reactions for FSME-IMMUN) and AEs collected on case report form at each visit (non-systematic assessment).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	8.1

Reporting groups

Reporting group title	3 or 4 Doses FSME--IMMUN

Reporting group description:

Subjects received primary immunization (3 vaccinations at 0, 1 and 6 Month with FSME-IMMUN 0.25 mL) in study 209 [NCT00161863] were offered a booster dose (4th dose) 3-, 4-, or 5-year after the third vaccination, depending on their TBE titers. Subjects with high TBE antibody levels (ELISA > 1000 VIE U/ml and positive NT result) at 24, 34, 46, and/or 58 months after the third vaccination were not to receive the 4th dose.

Serious adverse events	3 or 4 Doses FSME--IMMUN		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 358 (0.56%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Chest injury; Spinal cord injury cervical			
subjects affected / exposed	1 / 358 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radius fracture; Skull fractured base; Spinal cord injury			
subjects affected / exposed	1 / 358 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	3 or 4 Doses FSME--IMMUN		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 358 (9.22%)		
Vascular disorders			
Haematoma; Road traffic accident			
subjects affected / exposed	1 / 358 (0.28%)		
occurrences (all)	1		
Surgical and medical procedures			
Dental operation			
subjects affected / exposed	1 / 358 (0.28%)		
occurrences (all)	1		
Nail operation			
subjects affected / exposed	1 / 358 (0.28%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 358 (0.56%)		
occurrences (all)	2		
Injection site erythema			
subjects affected / exposed	1 / 358 (0.28%)		
occurrences (all)	1		
Injection site induration			
subjects affected / exposed	5 / 358 (1.40%)		
occurrences (all)	5		
Injection site pain			
subjects affected / exposed	29 / 358 (8.10%)		
occurrences (all)	40		
Injection site swelling			
subjects affected / exposed	4 / 358 (1.12%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	1 / 358 (0.28%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 358 (0.28%)		
occurrences (all)	1		

Immune system disorders			
Allergy to animal; Seasonal allergy			
subjects affected / exposed	1 / 358 (0.28%)		
occurrences (all)	1		
Psychiatric disorders			
Attention deficit/hyperactivity disorder			
subjects affected / exposed	1 / 358 (0.28%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	1 / 358 (0.28%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 358 (0.28%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	2 / 358 (0.56%)		
occurrences (all)	2		
Laceration			
subjects affected / exposed	1 / 358 (0.28%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 358 (0.28%)		
occurrences (all)	1		
Headache (SR)			
subjects affected / exposed	5 / 358 (1.40%)		
occurrences (all)	5		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 358 (0.28%)		
occurrences (all)	1		
Conjunctivitis allergic			
subjects affected / exposed	1 / 358 (0.28%)		
occurrences (all)	1		
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all)	1 / 358 (0.28%) 1		
Enteritis subjects affected / exposed occurrences (all)	1 / 358 (0.28%) 1		
Vomiting subjects affected / exposed occurrences (all)	2 / 358 (0.56%) 2		
Nausea subjects affected / exposed occurrences (all)	1 / 358 (0.28%) 1		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	1 / 358 (0.28%) 1		
Dermatitis allergic subjects affected / exposed occurrences (all)	1 / 358 (0.28%) 1		
Eczema subjects affected / exposed occurrences (all)	1 / 358 (0.28%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 358 (0.28%) 1		
Arthralgia (SR) subjects affected / exposed occurrences (all)	1 / 358 (0.28%) 1		
Myalgia subjects affected / exposed occurrences (all)	2 / 358 (0.56%) 2		
Infections and infestations Acute tonsillitis subjects affected / exposed occurrences (all)	1 / 358 (0.28%) 1		

Gastroenteritis subjects affected / exposed occurrences (all)	1 / 358 (0.28%) 1		
Impetigo subjects affected / exposed occurrences (all)	1 / 358 (0.28%) 1		
Laryngotracheo bronchitis subjects affected / exposed occurrences (all)	2 / 358 (0.56%) 2		
Mycoplasma infection subjects affected / exposed occurrences (all)	1 / 358 (0.28%) 1		
Otitis media subjects affected / exposed occurrences (all)	2 / 358 (0.56%) 2		
Paronychia subjects affected / exposed occurrences (all)	1 / 358 (0.28%) 1		
Pharyngitis subjects affected / exposed occurrences (all)	1 / 358 (0.28%) 1		
Tonsillitis streptococcal subjects affected / exposed occurrences (all)	2 / 358 (0.56%) 3		
Viral infection subjects affected / exposed occurrences (all)	12 / 358 (3.35%) 12		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	1 / 358 (0.28%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2006	The clinical study was prolonged for children and adolescents who still showed highly positive TBE virus antibody concentrations as determined by ELISA (>1000 VIE U/mL) and positive NT titers (>=10) at approximately 3 years after the third vaccination. The protocol was amended to include further follow-up of TBE antibody persistence at 46 and 58 months after the third vaccination, as well as a booster vaccination offered at either Month 48 or Month 60 after the third vaccination in study 209, depending on individual TBE antibody levels. A total of 172 subjects who had not received the first booster vaccination at Month 36 after the third vaccination in study 209 were invited for this study prolongation. The extension was introduced to investigate seropersistence beyond 3 years and consequently to obtain clinical data to identify the optimal booster interval for FSME-IMMUN 0.25 mL.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported