CLINICAL STUDY PROTOCOL

FSME-IMMUN 0.25 ml Junior and
FSME-IMMUN 0.5 ml

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)

Short Title: TBE SEROPERSISTENCE AFTER FIRST BOOSTER IN CHILDREN (FOLLOW-UP TO STUDY 700401)

PROTOCOL NUMBER: B9371021 (Formerly Baxter 700802)

AMENDMENT 4: 25 JUN 2015 (including non-substantial changes upon sponsorship change)

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Study Sponsor(s): **Pfizer, Inc.**
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1. STUDY PERSONNEL

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1.1 Study Organization

The name and contact information of the individuals involved with the study (e.g. Investigator(s), Sponsor's representative(s), laboratories, steering committees, data monitoring committees (DMCs), and ethics committees (ECs) will be maintained by the Sponsor and provided to the Investigator.

2. SERIOUS ADVERSE EVENT REPORTING

The Investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs) to the ECs. For information on the definition and assessment of adverse events (AEs), refer to Section 12.2.

ALL SAEs ARE TO BE REPORTED ON THE CLINICAL TRIAL SERIOUS ADVERSE EVENT (CT SAE) REPORT FORM AND FAXED TO THE SPONSOR WITHIN 24 HOURS OF BECOMING AWARE OF THE EVENT

Austria **Fax:** PPD
Germany **Fax: Toll-Free (local):** PPD **From Abroad:** PPD
Poland **Fax: Toll-Free (local):** PPD **Alt. 1:** PPD

3. SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product (IP)	FSME-IMMUN 0.25 ml Junior; FSME-IMMUN 0.5 ml
Name(s) of Active Ingredient(s)	Tick-Borne Encephalitis Virus (strain Neudoerfl)
CLINICAL CONDITION(S)/INDICATION(S)	
• Active (prophylactic) immunization against TBE	
PROTOCOL NUMBER	B9371021 (Formerly Baxter 700802)
PROTOCOL TITLE	Open-label Phase IV Study to Investigate the Seropersistence of Tick-Borne Encephalitis (TBE) Virus Antibodies after the First Booster Vaccination and the Response to a Second Booster Vaccination with FSME-IMMUN in Children,Adolescents and Young Adults (Follow-Up to Study 700401)
Short Title	TBE Seropersistence after First Booster in Children, Adolescents and Young Adults (Follow-Up to Study 700401)
STUDY PHASE	Ph IV (post-marketing)
PLANNED STUDY PERIOD	
Initiation	March 2009
Completion	June 2017
Duration	Approximately 8 years
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
• The main purpose of this study is to assess the seropersistence of TBE virus antibodies in children, adolescents and young adults who received the first booster vaccination with either FSME-IMMUN 0.25 ml Junior or FSME-IMMUN 0.5 ml in Study 700401.	
Primary Objective	
• To assess 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 ml Junior or FSME-IMMUN 0.5 ml by means of neutralization test (NT) (according to *Adner et al., 2001* [1]) and ELISA (IMMUNOZYM FSME Immunoglobulin G [IgG]).	
Secondary Objective(s)	
• To assess the antibody response to a second booster vaccination with either FSME-IMMUN 0.25 ml Junior or FSME-IMMUN 0.5 ml administered in the present study, by means of ELISA and NT. • To assess the safety of FSME-IMMUN 0.25 ml Junior or FSME-IMMUN 0.5 ml after administration of the second booster vaccination in the present study.	

STUDY DESIGN	
Study Type	Immunogenicity
Control Type	Not applicable
Study Indication Type	Prevention
Blinding Schema	Open-label
Study Design	This is a phase IV, follow-up, open-label, multicenter study in a total of 202 children, adolescents and young adults who received their first TBE booster vaccination in Study 700401 with the aim to assess seropersistence of TBE antibodies at yearly intervals from approximately 3 years (38 months) to 10 years (118 months) after the first booster vaccination (as applicable), as well as antibody response to a second booster vaccination with either FSME-IMMUN 0.25 ml Junior or FSME-IMMUN 0.5 ml according to the subject's age. Timing of the second booster vaccination will depend on the level of serum TBE antibodies detected at the defined assessment time points. Subjects who may not be protected against TBE for an entire further tick season (NT titer ≤ 20 and / or ELISA value ≤126 VIE U/ml) will be invited to receive the second booster vaccination at either the 40, 48, 60, 72, 84, 96, 108, or 120 month time point.
Planned Duration of Subject Participation	Approximately 7 years
Primary Endpoint	
Immunogenicity: • Seropositivity rate as determined by NT from approximately 3 years (38 months) to 10 years (118 months) after the first booster vaccination administered in Study 700401 and after the second booster vaccination administered in this study.	

Secondary Endpoint(s)

Immunogenicity:

- Seropositivity rate as determined by ELISA from approximately 3 years (38 months) to 10 years (118 months) after the first booster vaccination in Study 700401 and after the second booster vaccination in this study;
- Antibody response as determined by ELISA from approximately 3 years (38 months) to 10 years (118 months) after the first booster vaccination in Study 700401 and after the second booster vaccination in this study;
- Antibody response as determined by NT from approximately 3 years (38 months) to 10 years (118 months) after the first booster vaccination in Study 700401 and after the second booster vaccination in this study;
- Fold increase of antibody concentration determined by ELISA after the second booster vaccination as compared to before the second booster vaccination in this study;
- Fold increase of antibody titer determined by NT after the second booster vaccination as compared to before the second booster vaccination in this study.

Safety:

- Injection site reactions observed in the period from the second booster vaccination until the following blood draw;
- Systemic reactions observed in the period from the second booster vaccination until the following blood draw.

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION

Investigational Product(s)	**FSME-IMMUN 0.25 ml Junior (**1.2 µg TBE antigen/0.25 ml) **FSME-IMMUN 0.5 ml (**2.4 µg TBE antigen/0.5 ml) **Dosage form**: solution/suspension; injectable **Dosage frequency**: Once
Mode of Administration	Intramuscular

SUBJECT SELECTION

Planned Number of Subjects	202 (Study population will consist of subjects who were administered the first booster vaccination in Study 700401 at 3 or 4 years after the third vaccination in Study 209).

Inclusion Criteria

Subjects who participated in Study 700401 and meet ALL of the following criteria are eligible for participation in this study:

- Subject / parent(s) / legal guardian(s) provide(s) written informed consent (according to national law);
- Subject provides written assent to the study according to age and capacity of understanding;
- Subject received the first booster vaccination with either FSME-IMMUN 0.25 ml Junior or FSME-IMMUN 0.5 ml during the course of Study 700401;
- Blood was drawn after the first booster vaccination in Study 700401;
- Subject / parent(s) / legal guardian(s) understand(s) the nature of the study and is / are willing to comply with the requirements of the protocol (e.g., return for follow-up visits, completion of the Subject Diary).

Exclusion Criteria
Subjects who participated in Study 700401 and meet ANY of the following criteria are not eligible for participation in this study: • Subject received any TBE vaccination since his / her first booster vaccination in Study 700401; • Subject has a history of infection with or vaccination against other flaviviruses (e.g., Dengue fever, yellow fever, Japanese B encephalitis) since his / her first booster vaccination in Study 700401; • Subject is known to be HIV positive (a special HIV test is not required for the purpose of the study) since his / her first booster vaccination in Study 700401; • Subject received a blood product or immunoglobulins within 90 days before any blood draw or in the period between the blood draw and the booster vaccination (as applicable); • Subject has a known or suspected problem with drug or alcohol abuse (> 4 liters of wine/week or equivalent level of other alcoholic beverages); • Subject / parent(s) / legal guardian(s) is / are in a dependent relationship with the study investigator or with a study team member. Dependent relationship includes close relatives (i.e., children or grandchildren, partner / spouse, siblings) as well as employees of the Investigator or the site conducting the study.

Eligibility criteria for booster vaccination

Subjects who meet ANY of the following criteria are not eligible for the booster vaccination:

- Subject is not clinically healthy (i.e., the physician would have reservations vaccinating with a TBE vaccine outside the scope of a clinical trial);
- Subject is suffering from a disease (e.g., autoimmune disease) or is undergoing a form of treatment (e.g., systemic corticosteroids) that can be expected to influence immunological functions;
- Subject has developed severe allergic reactions, in particular a sensitivity or allergy to any component of the vaccine, since the first booster vaccination in Study 700401;
- If female - subject is pregnant or lactating;
- Subject has participated in another clinical study involving an IP or medical device within 30 days prior to the planned booster vaccination or is scheduled to participate in another clinical study involving an IP or medical device.
- Females capable of bearing children if they do not agree to employ adequate birth control measures from 4 weeks before the booster vaccination until the end of the study.

Vaccination will be **delayed** if one of the following applies:

- Subject has an acute illness with or without elevated body temperature (≥ 37.5°C) within 3 days prior to the scheduled booster vaccination. The subject may be vaccinated at a repeat visit provided that the illness has resolved (body temperature < 37.5°C);
- Subject has received any live vaccine within 4 weeks or any inactivated vaccine within 2 weeks prior to the scheduled booster vaccination. Vaccination may be performed when an interval of 4 or 2 weeks, respectively, has passed;
- Subject has received antipyretics within 4 hours prior to the scheduled time of vaccination. Vaccination may be performed at a later date;
- Subject was bitten by a tick within 4 weeks prior to the scheduled booster vaccination. Vaccination shall be postponed until an interval of 4 weeks has passed;
- Subject has donated blood or plasma within 30 days of the scheduled booster vaccination. Vaccination shall be postponed until an interval of 30 days has passed.

STATISTICAL ANALYSIS

Sample Size Calculation

A total of 202 subjects who were administered the first booster vaccination in Study 700401 at 3 or 4 years after the third vaccination in Study 209 will be invited to participate in this study. Of these, approximately 175 study participants are expected to return and provide information on antibody persistence after the first booster vaccination with either FSME-IMMUN 0.25 ml Junior or FSME-IMMUN 0.5 ml. With this sample size, the 95% confidence interval (CI) of the seropositivity rate will extend no more than 5.8% from the observed rate assuming the observed rate lies in the region of 90%.

Planned Statistical Analysis

Point estimates and 95% confidence intervals for the seropositivity rate at each time point when blood is drawn after the booster vaccination in Study 700401 and separately at each time point after the booster vaccination in this study as measured by NT will be calculated.

The dependence of seropositivity of study participants on demographic factors (age, weight, gender) at yearly intervals from approximately 3 years (38 months) to 10 years (118 months) after the first booster vaccination will be analyzed by logistic regression at the end of the study period.

The antibody levels as measured by NT and ELISA at each blood draw after the first booster will be used to determine the annual decline rate.

The analysis of immunogenicity before the second booster vaccination will be carried out separately in the three age classes defined previously in Study 209. Subjects will remain in the same age class they were assigned to at the beginning of Study 209 (1 - 2 years, 3 – 6 years, 7 – 15 years). For the analysis of immunogenicity and safety after the booster vaccination the oldest age class will be further divided into those who received FSME-IMMUN 0.25 ml Junior and those who received FSME-IMMUN 0.5 ml.

The occurrence of fever and the 95% confidence interval of the probability of occurrence will be given. The fever rate after the second booster vaccination will be categorized by severity grade.

Local and systemic reaction rates, other than fever, after the booster vaccination will be provided in tabular format, and the probabilities of the occurrence of the adverse event (AE) rates and their 95% confidence intervals will be calculated.

For each symptom queried in the Subject Diary, the number of subjects who experienced the symptom, as well as the probabilities of the occurrence and the 95% confidence interval will be given.

4. TABLE OF CONTENTS

5. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
B19V	Parvovirus B 19
CRF	Case report form
CRO	Contract research organization
CTC	Common Toxicity Criteria
DMC	Data monitoring committee
EC	Ethics committee
ELISA	Enzyme-linked immunosorbent assay
FSME	*Frühsommer-Meningo-Enzephalitis* – German term for "tick-borne encephalitis"
FSME-IMMUN 0.25 ml Junior	TBE vaccine for children
FSME-IMMUN 0.5 ml	TBE vaccine for adults
GCP	Good Clinical Practice
GDP	Good Documentation Practice
GmbH	*Gesellschaft mit beschränkter Haftung* – German term for a company which does not trade its shares on the stock market
GMC	Geometric mean concentration
GMT	Geometric mean titer
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HEV	Hepatitis E Virus
HIV	Human immunodeficiency virus
HSA	Human serum albumin
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive care unit
IgG	Immunoglobulin G

Abbreviation	Definition
IP	Investigational product
MedDRA	Medical Dictionary for Regulatory Activities
NT	Neutralization test
SAE	Serious adverse event
SIC	Subject identification code
SmPC	Summary of product characteristics
SOP	Standard operating procedure
TBE	Tick-borne encephalitis
Th	Thiomersal
VIE U/ml	Vienna Units per milliliter (unit of anti-TBE IgG concentration as determined by the ELISA test kit Immunozym FSME-IgG; PROGEN Biotechnik Heidelberg, Germany)
SAER	Serious adverse event report

6. BACKGROUND INFORMATION

Tick-borne encephalitis (TBE) virus is a member of the family Flaviviridae, which comprises approximately 70 different viruses that cause many serious diseases in a wide variety of vertebrates, including humans. Among the flaviviruses, TBE virus has one of the highest impacts as a human pathogen, as indicated by the disease prevalence in endemic areas in certain parts of Europe and the East. The clinical course of the disease is largely determined by TBE virus subtype. By sequence analysis of TBE virus isolates from different endemic areas, three subtypes of the virus have been identified: Far-Eastern, Siberian and European/Western.[2;3]

The distribution of the TBE virus covers almost the entire southern part of the nontropical Eurasian forest belt, from Alsace Lorraine in the west to Vladivostok and northern and eastern regions of China in the east through to Hokkaido in Japan. In Europe, changes in the endemicity of TBE have recently been observed: several new TBE foci have been found or rediscovered in the Nordic countries, such as Bornholm in Denmark, southern Norway and several foci in the south of Sweden.[4;5]

In Europe, eight species of ticks, the main vector for the disease, have been identified so far that are capable of transmitting TBE virus. Ixodes ricinus, the common castor bean tick, is the primary vector and thus is mainly responsible for the spread of the virus in western and central Europe and the European region of Russia.[6]

6.1 Description of Investigational Product

FSME-IMMUN 0.25 ml Junior / FSME-IMMUN 0.5 ml is a formaldehyde-inactivated, sucrose gradient purified TBE virus (strain Neudoerfl) antigen solution, adsorbed on aluminum hydroxide (0.17 mg Al^{3+} / 0.35 mg Al^{3+}, respectively), hydrated and stabilized with human serum albumin (HSA). FSME-IMMUN vaccine is thiomersal free. The TBE antigen content in FSME-IMMUN 0.25 ml Junior is approximately 1.2 µg, whereas in FSME-IMMUN 0.5 ml it is approximately 2.4 µg (Table 6.1-1). The pharmacodynamic effect of the product consists of the induction of a sufficiently high concentration of anti-TBE antibodies to provide protection against TBE virus.

Table 6.1-1
Composition of TBE Vaccines

Composition of a single dose	FSME-IMMUN 0.25 ml	FSME-IMMUN 0.5 ml
Formaldehyde-inactivated TBE virus	target 1.2 µg (range 1.00-1.38 µg)	target 2.4 µg (range 2.00 – 2.75 µg)
Origin of production virus seed	supernatant from chick embryo cells*	supernatant from chick embryo cells*
Aluminum hydroxide, hydrated	0.17 mg Al^{3+}	0.35 mg Al^{3+}
Human serum albumin	0.25 mg	0.5 mg
Sodium chloride	1.725 mg	3.45 mg
Disodium hydrogen phosphate	0.11 mg	0.22.mg
Potassium dihydrogen phosphate	0.023 mg	0.045 mg
Sucrose	max. 7.5 mg	max 15 mg
Formaldehyde	max. 2.5 µg	max. 5 µg
Protaminsulfate	max. 0.25 µg (in traces)	max. 0.5 µg (in traces)
Neomycin and Gentamicin	in traces	in traces
Water for injection	ad 0.25 ml	ad 0.5 ml

* infected with working virus seed generated from chick embryo cells

Both FSME-IMMUN 0.25 ml Junior and FSME-IMMUN 0.5 ml are licensed for intramuscular injection. The vaccines will be administered in accordance with the Summary of Product Characteristics (SmPC): FSME-IMMUN 0.25 ml Junior is indicated for children and adolescents aged 1-15 years (until the last day before the 16th birthday) whereas FSME-IMMUN 0.5 ml has been approved for use in adults from 16 years of age (i.e. from the 16th birthday).

According to the current SmPC for FSME-IMMUN 0.25 ml Junior / FSME-IMMUN 0.5 ml, the first booster vaccination should be given at 3 years after completion of the primary vaccination series (which consists of 3 vaccinations). Subsequent booster vaccinations are recommended at 3 to 5 year intervals in children and adolescents as well as in adults up to 60 years of age.

The Sponsor will provide the Investigator with sufficient vaccine to conduct the study as well as the appropriate certificates of analysis for the investigational products.

6.2 Clinical Condition/Indication

6.2.1 Clinical Characteristics

After Lyme disease, TBE is the most prevalent tick-transmitted disease in Europe.[7] The typical course of the Western subtype is biphasic and can be outlined as follows: the incubation period, which is clinically silent, may last between 2 and 28 days [8], but in most cases it lasts approximately 8 days.[9] The first stage, which may last for 1 to 8 days, corresponds to the viremic phase. Exceptionally high initial fevers may occasionally occur, rising as high as 40.9°C.[10;11] These may be accompanied by headache, malaise and muscle pain, lasting about 4 days.[12]

An afebrile interval follows the first stage of TBE, and lasting 3 to 21 days (median 7 days [12]). During this time, patients are usually free of symptoms. Another sudden rise in temperature marks the beginning of the second stage. Only 20-30% of those infected with the TBE virus proceed into the second phase of the disease. The clinical manifestations of this second febrile episode are far more serious and involve the central nervous system with symptoms of meningitis (e.g., fever, headache, and a stiff neck) or encephalitis (e.g., drowsiness, confusion, sensory disturbances, and/or motor abnormalities such as paralysis) or meningoencephalitis.[10]

Hospitalization varies between 3 days and 40 weeks [13;14], depending on the severity of the illness. TBE-infected patients older than approximately 40 years of age increasingly develop the encephalitic form of the disease. In elderly patients, especially those older than 60 years of age, TBE can take a severe course, leading to paralysis and occasionally resulting in death.[15;16] Paralysis occurs in 30% of patients who enter the acute phase of the illness.[17]

Not all those infected with TBE run the entire course of the disease. In approximately 65% of cases, the infection remains silent, although viremia can be demonstrated; in some cases, the patient presents the clinical picture of the initial phase of TBE, but the symptoms subside without developing into full-blown TBE.

6.2.2 Clinical Course in Children

Persons of all ages are thought to be equally susceptible to infection. In Slovenia between 1959 and 2000, children represented 23.5% of the 1578 confirmed TBE cases in the country.[7] Direct comparison of clinical and epidemiological characteristics of TBE in

children and adults has revealed differences in several clinical and laboratory features, but has corroborated the conclusion that the course of illness is the same in both groups.[18]

Although TBE in children is a milder illness than in adults, an unusually high percentage of children experiencing a severe course of TBE and development of neurologic sequelae were identified in a retrospective study with patients (aged 0 to 15 years) hospitalized between 1993 and 1998 at the Department of Infectious Diseases in Ljubljana, Slovenia.[19;20] Of 133 children diagnosed with TBE infection, 49% had aseptic meningitis, 49% had meningoencephalitis and 3% had meningoencephalomyelitis. Seven patients (5.2%) with cerebrospinal fluid changes, compatible with aseptic meningitis, and an abnormal electroencephalogram were treated in the intensive care unit (ICU).

Other studies in children (up to 14 years of age) with a history of TBE, which were published between 1962 and 1999, showed 78% meningitis, 21% meningoencephalitis and 1% encephalomyelitis cases.[20;21;22;23;24;25;26] Rakar reported on sequelae in 6 out of 160 children (paresis, seizures, emotional disturbance), who were studied in Slovenia between 1978 and 1992.[26] However, the medical details of children with an unfavorable prognosis have mostly been presented as individual reports. Roggendorf and colleagues described a severe case of meningoencephalitis in a child (12 years old) who experienced epileptic seizures after 9 months of hospitalization.[27] Failure to recognize abdominal symptoms as criteria of the prodromal stage of TBE has been reported as a reason for fatal outcome of the disease resulting in TBE-induced brainstem encephalitis and general sinus thrombosis.[24] In 1992, Grubbauer and colleagues reported a 3.5 month old baby experiencing severe meningoencephalitis resulting from TBE, which led to an epileptic state and required neurointensive care.[28] The first neonatal case of TBE was reported by Jones and colleagues (*2007*) [29] in a 17-day old newborn resulting in severe neurologic impairment.

In Austria, between 1971 and 1981, a period when TBE vaccination was not performed in children (the first TBE vaccine was formulated for adult use and became available in Austria in 1976), approximately 540 cases of TBE infection in children were observed (personal communication PPD , Institute of Virology, Medical University of Vienna) giving a mean incidence rate of approximately 49 cases per year. In Styria, between 1980 and 1990, four TBE-infected children were admitted to an ICU (however, these children did not suffer from any sequelae).[30] Seven children diagnosed with TBE also suffered from different sequelae: epilepsy (n=2), moderate to severe hypacusis (n=2), transient hypacusis (n=2) and one child with mild hypacusis.[31]

These data demonstrate that the course of TBE in children and adolescents can be associated with an unfavorable outcome and permanent neurological damage. Due to the risk of a severe course of the disease, immunization against TBE is also recommended for infants and children living in, or traveling to, highly endemic areas.

6.3 Population to be Studied

A total of 202 healthy children, adolescents and young adults of both genders who participated in Study 700401 and received the first booster vaccination with either FSME-IMMUN 0.25 ml Junior or FSME-IMMUN 0.5 ml at 3 or 4 years after the third vaccination will comprise the subject population of the study.

The majority of subjects will be enrolled in the current study in late spring 2009 at approximately 38 months after their first booster vaccination in Study 700401 (which they received at 3 years after their third vaccination).

Those 29 subjects who were administered the first booster vaccination at 4 years after their third vaccination in Study 700401, will enter the current study in 2010. For these subjects the first visit will be shifted to take place at approximately 34 months after their first booster vaccination.

6.4 Findings from Nonclinical and Clinical Studies

6.4.1 Clinical Experience with FSME-IMMUN 0.5 ml in Adults

The safety and immunogenicity of FSME-IMMUN 0.5 ml has been evaluated by Baxter in eleven clinical studies in adults, including two studies investigating either immunogenicity or safety only. One study is currently still ongoing (B9371010, Formerly Baxter 691101), follow up to Study 223/690701).

Study **IMAG-062** was a prospective, four-arm, randomized, controlled, double blind phase III study in 1191 subjects. The objective of this study was to assess the equivalence of FSME-IMMUN produced by the new production method (chick-chick), either with or without thiomersal, with FSME-IMMUN produced by the previous production method (mouse brain). To this end, the subjects were assigned to receive three vaccinations with one of the following formulations:

- FSME-IMMUN (chick-chick) without thiomersal (FSME-IMMUN 0.5 ml);
- FSME-IMMUN (chick-chick) with thiomersal;
- FSME-IMMUN (mouse brain) with thiomersal;
- Placebo.

FSME-IMMUN 0.5 ml was shown to be highly immunogenic and equivalent to the previous generation FSME-IMMUN vaccine in terms of seroconversion rate as determined by Enzyme-Linked Immunosorbent Assay (ELISA) and neutralization test (NT) after the second vaccination (28–35 days after first vaccination). A seroconversion rate of 92.9% was achieved with FSME-IMMUN 0.5 ml, and 98.2% with FSME-IMMUN. Statistical equivalence of the vaccines was shown, as the difference between these rates (5.3%) is within a range of ± 10%. After the third vaccination, the seroconversion rate was 100% with both FSME-IMMUN and FSME-IMMUN 0.5 ml. After completion of the primary vaccination series, subjects who had received the placebo were randomized to receive three vaccinations with one of the study vaccines. The seroconversion rates with FSME-IMMUN 0.5 ml as determined by ELISA and NT were 97.1% after the second and 96.6% after the third vaccination.

FSME-IMMUN 0.5 ml was shown to be well-tolerated; no severe, serious or unexpected AEs occurred within the observation period after vaccination with FSME-IMMUN 0.5 ml. In Parts A and B, most AEs after vaccination were mild (11.8% after the first,

4.1% after the second and 8.3% after the third vaccination), with a few moderate AEs (1.7% after the third vaccination only). Similar tendencies were observed in Part C.

A dose-finding study (Study **201**) to determine the optimal dosage of FSME-IMMUN 0.5 ml with respect to safety and immunogenicity was conducted in 405 adults aged 16 to 65 years.[32] The subjects were randomized to receive two vaccinations administered at an interval of 21 to 35 days with one of three different antigen amounts: 0.6 µg, 1.2 µg or 2.4 µg. Subjects received a third vaccination with the same antigen dose administered in this study during the follow-up Study 202. The seroconversion rates determined by ELISA and/or NT after the second vaccination were 85.8%, 96.9% and 97.0% with the doses 0.6 µg, 1.2 µg and 2.4 µg respectively. The 2.4 µg dose was determined to be the optimal dose, firstly as only the 1.2 µg and 2.4 µg doses induced a sufficiently high seroconversion rate (according to the predefined criteria), and secondly because the 2.4 µg dose was found to be non-inferior to the 1.2 µg dose with respect to fever rate after the first vaccination.

The conclusion of the dose-finding study on FSME-IMMUN 0.5 ml was confirmed by the results of a follow-up study (Study **202**), in which a third vaccination was administered. The 2.4 µg dose was found to be the optimal dose of the FSME-IMMUN 0.5ml vaccine for adults, as it induced a 100% seroconversion rate and a low rate of AEs after the third vaccination.[32]

Study **208** was designed as a single-blind, randomized, multicenter safety study compared two TBE vaccines in 3966 healthy subjects aged 16 to 65 years. FSME-IMMUN 0.5 ml was found to be non-inferior to Encepur with respect to fever rate after the first vaccination, as the upper limit of the 95% confidence interval of the difference in fever rate after the first vaccination was below the predefined +3% limit. Fever after the first vaccination was mainly mild in nature and occurred at a very low frequency (0.8%) in the FSME-IMMUN 0.5 ml study group, compared to the Encepur study group, in which a rate of 5.6% was determined. Only one moderate fever case was reported and this case occurred following vaccination with Encepur. As observed for the overall fever rate after the first vaccination, fever classed as being related to the first vaccination was also considerably lower in the FSME-IMMUN 0.5 ml study group (0.6%) than in the Encepur group (4.9%). Overall, the study demonstrated that the FSME-IMMUN 0.5 ml vaccine is safe and induces considerably lower reaction rates than Encepur.[33]

An open-label, multicenter, phase III, follow-up study to Study 208 (Study **213**) investigated the safety of the third vaccination of FSME-IMMUN 0.5 ml in subjects aged 16 to 66 years who had received the first two vaccinations with either FSME-IMMUN 0.5 ml (n=2790) or Encepur (n=915) during Study 208. Immunogenicity variables were assessed pre- and post-vaccination in a subgroup of subjects (n=566 analyzed). Regardless of whether FSME-IMMUN 0.5 ml or Encepur had been administered for the two previous vaccinations in Study 208, seroconversion rates as determined by ELISA and/or NT after the third vaccination with FSME-IMMUN 0.5 ml (compared to baseline) were very high (99.5% and 99.3% respectively). The geometric mean concentrations (GMCs, as determined by ELISA) after the third vaccination were higher in the FSME-IMMUN 0.5 ml only group (1935.7 VIE U/ml vs. 1508.7 VIE U/ml), while the geometric mean titers (GMTs, as determined by NT) after the third vaccination were higher in the group of subjects who had previously received Encepur (259.0 vs. 371.4). Local and systemic reactions were mainly mild. Fever occurred at a negligible level (0.5%). In summary, these results demonstrate the excellent safety profile of the FSME-IMMUN 0.5 ml vaccine for the third vaccination in healthy adults. The results further confirm that, regardless of which TBE vaccine was administered for the first two vaccinations, a third vaccination with FSME-IMMUN 0.5 ml is well tolerated and induces a strong immune response when administered 6 months after the first vaccination.[33]

Study **223** was an open-label follow-up study to Study 213 to investigate TBE antibody persistence at 2 and 3 years after the third TBE vaccination with FSME-IMMUN 0.5 ml, as well as TBE antibody response to a booster vaccination with FSME-IMMUN 0.5 ml (administered 3 years after the third vaccination) by means of ELISA and NT (n=328 analyzed). Local and systemic reactions were monitored after administration of the booster vaccination. [redacted] As expected, immune response was age dependent, with older subjects (aged 51-67 years) attaining GMC and GMT values (determined one month, two and three years after the third vaccination in Study 213) which were approximately half of the values for younger subjects(18-50 years of age). The majority of subjects experienced no reaction to the booster vaccination. The rate of occurrence of local and systemic adverse events was low, as expected with the administration of a booster vaccination three years after the third vaccination.

The seropositivity data obtained three years after the third vaccination suggest that it is sufficient for the first booster to be administered three years after the completion of the primary vaccination series. This study also demonstrated that FSME-IMMUN 0.5ml is extremely well tolerated as a booster vaccination.

Study 225 investigated the safety and immunogenicity of 2 vaccinations with FSME-IMMUN "NEW" 0.5 ml administered using a rapid immunization schedule (Day 0, Day 12±2) in healthy adults aged 16 to 65 years (n=60). The main objective of the study was to investigate the antibody kinetics after the second vaccination in order to establish the earliest time point at which vaccinees attained seropositive antibody levels. A total of 60 subjects received both vaccinations in this clinical study. Blood was drawn from each subject prior to the first vaccination and on Days 3, 7, 14, 21 and 42 after the second vaccination. Of the 60 subjects enrolled, 4 were seropositive for TBE virus antibody prior to the first vaccination and were excluded from immunological analyses. The seropositivity rates as determined by ELISA among the remaining 56 subjects reached 92.9% by Day 14 and 98.2% by Day 42 after the second vaccination. Seropositivity rates determined by NT after the second vaccination were higher and increased more rapidly than the corresponding rates determined by ELISA. The proportion of subjects who were seropositive as determined by NT on Day 3 was 89.3% and the rate increased to 98.2% by Day 14. At Days 21 and 42 after the second vaccination all subjects showed seropositive titers as measured by NT.

Safety constituted a secondary endpoint in the study, and was measured by the occurrence of local and systemic reactions after each vaccination. Safety data were collected on all 60 subjects through study completion on Day 42 following the second vaccination. No SAEs were reported after either vaccination in the study. Among the non-serious AEs reported in the course the study, the majority were mild, very few moderate and none severe. Local pain and tenderness were the most frequently reported queried local symptoms.

The results from Study 225 demonstrate that rapid immunization comprising two vaccinations (on Days 0 and 12 ± 2) with FSME-IMMUN 0.5 ml results in high seropositivity rates by Day 14 after the second vaccination. In addition, two vaccinations with FSME-IMMUN 0.25 ml given according to a rapid immunization schedule were well tolerated by the subjects participating in this study.

Study **690501** investigated the immunogenicity and safety of a third vaccination with FSME-IMMUN 0.5 ml given approximately 12 months after the second vaccination in Study 225. In Study 225, two vaccinations were given using a rapid immunization schedule 12 ± 2 days apart. In Study 690501 a total of 44 subjects received two vaccinations with FSME-IMMUN "NEW" 0.5 ml, and 41 were included in the immunogenicity dataset. Seropositivity rates for TBE virus antibody were determined by ELISA and NT separately at 3, 7, 14 and 21 days after the third vaccination. Immunogenicity results obtained just before the third vaccination was administered showed that titers had decreased to levels very close to or below the seropositivity cut-off for both tests (GMC 113 VIE U/ml; ELISA >126 VIE U/ml is considered positive and GMT 13.4; GMT ≥10 is considered positive). Following the third vaccination, a strong antibody response was observed, with maximum GMC of 2938.8 VIE U/ml and GMTs of 360.2 at Day 21 post-vaccination. At Day 3 post-vaccination, 36.6% demonstrated seropositivity according to ELISA, while NT only analysis determined a higher seropositivity rate of 78.0% of all subjects. All (100%) subjects were determined to be seropositive by Day 7 post-vaccination and at all later assessment dates in both tests. The majority of subjects experienced no reaction to the vaccination and no SAEs were reported during this study. All local and systemic reactions were mild in nature and occurred at a frequency of 34.1% and 13.6% of subjects, respectively.

The results from Study 690501 support the need for the third vaccination for achieving longer term protection against TBE, and confirm existing data from previous studies (Studies 202 and 213) on the excellent immunogenicity of the third vaccination with FSME-IMMUN 0.5 ml. This study also verified previous clinical experience that the third vaccination with FSME-IMMUN 0.5 ml is safe for use in a healthy adult population.

Study **690601** was designed to evaluate the immunogenicity and safety of FSME-IMMUN 0.5 ml with the first and second vaccination being administered according to the rapid immunization schedule (12±2 days apart) and the third vaccination administered about 6 months after the first dose in healthy adults (n=330). The seropositivity rates attained in Stratum A (16- 49 years) and Stratum B (≥ 50 years) after the second vaccination as determined by ELISA, significantly increased from Day 7 (7.8% and 5.7%, respectively) to Day 14 (73.9% and 48.8%, respectively) and reached maximum levels at Day 21 (84.3% and 69.6%, respectively). Seropositivity rates determined by NT after the second vaccination were higher and increased more rapidly than the corresponding rates determined by ELISA. The proportion of subjects who had

seropositive titers at Day 7 as determined by NT was 76.5% and 48.4% in Stratum A and Stratum B, respectively. Rates of 94.8% and 80.9% (Day 14) and 96.7% and 88.0% (Day 21) were determined respectfully for the two age strata.

After the third vaccination an increase in seropositive ELISA titers was seen at Day 7 (Stratum A: 87.6%; Stratum B: 65.4%) with the highest rates found at Day 21 (Stratum A: 99.3% and Stratum B: 96.1%). This trend was also observed in the NT, with rates of 97.2% and 84.3% at Day 7, and maximum rates of 100% and 98.7% at Day 21 in Stratum A and B, respectively, after the third vaccination.

There were no SAEs related to vaccination reported during this study. All local reactions which occurred after the first and second vaccinations were mild or moderate in nature and were more often reported in Stratum A (17.6% and 19.2%, respectively), than in Stratum B (13.5% and 17.3%, respectively). Systemic reactions were also rated as mild and not clinically relevant.

Overall, results of this study demonstrated that basic immunization with two vaccinations given according to the rapid immunization schedule induces seropositivity in the majority of subjects in both age strata. After the third vaccination, only 1 subject in Stratum B was found to be unresponsive to vaccination as determined by both ELISA and NT. Furthermore, FSME-IMMUN 0.5 ml has been demonstrated to be safe and well tolerated upon administration according to the rapid immunization schedule.

Study **690701** was an open-label follow-up study to Study 223 to investigate TBE antibody persistence at approximately 27, 34, 46 and 58 months after the first TBE booster vaccination with FSME-IMMUN 0.5 ml by means of ELISA and NT. A second booster vaccination with FSME-IMMUN 0.5 ml was administered depending on the level of serum TBE antibodies detected at the defined assessment time points. The antibody response was assessed approximately 1 month after the booster vaccination. The study was initiated in 2007 and was completed in March 2011.

6.4.2 Clinical Experience with FSME-IMMUN 0.25 ml in Children

Ten clinical studies and one postmarketing surveillance have been completed in children with FSME-IMMUN 0.25 ml (1.2 µg TBE virus antigen).

The aim of **Postmarketing surveillance 197** was to observe the occurrence of fever following the first vaccination with half the dosage of FSME-IMMUN 0.5 ml. The

surveillance was carried out by registered pediatricians and general practitioners in Austria, between January 08, 2001 and August 23, 2001. A total of 1922 children, aged 6 months to 12 years, were vaccinated at 110 medical centers throughout Austria. Each child was observed closely and rectal temperature measurements were taken (by the parents/legal guardian) for a total of four days after vaccination (including vaccination day).[34] The majority of children were aged between 1 and 3 years (n=1198). Fever rates were highest in 1 – 2 year old children and an overall fever occurrence of 20.3 % was observed across all age groups.

Study 198 was an open, multicenter pilot study that examined the immunogenicity and safety of two vaccinations (administered 14-32 days apart) with 1.2 µg TBE antigen FSME-IMMUN "NEW" 0.25 ml in 101 children aged 1-12 years. Considering the high vaccination rate in children over the age of 4 years in Austria, the majority of children enrolled in the study were, as expected, aged 1 to 3 years (92.1%). The aim of the study was to examine the seroconversion rates of FSME-IMMUN 0.25 ml after the second vaccination, as well as the tolerability, assessed by body temperature measurements and monitoring of adverse events, after the first and second vaccinations in children.

High seroconversion rates (99%) as determined by ELISA were observed after the second vaccination. Most AEs were mild and transient in nature and none were graded as severe. Fever related to the first vaccination occurred in 29.7%; most cases were mild and none were severe. The most common systemic AEs (apart from fever) were appetite loss and sleep disorders after the first vaccination.

Study 215 was designed as an open, multicenter, follow-up phase II study to Study 198 for all subjects aged 1-12 years who had received two vaccinations with FSME-IMMUN "NEW" 0.25 ml (1.2 µg TBE antigen) during Study 198. The study investigated safety and immunogenicity of the third vaccination, administered 9-10 months after the second vaccination, as measured by seroconversion rates and adverse event monitoring.

Serological results of this study showed that the third vaccination with the 1.2 µg TBE antigen is highly immunogenic. After the third vaccination, a seroconversion rate of 100% was observed (98/98 children).

Systemic reactions were rare and mild to moderate in intensity. The most commonly reported systemic AEs were appetite loss and sleep disorders. Fever was reported in 12 cases and 9 of these were judged by the Investigator as related to the third vaccination.

The most commonly reported local reaction was injection site pain. There were no local reactions graded as severe.

Study 199 was a double-blind, randomized, multicenter dose-finding study that assessed the safety and immunogenicity of the first two doses of FSME-IMMUN "NEW" 0.25 ml administered 21-35 days apart in 643 subjects aged 1-6 years (until the last day before the 6th birthday). Subjects were assigned to one of three study arms (0.3 µg, 0.6 µg and 1.2 µg antigen) at a ratio of 1:1:1 using a blocked randomization system with a block size of > 3. The primary aim of the study, with respect to safety, was to select the highest dose of FSME-IMMUN "NEW" that is non-inferior (with respect to fever rate after the first vaccination) to the lowest eligible dose (as determined by immunogenicity).

With regards to immunogenicity, only the doses at which the lower limit of the 95% confidence interval of the seroconversion rate was not lower than 85% were included in the analysis. As calculated from the results of ELISA and/or NT, seroconversion rates after the second vaccination were high (>93%) with all three investigated doses (93.2%, 98.1% and 100% after vaccination with 0.3 µg, 0.6 µg and 1.2 µg TBE antigen, respectively). These results confirmed the induction of sufficient seroconversion rates with all three doses, therefore all three doses were included in the analysis of the optimal dose. The 1.2 µg dose was shown to be the optimal dose due to predefined safety criteria (i.e. to select the highest dose of TBE antigen that is non-inferior (with respect to fever after the first vaccination) to the lowest eligible dose (as determined by immunogenicity).

Occurrence of fever after the first vaccination was not dose-dependent. Fever cases were predominantly mild in intensity and none were severe. Fever occurrence was age-dependent with the highest fever rate occurring in children 1 and 2 years of age (33.3% and 19.7%, respectively) and lower rates observed among children aged 5 years (6.3% of the total age group).

The 1.2 µg dose was determined to be safe for children aged 1-6 years and was determined to be the optimal dose of FSME-IMMUN "NEW" 0.25 ml in children in this age group.

Study 206 was designed as a follow-up study to Study 199 for subjects (aged 1 – 6 years) who had received the first two vaccinations as part of Study 199 (n=625). In Study 206, the safety and immunogenicity of the third vaccination (administered 6 months

(± 14 days) after the first vaccination) was examined. Subjects received the same dose (0.3 µg, 0.6 µg or 1.2 µg antigen) as for the previous two vaccinations.

The seroconversion rate as determined by ELISA and/or NT was highest in the 1.2 µg dose group (100%) with rates of 99.5% and 98.5% observed in the 0.6 µg and 0.3 µg dose groups, respectively The 1.2 µg dose was shown to be the optimal dose due to the predefined safety criteria.

Fever occurrence after the third vaccination was not dose-dependent. Systemic reactions as a whole showed no dose-dependent response. Restlessness and insomnia were the most frequently reported systemic reactions. The occurrence of local reactions after the third vaccination was also comparable between the three study groups.

Study 205 was a double-blind, randomized, multicenter dose-finding study that assessed the safety and immunogenicity of the first two doses of FSME-IMMUN "NEW" 0.25 ml in 644 subjects aged 6-15 years (until the last day before the 16th birthday). Subjects were assigned to one of three study arms (0.3 µg, 0.6 µg and 1.2 µg antigen) at a ratio of 1:1:1 using a blocked randomization system with a block size of > 3. The two vaccinations were administered 21-35 days apart.

Seroconversion rates calculated from ELISA and /or NT were high (>96%) with both 0.6 µg and 1.2 µg doses of TBE vaccine. The lower rates of the 0.3 µg dose led to exclusion of this dose from the analysis of the optimal dose.

No difference in the fever rate was observed between the study groups. Fever after the first vaccination was predominantly mild and no severe fever cases were reported. No clear age-dependency trend was found with respect to fever after either vaccination. No dose-dependency was observed with the occurrence of local and systemic reactions after the first vaccination. Fatigue and headache were the most frequently reported systemic reactions in this study.

The 1.2 µg dose was determined to be safe for use and, according to both immunogenicity and safety criteria, was found to be the optimal dose of FSME-IMMUN 0.25 ml in children aged 6-16 years.

Study 207 was designed as a follow-up study to Study 205 for subjects (aged 6 – 16 years) who had received the first two vaccinations as part of Study 205

(n= 618). In Study 207, the safety and immunogenicity of the third vaccination (administered 6 months (± 14 days) after the first) was examined. Subjects received the same dose (0.3 µg, 0.6 µg or 1.2 µg antigen) as for the previous two vaccinations.

After the third vaccination, the seroconversion rate as determined by ELISA and/or NT was the highest in the 1.2 µg dose group (100%), with rates of 99.1% and 95.8% observed in the 0.3 µg, 0.6 µg dose groups, respectively.

Fever occurrence after the third vaccination was low and no dose-dependency was observed. Local and systemic reactions were predominantly mild and not dose-dependent in frequency. The most commonly reported local reaction was injection site pain. Headache and fatigue were the most frequent systemic reactions, which occurred at a low rate and were comparable between study groups.

These results demonstrated that the 1.2 µg TBE-virus antigen dose of FSME-IMMUN 0.25 ml – which was found to be the optimal dose according to pre-defined criteria in Study 205 – is safe and highly immunogenic for the third vaccination in children and adolescents aged 6 – 16 years.

In **Study 209**, the safety of five consecutive lots of FSME-IMMUN "NEW" 0.25 ml (1.2 µg TBE antigen) was investigated in healthy children aged 1-15 years, who received 3 consecutive vaccinations (the first two 21-35 days apart; the third vaccination 6 months ±14 days after the first). The main objective was the assessment of fever rate after the first vaccination in three different age groups (1-2 years, 3-6 years, 7-15 years), and to assess lot consistency. In addition, immunogenicity was investigated by ELISA and NT in a subgroup of subjects. A total of 2419 children were enrolled in Part A of the study, which comprised the first and second vaccinations. The third vaccination was administered in Part B of the study, in which 2404 subjects who had completed Part A of the study were enrolled.

A high overall seroconversion rate (96%) was observed 21-35 days after the second vaccination as determined by ELISA and/or NT. After the third vaccination, all subjects were shown to have seroconverted compared to baseline.

As expected, fever occurred at a substantially lower rate after the second and third vaccination than after the first vaccination, and was more frequently observed in younger than in older children after all three vaccinations. The majority of fever cases after all

three vaccinations were mild, and most fever cases subsided within 24 hours. No severe fever was observed after the first vaccination.

Local reactions occurred less frequently after the second and third vaccinations than after the first. After all three vaccinations, the majority of local reactions were mild and the lowest frequency was reported in children aged 1-2 years, with comparable rates of local reactions in the 3-6 years and 7-15 years age groups. As expected, the most common local reactions after vaccination were local pain and tenderness.

The majority of systemic reactions (excluding fever) after all three vaccinations were mild. Systemic reactions (excluding fever) were reported most frequently in children aged 1–2 years, however, no significant difference was observed between the age groups. Headache was the most frequently reported systemic reaction, followed by restlessness (in subjects aged 1-5 years only), fatigue (in subjects aged 6-15 years only), myalgia and malaise (in subjects aged 6-15 years only).

These results confirm the consistent safety and high immunogenicity of FSME-IMMUN 0.25 ml for the vaccination of children and adolescents aged 1-15 years.

Study 700401 was designed to investigate the seropersistence of TBE antibodies approximately 24, 34, 46 and 58 months after completion of the primary immunization schedule (3 vaccinations administered at months 0, 1 and 6 in Study 209) with FSME-IMMUN 0.25 ml in children and adolescents aged 3 to 18 years. Subjects were offered a booster vaccination at either 36, 48 or 60 months after the third vaccination with either FSME-IMMUN 0.25 ml or FSME-IMMUN 0.5 ml according to their age, depending on their individual TBE antibody levels. The antibody response was again assessed approximately 1 month after the booster vaccination. The study was completed in July 2009.

Study 700501 aimed to investigate the seropersistence of TBE virus antibodies approximately 3 years after a booster vaccination with FSME-IMMUN 0.25 ml Junior in children who participated in Study IMAG-146A and were administered three vaccinations with either Ticovac 0.25 ml or Ticovac 0.5 ml (without HSA) during this study. Children were aged 6 months – 3 years at the time of their first vaccination. The analysis of the primary endpoint (seropositivity rate measured by ELISA and/or NT) showed that all (100%) subjects had seropositive levels of TBE virus antibodies approximately 3 years after the first booster vaccination. The results of this study confirm

the excellent immunogenicity of the primary vaccination series followed by a booster vaccination with FSME-IMMUN 0.25 ml Junior 3 to 4 years after the third vaccination.

Study 700801 was designed as a single-blind, randomized, phase III b multicenter study aiming to investigate the immunogenicity, safety and interchangeability of FSME-IMMUN 0.25 ml Junior with Encepur 0.25 ml Children administered according to a conventional schedule (three vaccinations administered at 0, 28 and 360 days). In this study children aged 1 – 11 years will be administered the first and second vaccinations with either FSME-IMMUN 0.25 ml Junior or Encepur 0.25 ml Children and the third vaccination with FSME-IMMUN 0.25 ml Junior only. The study was completed February 2010.

6.5 Relevant Literature and Data

Relevant literature and data are discussed in Section 6.1 to Section 6.4.

Complete information for this compound may be found in the SmPC, the single reference safety document for this study.

6.6 Evaluation of Anticipated Risks and Benefits of the Investigational Product(s) to Human Subjects

6.6.1 Possible Benefits for the Subject

During this study, in accordance with the current recommendation in the SmPC, subjects will be offered the second TBE booster vaccination with either FSME-IMMUN 0.25 ml Junior or FSME-IMMUN 0.5 ml according to their age, following a first booster administered during the course of Study 700401. The recommendation regarding booster intervals as given in the SmPC was based on retrospective analysis of TBE antibody seropersistence in adults. However, so far there are only limited prospective clinical data from studies conducted in children to investigate seropersistence of TBE antibodies.

Although children generally show a very good immune response after vaccination with FSME IMMUN, isolated cases of vaccination failures have been observed. Therefore in this study TBE antibodies seropersistence will be investigated in the three sub-populations - children, adolescents and young adults who received their primary vaccination series at the age of 1-15 years in Study 209 and their first booster vaccination in the context of Study 700401, 3-4 years after the third vaccination. Blood obtained at yearly intervals from approximately 3 to 10 years after the first booster vaccination will allow for determination of the subject's level of TBE antibodies in order to assess the individual need for a second booster vaccination and to avoid an unnecessary early booster. A blood draw after the second booster vaccination will be performed to investigate the booster response. These results will be communicated to the subjects.

6.6.2 Possible Benefits for Society

At present, prospective clinical trial data on long-term TBE serum antibody persistence after vaccination are limited, particularly in children and adolescents. This study will provide information on antibody status at yearly intervals from approximately 3 to 10 years after the first booster with FSME-IMMUN administered 3-4 years after the completion of the primary vaccination series. Results of this study will contribute to identification of the optimal booster interval and thereby influence future TBE vaccination practices. This study will further investigate TBE antibody persistence in subjects who started their primary vaccination with FSME-IMMUN 0.25 ml Junior at the age of 12 – 15 years, to confirm the appropriateness of the priming dose in this age group.

6.6.3 Possible Risks / Inconveniences for the Subject

As a result of drawing blood, pain, hematoma, and, in very rare cases, infection at the blood sample site may occur. In order to minimize pain, a local anesthetic cream or plaster (e.g. EMLA®) may be offered for application at the venipuncture site prior to each blood draw for younger children.

The most commonly reported AEs after administration of TBE vaccines in children are pain at the injection site, injection site tenderness and headache. As is the case with all inactivated vaccines, redness, induration and/or swelling at the injection site can also occur after TBE vaccination.

Undesirable systemic reactions such as fatigue, malaise, nausea, vomiting, muscle or joint pain, appetite loss and sleep disorders may also be observed.

Fever may occur in children after the first immunization in particular in the very young. In general, the fever subsides within 24 hours. Fever rates reported after the second vaccination are generally lower as compared to the fever rates after the first vaccination. In very rare cases, febrile convulsions in small children have been reported, in particular after administration of the first dose. However, in the context of this study, a low fever rate is expected after the booster vaccination due to the age of the study subjects. In case of fever antipyretic therapy should be considered.

As with any vaccination, allergic reactions, including anaphylactic shock, cannot be completely ruled out, although their occurrence in connection with vaccination is extremely rare. Anaphylactic reactions to vaccines, including TBE vaccines, are very rare, but can occur. Therefore, appropriate emergency equipment and medication must be at hand whenever an immunization is performed.

In the presence of an autoimmune disorder (e.g. multiple sclerosis) or respective genetic disposition, vaccination might have an adverse effect on the course of the disease.

As with any other vaccination, central and peripheral nervous system disturbances cannot be completely ruled out.

All AEs stated in the package insert for FSME-IMMUN 0.5 ml or FSME-IMMUN 0.25 ml Junior can also occur after administration of the vaccine.

The occurrence of unknown adverse effects cannot be excluded with the administration of any medicinal product. This statement also applies to this clinical study.

6.7 Compliance Statement

This study will be conducted in accordance with this protocol, the International Conference on Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996) [35], the European Clinical Trial Directive and the GCP Directive (2001/20/EC [36] and 2005/28/EC [37], respectively), and applicable national and local regulatory requirements.

7. STUDY PURPOSE AND OBJECTIVES

7.1 Study Purpose

The main purpose of this study is to assess the seropersistence of TBE virus antibodies in children, adolescents and young adults who received the first booster vaccination with either FSME-IMMUN 0.25 ml Junior or FSME-IMMUN 0.5 ml in Study 700401.

The current protocol is being conducted to obtain prospective clinical trial data on long-term TBE serum antibody persistence beyond the first booster and to verify the current TBE booster recommendations. The study investigates TBE virus antibody persistence at yearly intervals from approximately 3 years (38 months) to 10 years (118 months) after the first booster vaccination (as applicable). The decision whether to administer the second booster vaccination in this study and the timing thereof will depend on the level of serum TBE antibodies detected at the defined assessment time points. Subjects who may not be protected against TBE for an entire further tick season (NT titer ≤ 20 and / or ELISA value ≤ 126 VIE U/ml), should be invited to receive the booster vaccination at either the 40, 48, 60, 72, 84, 96, 108, or 120 month time point. Recommendations as to whether or not to administer the booster vaccination will be given by the Sponsor on an individual basis. The Data Monitoring Committee (DMC) will be consulted for their opinion in case of inconclusive serological data (e.g. contradictory results in ELISA and NT).

The cut-off level for an NT titer of 1:20 as described above was chosen based on the annual decline rate determined in the precursor studies 209 and 700401[i], in which antibody persistence was investigated 1, 24 , 34, 46 and 58 months after completion of the TBE primary vaccination series. Annual decline rates were calculated on the basis of log-transformed antibody titers. The mean annual decline rates determined for subjects aged 1-2 years, 3 – 6 years and 7 – 15 years were -0.50, -0.38 and -0.46, respectively. Therefore, an NT titer of 20 at a specified time point would on average be reduced to 12.2, 13.6 or 12.6 within a year for the 3 age categories, respectively, which is just above the cut-off level for seropositivity (NT ≥ 1:10). Also, subjects should receive the booster vaccination in the current study if their ELISA value has declined below the level of seropositivity, i.e. ≤ 126 VIE U/ml.[38]

[i] Study 700401: 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. Statistical Analysis dated November 24, 2008

7.2 Primary Objective

To assess 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 ml Junior or FSME-IMMUN 0.5 ml by means of NT (according to *Adner et al., 2001*) [1] and ELISA [IMMUNOZYM FSME Immunoglobulin G (IgG)] .

7.3 Secondary Objectives

7.3.1 Immunogenicity

To assess the antibody response to a second booster vaccination with either FSME-IMMUN 0.25 ml Junior or FSME-IMMUN 0.5 ml administered in the present study, by means of ELISA and NT.

7.3.2 Safety

To assess the safety of FSME-IMMUN 0.25 ml Junior or FSME-IMMUN 0.5 ml after administration of the second booster vaccination in the present study.

8. STUDY DESIGN

8.1 Overall Study Design

This is a phase IV, follow-up, open-label, multicenter study in a total of 202 children, adolescents and young adults who received their first TBE booster vaccination in Study 700401 with the aim to assess seropersistence of TBE antibodies at yearly intervals from approximately 3 years (38 months) to 10 years (118 months) after the first booster vaccination (as applicable), as well as antibody response to a second booster vaccination with either FSME-IMMUN 0.25 ml Junior or FSME-IMMUN 0.5 ml according to the subject's age.

Blood draws will be performed to assess the seropersistence of TBE virus antibodies at yearly intervals from approximately 3 years (38 months) to 10 years (118 months) after the first booster vaccination previously administered during Study 700401.

Timing of the second booster vaccination will depend on the level of serum TBE antibodies detected at the defined assessment time points. Subjects who may not be protected against TBE for an entire further tick season as confirmed by relatively low TBE serum antibody levels evaluated by NT and / or ELISA (i.e. NT titer ≤ 20 and / or ELISA value ≤ 126 VIE U/ml), will be invited to receive the second booster vaccination at either the 40, 48, 60, 72, 84, 96, 108, or 120 month time point (see Section 10.3.2). Recommendations as to whether or not to administer the booster vaccination will be given by the Sponsor on an individual basis. The Data Monitoring Committee will be consulted for their opinion in case of inconclusive serological data (e.g., contradictory results in ELISA and NT).

A blood draw will be performed approximately 21 - 35 days after vaccination to assess the booster response.

The overall study design is illustrated in Figure 20.1-1 and Figure 20.1-2 (Supplement 20.1).

8.2 Duration of Study Period(s) and Subject Participation

The overall duration of the study is approximately 8 years from study initiation (i.e. first subject enrolled) to study completion (i.e. last subject last visit).

The subject participation period is approximately 7 years from enrollment to subject completion (i.e. last study visit), unless the booster vaccination is administered at an earlier time point or the subject is prematurely discontinued.

8.3 Endpoints

8.3.1 Primary Endpoint

The primary endpoint is:

Immunogenicity:

- Seropositivity rate as determined by NT from approximately 3 years (38 months) to 10 years (118 months) after the first booster vaccination administered in Study 700401 and after the second booster vaccination administered in this study.

8.3.2 Secondary Endpoints

8.3.2.1 Immunogenicity

- Seropositivity rate as determined by ELISA from approximately 3 years (38 months) to 10 years (118 months) after the first booster vaccination in Study 700401 and after the second booster vaccination in this study;
- Antibody response as determined by ELISA from approximately 3 years (38 months) to 10 years (118 months) after the first booster vaccination in Study 700401 and after the second booster vaccination in this study;
- Antibody response as determined by NT from approximately 3 years (38 months) to 10 years (118 months) after the first booster vaccination in Study 700401 and after the second booster vaccination in this study;
- Fold increase of antibody concentration determined by ELISA after the second booster vaccination as compared to before the second booster vaccination in this study;
- Fold increase of antibody titer determined by NT after the second booster vaccination as compared to before the second booster vaccination in this study.

8.3.2.2 Safety

- Injection site reactions observed in the period from the second booster vaccination until the following blood draw;
- Systemic reactions observed in the period from the second booster vaccination until the following blood draw.

8.4 Randomization and Blinding

This is an un-randomized, open-label clinical study. Subjects will be vaccinated with either FSME-IMMUN 0.25 ml Junior or FSME-IMMUN 0.5 ml according to their age.

8.5 Study Stopping Rules

The study may be prematurely terminated if SAEs or other significant vaccine related side effects occur. In addition, the Sponsor may stop the entire study for any medical reason at any time.

In the event of premature study termination resulting from an AE, clinical and / or laboratory investigations that are beyond the scope of the required study may be performed as part of the evaluation of the event. These investigations will take place under the direction of the Investigator in consultation with the Sponsor, and the details of the outcome will be reported to the appropriate regulatory authorities by the Sponsor.

8.6 Investigational Product(s)

8.6.1 Packaging, Labeling, and Storage

8.6.1.1 Dosage Form for Investigational Products

The dosage form of both FSME-IMMUN 0.25 ml Junior and FSME-IMMUN 0.5 ml is suspension for injection in a pre-filled syringe.

8.6.1.2 Packaging and Labeling

The investigational product will be provided in single-use pre-filled syringes. One single dose of FSME-IMMUN 0.5 ml contains 2.00 – 2.75 µg (target: 2.4 µg) TBE antigen. One single dose of FSME-IMMUN 0.25 ml Junior contains half the adult dose, i.e. 1.00-1.38 µg (target 1.2 µg) TBE antigen. After shaking, the vaccine is an off-white, opalescent suspension.

The investigational product will be labeled according to the valid regulatory requirements

for clinical trials.

8.6.1.3 Storage

The vaccine must be stored under refrigeration at +2°C to +8°C, with a minimum-maximum thermometer).The vaccine must be protected from light. Deep freezing and storage at higher temperatures should be avoided because of potential impairment of immunogenicity and tolerability.

In order to guarantee proper storage conditions, the temperature shall be checked and documented daily on forms provided by the Sponsor.

FSME-IMMUN 0.5 ml and FSME-IMMUN 0.25 ml Junior pre-filled in “readyject” type syringes (with integrated needle) have a shelf-life of 30 months, and for FSME-IMMUN Junior “Tip Cap” the shelf-life is 30 months from the date of manufacture. The vaccine must not be used after the expiry date indicated on the package.

The Investigator should inform the monitor about any temperature deviations on a regular basis. In case of accidental freezing of the vaccine, the Sponsor must be contacted immediately for further follow-up decision.

8.6.2 Administration

8.6.2.1 Route of administration

The vaccine should be given by intramuscular injection into the right or left upper arm (deltoid muscle).

8.6.2.2 Vaccine preparation

Before vaccine administration:

- the syringe should reach room temperature before administration of the vaccine;
- the syringe should be shaken for five to ten seconds;
- the syringe should be checked visually for foreign particulate matter and / or variation in physical appearance before administration of the vaccine. Syringes found to contain particulate matter, to be discolored or to leak may not be used.

8.6.2.3 Vaccine administration

Before vaccine administration:

- "Readyject" type syringe (with integrated needle): detach the needle guard;
- Tip cap syringe: remove the tip-cap and attach the needle provided by the Sponsor to the syringe.
- the injection site should be prepared according to standard clinical procedures;
- the vaccine should be given by intramuscular injection into the right or left upper arm (deltoid muscle);
- under no circumstances should FSME-IMMUN be administered intravascularly, as this could lead to hypersensitivity reactions such as shock.
- for further information please refer to the Pharmacy Manual provided in the Investigator File.

Each subject will receive one vaccination according to his / her age as described in Section 10.3.2.2 of Study Procedures.

Anaphylactic reactions to vaccines, including TBE vaccines, are very rare, but can occur. Therefore, appropriate emergency equipment and medication must be at hand whenever an immunization is performed.

8.6.3 Description of Treatment

A second booster vaccination will be administered with either FSME-IMMUN 0.25 ml Junior or FSME-IMMUN 0.5 ml according to the subject's age. Timing of the vaccination will depend on the level of serum TBE antibodies detected at the defined assessment time points. Subjects who may not be protected against TBE for an entire further tick season as confirmed by relatively low TBE serum antibody levels evaluated at yearly intervals from approximately 3 years (38 months) to 10 years (118 months) after the first booster (NT titer ≤20 and / or ELISA value ≤ 126 VIE U/ml) will be invited to receive the second booster vaccination at either the 40, 48, 60, 72, 84, 96, 108, or 120 month time point.

8.6.4 Investigational Product Accountability

The Investigator will ensure that IP is stored as specified in the protocol and that the storage area is secured, with access limited to authorized study personnel, as described in the Clinical Study Agreement. The Investigator will maintain records that the IP was

received, including the date received, drug identity code, date of manufacture or expiration date, amount received and disposition. IP must be dispensed only at the institution specified for each study site. Records will be maintained that include the subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP will be returned to the Sponsor or Sponsor's representative after study completion/termination, or destroyed with the permission of the Sponsor in accordance with applicable laws and study site procedures, as described in the Clinical Study Agreement. If IP(s) is to be destroyed, the Investigator will provide documentation in accordance with Sponsor's specifications.

8.7 Data Recorded Directly on Case Report Forms

The Sponsor will provide a list of data, if any, that are to be entered directly into the CRF, and are therefore considered source data.

9. SUBJECT SELECTION, WITHDRAWAL, AND DISCONTINUATION

9.1 Inclusion Criteria

Subjects who participated in Study 700401 and meet ALL of the following criteria are eligible for participation in this study:

- Subject / parent(s)/legal guardian(s) provide(s) written informed consent (according to national law);
- Subject provides written assent to the study according to age and capacity of understanding;
- Subject received the first booster vaccination with either FSME-IMMUN 0.25 ml Junior or FSME-IMMUN 0.5 ml during the course of Study 700401;
- Blood was drawn after the first booster vaccination in Study 700401;
- Subject / parent(s) / legal guardian(s) understand(s) the nature of the study and is/are willing to comply with the requirements of the protocol (e.g. return for follow-up visits, completion of the Subject Diary).

9.2 Exclusion Criteria

Subjects who participated in Study 700401 and meet ANY of the following criteria are not eligible for participation in this study:

- Subject received any TBE vaccination since his/her first booster vaccination in Study 700401;
- Subject has a history of infection with or vaccination against other flaviviruses (e.g., Dengue fever, yellow fever, Japanese B encephalitis) since his / her first booster vaccination in Study 700401;
- Subject is known to be HIV positive (a special HIV test is not required for the purpose of the study) since his/her first booster vaccination in Study 700401;
- Subject received a blood product or immunoglobulins within 90 days before any blood draw or in the period between the blood draw and the booster vaccination (as applicable);
- Subject has a known or suspected problem with drug or alcohol abuse (> 4 liters of wine/week or equivalent level of other alcoholic beverages);
- Subject / parent(s) / legal guardian(s) is / are in a dependent relationship with the study investigator or with a study team member. Dependent relationship includes close relatives (i.e., children or grandchildren, partner / spouse, siblings) as well as employees of the Investigator or the site conducting the study.

9.3 Eligibility criteria for booster vaccination

Subjects who meet ANY of the following criteria are not eligible for the booster vaccination:

- Subject is not clinically healthy (i.e., the physician would have reservations vaccinating with a TBE vaccine outside the scope of a clinical trial);
- Subject is suffering from a disease (e.g., autoimmune disease) or is undergoing a form of treatment (e.g., systemic corticosteroids) that can be expected to influence immunological functions;
- Subject has developed severe allergic reactions, in particular a sensitivity or allergy to any component of the vaccine, since the first booster vaccination in Study 700401;
- If female - subject is pregnant or lactating;
- Subject has participated in another clinical study involving an IP or medical device within 30 days prior to the planned booster vaccination or is scheduled to participate in another clinical study involving an IP or medical device.
- Females capable of bearing children if they do not agree to employ adequate birth control measures from 4 weeks before the booster vaccination until the end of the study.

9.4 Delay criteria

Vaccination will be delayed if one of the following applies:

- Subject has an acute illness with or without elevated body temperature (≥ 37.5°C) within 3 days prior to the scheduled booster vaccination. The subject may be vaccinated at a repeat visit provided that the illness has resolved (body temperature < 37.5°C);
- Subject has received any live vaccine within 4 weeks or any inactivated vaccine within 2 weeks prior to the scheduled booster vaccination. Vaccination may be performed when an interval of 4 or 2 weeks, respectively, has passed;
- Subject has received antipyretics within 4 hours prior to the scheduled time of vaccination. Vaccination may be performed at a later date;
- Subject was bitten by a tick within 4 weeks prior to the scheduled booster vaccination. Vaccination shall be postponed until an interval of 4 weeks has passed;

- Subject has donated blood, blood fractions or plasma within 30 days of the scheduled booster vaccination. Vaccination shall be postponed until an interval of 30 days has passed.

9.5 Withdrawal and Discontinuation

Any subject may voluntarily withdraw (i.e., reduce the degree of participation in the study) consent for continued participation and data collection at any time during the study. The reason for withdrawal will be recorded on the Completion / Termination CRF. The data collected on withdrawn subjects will be used in the analysis and included in the clinical study report.

Discontinuation (i.e., complete withdrawal from study participation) may be due to dropout (i.e., active discontinuation by subject) or loss to follow-up (i.e. discontinuation by subject without notice or action). Additionally, the Investigator and Sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject.

Subjects also will be withdrawn from treatment or discontinued from further study participation for the following reasons:

- The subject becomes pregnant. IP exposure will be discontinued. Attempts will be made to follow her through completion of the pregnancy. The Investigator will record a narrative description of the course of the pregnancy and its outcome;
- The subject begins lactating. IP exposure will be discontinued. The Investigator will record a narrative description of the course of the baby's development;
- Participation in another investigational drug or medical device study within 30 days prior to the planned booster vaccination or is scheduled to participate in another clinical study involving an IP or medical device.

The Investigator should provide the Sponsor with a written account of any reasons for early withdrawal. The Investigator will attempt to complete all discharge procedures simultaneously to the subject being discontinued from the study.

For all subjects discharged prematurely the Investigator should make an effort to ensure that the subject comes to a final examination visit and complete the study completion page in the CRF (see Section 10.6).

Dropouts and subjects who do not complete the entire study for any reason will not be

replaced.

10. STUDY PROCEDURES

10.1 Informed Consent and Enrollment

Any healthy volunteer who / whose parent(s) / legal guardian(s) provide(s) informed consent (i.e., signs and dates the informed consent form and assent form, if applicable) is considered enrolled in the study.

The Investigator will inform the subject / parent(s) / legal guardian(s) (as applicable) about the procedures, risks and benefits of the study. Fully informed, written assent / consent must be obtained from each subject and / or his / her parent(s) / legal guardian(s) prior to any assessment being performed. It is important that the subject is allowed sufficient time to decide on his / her participation in the study.

10.2 Subject Identification Code

The following series of numbers will comprise the Subject Identification Code (SIC): protocol number (e.g. 700802) to be provided by the Sponsor, 2-digit study site number (e.g., 02) to be provided by the Sponsor, and 4-digit subject number (e.g., 0003) reflecting the order of enrollment (i.e. signing the informed consent form). For example, the third subject who signed an informed consent form at study site 02 will be identified as Subject 700802-020003. All study documents (e.g., CRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC.

In this study, subjects will retain the SICs previously assigned to them in Study 700401 and Study 209.

10.3 Screening and Study Visits

The study site is responsible for maintaining an enrollment log that includes all subjects enrolled.

The overall study design is illustrated in Figure 20.1-1 and Figure 20.1-2 (Supplement 20.1). Details on the procedures to be performed at each study visit can be found in Supplement 20.2, Table 20.2-1, Schedule of Study Procedures and Assessments.

10.3.1 Screening

The screening visit is not applicable for this study.

10.3.2 Study visits

10.3.2.1 Blood draw (investigation of TBE antibody persistence)

Visit 1: 38 months ± 60 days after the booster vaccination in Study 700401[ii].
All subjects who were administered the first booster vaccination in Study 700401 will be invited for this visit. Subjects with relatively low TBE serum antibody levels (as described further) will proceed to Visit 4 (Booster vaccination) and Visit 5 (Post-booster Visit), as applicable (see Figure 20.1-1, Supplement 20.1).

Visit 2: 46 months ± 30 days after the booster vaccination in Study 700401.
This visit will only be applicable for those subjects who have not yet received the second booster vaccination. Subjects with relatively low TBE serum antibody levels will proceed to Visit 4 and Visit 5 (see Figure 20.1-1, Supplement 20.1).

Visit 3: 58 months ± 30 days after the booster vaccination in Study 700401.
This visit will only be applicable for those subjects who have not yet received the second booster vaccination. Subjects with relatively low TBE serum antibody levels will proceed to Visit 4 and Visit 5 (see Figure 20.1-1, Supplement 20.1).

Visit 6: 70 months ± 30 days after the booster vaccination in Study 700401.

Visit 7: 82 months ± 30 days after the booster vaccination in Study 700401.

Visit 8: 94 months ± 30 days after the booster vaccination in Study 700401.

Visit 9: 106 months ± 30 days after the booster vaccination in Study 700401.

Visit 10: 118 months ± 30 days after the booster vaccination in Study 700401.

These additional blood draw visits are only applicable for subjects who have not yet received the second booster vaccination. Subjects with relatively low TBE serum antibody levels will proceed to Visit 4 and Visit 5 (see Figure 20.1-2, Supplement 20.1).

[ii] The 29 subjects who were administered the first booster vaccination at the 4 year time point in Study 700401 and who will enter the current study in 2010 will have their Visit 1 at 34 months ± 60 days. For Visit 2 and Visit 3 the schedule is to be followed as described in the protocol.

The following assessments will be performed:

- Verification of the signed and dated informed consent/assent of the subject prior to any procedures being done (at Visit 1 ONLY);
- Inclusion and exclusion criteria (see Section 9.1 and Section 9.2);
- Demographic data (at Visit 1 ONLY);
- Medical history with particular focus on significant medical events (e.g., events fulfilling SAE criteria) experienced in the time period from the last study visit in Study 700401 until Visit 1 in this study, and between each blood draw visit, as applicable;
- History of tick-bites (either since the last visit in Study 700401 or since the last blood draw visit in this study, as applicable);
- Vital signs (weight and height);
- Physical examination;
- Blood draw of 5 ml for determination of TBE virus antibodies by ELISA and NT;
- Recording of any AEs in association with study procedures (e.g. blood draw) on the appropriate CRF page.

Serum TBE virus antibody levels measured by ELISA and NT at yearly intervals from approximately 3 years (38 months) to 10 years (118 months) after the first booster vaccination will be communicated to the centers as soon as they are available and will serve as a basis for determining whether to administer the booster. Subjects with relatively low TBE serum antibody levels (NT titer ≤20 and / or ELISA value ≤ 126 VIEU/ml) at the 40, 48, 60, 72, 84, 96, 108, or 120 month time point may not be considered protected against TBE for an entire further tick season. Recommendations will be given by the Sponsor on an individual basis. The Data Monitoring Committee (DMC) will be consulted for their opinion in case of inconclusive serological data (e.g., contradictory results in ELISA and NT).

10.3.2.2 Booster Vaccination Visit

Visit 4: (40 months ± 60 days, or 48, 60, 72, 84, 96, 108, or 120 months ± 30 days after the booster vaccination in Study 700401, as applicable (see Figure 20.1-1 and Figure 20.1-2, Supplement 20.1[iii]).

A booster vaccination will be administered to subjects who may not be protected against TBE for an entire further tick season, as determined by antibody levels detected at each blood draw (NT titer ≤ 20 and / or ELISA value ≤ 126 VIEU/ml).

For subjects who do not receive their second TBE booster vaccination during the entire course of this study due to sufficiently high TBE virus antibody levels, a booster vaccination will be offered free of charge at an appropriate time point outside the scope of this clinical study.

10.3.2.2.1 Before the booster vaccination

The following assessments will be performed:

- Review of inclusion and exclusion criteria (see Section 9.1 and Section 9.2);
- History of tick bites since last blood draw visit, as applicable;
- Medical History since last blood draw visit, as applicable;
- Vital signs (body temperature measured orally, pulse rate and blood pressure measured when subjects are in the sitting position);
- Physical examination;
- Females will be asked if first menstruation occurred since the last blood draw visit, as applicable. If menarche occurred, it shall be documented in the medical history and CRF;
- Pregnancy test (urine) in females capable of bearing children;
- Eligibility criteria for the booster vaccination (see Section 9.3);
- Delay criteria for the booster vaccination (see Section 9.4);

[iii] For subjects who received their first booster in Study 700401 at 3 years after the third vaccination and were considered as not protected against TBE after Visit 1 in this study, Visit 4 will be performed at 40 months ± 60 days. If a subject who was administered the first booster vaccination at the 4 year time point in Study 700401 is considered as not protected against TBE after Visit 1 in this study, he/she will proceed to the Booster Visit (Visit 4) at 36 months ± 60 days.

10.3.2.2.2 Booster vaccination

BEFORE ADMINISTRATION: WARM SYRINGE TO ROOM TEMPERATURE AND SHAKE SYRINGE VIGOROUSLY FOR FIVE TO TEN SECONDS.

The study site must have appropriate equipment and adequately trained personnel available to respond to anaphylaxis or other possibly severe acute, post-immunization adverse reactions to vaccines.

The vaccine will be given by intramuscular injection into the right or left upper arm (deltoid muscle).

Subjects will be administered either FSME-IMMUN 0.25 ml Junior or FSME-IMMUN 0.5 ml according to their age: FSME-IMMUN 0.25 ml Junior will be administered to children and adolescents up to 16 years of age and FSME-IMMUN 0.5 ml to subjects aged 16 years and older.

10.3.2.2.3 Post vaccination observations

Following vaccination, the subjects will be observed for at least 30 minutes in order to provide appropriate emergency treatment should this be necessary. After the 30 minute observation period, the pulse will be taken. Any injection site reactions and systemic AEs will also be recorded.

The subject / subject's parent(s) / legal guardian(s) will receive a Subject Diary for documentation of AEs for a total period of 4 days (including the day of vaccination) after the booster vaccination. The Investigator must provide sufficient instructions to the subject / parents / legal guardians on how to document AEs. The entries in the Subject Diary will be evaluated and graded for severity and relatedness by the Investigator at the subject's next visit to the study site. These data will then be entered in the CRFs. The Subject Diaries are part of the source data.

For further details refer to Section 10.5, Subject Diary.

10.3.2.3 Post-Booster Visit

Visit 5: 21 – 35 days after Visit 4

The following activities will be performed:

- Vital signs (pulse rate and blood pressure measured when subjects are in the sitting position);
- Physical examination;
- Collect and review the Subject Diary. The Investigator will ask whether any other observations or abnormalities not recorded in the Subject Diary were observed since Visit 4. The Investigator will document the observations recorded in the Subject Diary on the appropriate CRF page;
- Recording of any AEs since Visit 4 on the appropriate CRF page;
- Blood draw of 5 ml for determination of TBE virus antibodies by ELISA and NT;
- Complete Study Termination form.

10.3.3 Unscheduled Visit

An unscheduled visit can be held at any time after the booster vaccination if deemed necessary by the Investigator (e.g. follow-up on unexpected AEs or SAEs). Assessments performed at an unscheduled visit will be at the Investigator's discretion. In case of an unscheduled visit, the Investigator should complete the "Unscheduled Visit Form" in the CRF.

10.4 Medications and Non-Drug Therapies

The following medications are **not** permitted:

- any blood products or immunoglobulins - within 90 days before each blood draw, in the period between the blood draw and the second booster vaccination, and from the second booster vaccination until the Post-booster Visit;
- any treatment that can be expected to influence immunological functions (e.g., systemic corticosteroids) – within 30 days prior to the second booster vaccination until the Post-booster Visit.

  A subject who has taken any of these medications within the time frames specified above before administration of the second booster vaccination will be excluded / discontinued from this study. Administration of these medications between the second booster vaccination and the Post-booster Visit will be considered a protocol deviation;
- any live or inactivated vaccine given within 4 weeks or 2 weeks, respectively, before the second booster vaccination, until the Post-booster Visit.

  Any vaccination (except if given in medical emergencies such as tetanus or rabies infection) will be considered a protocol deviation.

The following medications and procedures will **delay** the booster vaccination:

- antipyretics received within 4 hours prior to the scheduled time of vaccination
- any live or inactivated vaccine received within 4 or 2 weeks before the booster vaccination, respectively.
- donation of blood, blood fractions or plasma within 30 days prior to the scheduled booster vaccination. Subjects are further requested to refrain from donation of blood, blood fractions and plasma until the Post-booster Visit (Visit 5).

For further details on Delay Criteria refer to Section 9.4.

Usage of any other medications or non-drug therapies is not restricted.

10.5 Subject Diary

The subject or subject's parent(s)/legal guardian(s) will receive a Subject Diary for documentation of AEs for a total period of four days (including the day of vaccination) after each vaccination. The Investigator must provide sufficient instructions to the subject and/or parent(s) / legal guardian(s) on how to document AEs.

The Subject Diary will be provided at Visit 4 (after the booster vaccination) to record the following information:

- Measurement of body temperature (orally, once every evening from vaccination until Day 3 after vaccination);
- Injection site reactions (swelling, induration, redness, injection site pain and tenderness, ecchymosis and hematoma);
- Systemic symptoms such as headache, nausea, vomiting, muscle pain, joint pain, swelling of the lymph nodes, malaise and fatigue;
- Other adverse events occurring after the booster vaccination;
- Any medication taken after vaccination (including antipyretics, vitamins and minerals for therapeutic use).

The Subject Diaries will be returned to the Investigator at the visit following vaccination.

The Subject Diary will serve as source documentation. Entries in the subject diaries will be transcribed onto the appropriate CRFs. Any entry on the CRF that does not correspond with an entry in the Subject Diary will be explained by the Investigator on the relevant Subject Diary page. The entries in the Subject Diary shall be verified and in case they constitute an AE shall be graded for severity and relatedness by the Investigator.

10.6 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, followed the protocol. Reasons for completion/discontinuation will be reported on the Completion/Termination CRF, including: completed, discontinuation due to an AE, discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], active discontinuation by subject, e.g., dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), study terminated by Sponsor, or other (reason to be specified by the Investigator, e.g., technical problems). Additional reasons may include failure to complete all baseline assessments, or subject / subject's legally acceptable representative requests withdrawal from participation in the study (i.e., active discontinuation). Regardless of the reason, all data available for the subject up to the time of completion/discontinuation should be recorded on the appropriate CRF.

Every effort will be made to have discontinued subjects complete the study completion / termination visit. The reason for discontinuation will be recorded on the CRF, and data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report.

In the event of subject discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the Investigator in consultation with the Sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the Sponsor.

10.7 Procedures for Monitoring Subject Compliance

Apart from filling in the Subject Diary, all study procedures are to be performed under the direct supervision of the Investigator/a licensed healthcare professional at the study site, and thus, no separate procedures will be used to monitor subject compliance.

11. ASSESSMENT OF IMMUNOGENICITY

11.1 Assessment of Immune Response

All samples will be handled according to the instructions for the preparation, storage and shipment of samples provided in the Investigator File.

Blood samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the subject's identity. Some of the samples may be stored by Pfizer for additional testing. The samples will not be used for any unrelated research, and no genetic testing will be performed. The samples will be stored for up to 15 years after the end of the study and then destroyed.

The subject or his / her parent(s) or legal guardian(s) may request that his/her/child's samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained.

TBE antibody response will be determined by means of ELISA using IMMUNOZYM FSME IgG test kit, Progen, Heidelberg, Germany, as well as by means of NT (according to *Adner et al., 2001*).[1]

The tests will be performed at the following laboratories:

- IMMUNOZYM FSME ELISA: [redacted], Austria;
- NT (according to *Adner et al., 2001*) [1]: [redacted] Austria.

In the ELISA IMMUNOZYM kit and the NT assay TBE virus antigen derived from strain Neudoerfl is used. ELISA values > 126 VIE U/ml obtained by the IMMUNOZYM ELISA will be considered positive.[38] NT titers ≥ 10 will be considered positive. At the end of the study, results of immunogenicity assessments will be provided to the Investigator for communication to the subjects.

12. ASSESSMENT OF SAFETY

12.1 Vaccine-Specific Safety Parameters Assessed

12.1.1 Body Temperature

To optimize the comparability of the documented body temperatures, all parent(s) / legal guardian(s) will be provided with a digital thermometer.

Body temperature should be measured once every evening from the day of vaccination until Day 3 after vaccination. If fever occurs, body temperature should be measured every 4 to 8 hours until it returns to normal. All values of temperature measurements should be documented in the Subject Diary including date and time. If fever occurs, all measurements, including the first value showing a return to normal body temperature, should be recorded in the Subject Diary.

All values of body temperature measurement from the day of vaccination until Day 3 after vaccination will be recorded by the Investigator in the CRF. If more than 1 body temperature value is recorded for a given day, the highest body temperature value will be documented by the Investigator on the appropriate CRF page.

Severity grading of fever will be performed according to the Common Toxicity Criteria manual (CTC, Version 3.0, December 12, 2003) [39], as follows:

mild:	38.0 - 39.0 °C
moderate:	>39.0 - 40.0 °C
severe:	> 40.0 °C

No prophylactic administration of antipyretic medications is envisaged in this study. However, upon consultation with the Investigator, the parents / legal guardian may give an appropriate antipyretic if necessary.

The digital thermometers provided by the Sponsor may be kept by the subjects after study termination.

12.1.2 Injection Site Reactions

The subject or his / her parent(s) or legal guardian(s) will be properly instructed and asked to monitor, measure and document injection site reactions occurring after the booster vaccination for a period of four days (including the day of vaccination). These reactions include swelling, induration, redness, injection site pain and tenderness, ecchymosis and hematoma. Further instructions on how to measure injection site reactions will be detailed in the Subject Diary.

Refer to Table 20.3-1 for Grading of Adverse Events – Vaccine-Specific Criteria.

12.2 Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered IP that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not related to the IP. An AE includes any event, regardless of the presumed causality between the event and the IP. Any subject experiencing an AE will be examined by a physician as soon as possible according to medical requirements. The physician in attendance will do whatever is medically necessary for the safety and well-being of the subject. The subject will remain under observation as long as medically indicated in the opinion of the Investigator. All abnormalities will be followed until resolved or until medically stabilized.

12.2.1 Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to safety within 24 hours of Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a Case Report Form (CRF), however a copy of the completed SAE Report form is maintained in the study master file.

12.2.2 Serious Adverse Event

A serious adverse event (SAE) is defined as an untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including fetal death)
- Is life-threatening – defined as an event in which the subject was, in the judgment of the Investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization – inpatient hospitalization refers to any inpatient admission, regardless of length of stay[iv].
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Results in congenital anomaly / birth defect
- Is a medically important event – a medical event that may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. Examples of such events are:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse
  - Reviewed and confirmed seroconversion for human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), or parvovirus B19 (B19V)

12.2.3 Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

[iv] Hospitalizations and elective surgeries planned prior to study entry are not considered SAEs if they are documented in the patients' medical records.

2. A male subject has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on a Serious Adverse Event (SAE) Report Form and Exposure During Pregnancy (EDP) supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must

document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

12.2.4 Non-Serious Adverse Event

A **non-serious** AE is an AE that does not meet the criteria of an SAE.

12.2.5 Severity

The Investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- **Mild**
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- **Moderate**
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequelae.
- **Severe**
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequelae, which require (prolonged) therapeutic intervention.

12.2.6 Causality

Causality is a determination of whether there is a reasonable possibility that an IP is etiologically related to/associated with the AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. Causality assessment includes, e.g. assessment of temporal relationships, dechallenge / rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the Investigator will assess the causal relationship between the IP and the AE using his/her

clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- **Not related** (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not related to the IP (i.e. does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
- **Unlikely related** (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
- **Possibly related** (both circumstances must be met)[v]
  - Follows a strong temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- **Probably related**[v]
  - Follows a reasonable temporal relationship to the administration of IP, including (any of the circumstances are met):
    - Reappearance of a similar reaction upon re-administration (positive rechallenge)
    - Positive results in a drug sensitivity test (skin test, etc.)
    - Toxic level of the IP as evidenced by measurement of the IP concentrations in the blood or other bodily fluid.

12.2.7 Preexisting Diseases

Preexisting diseases that are present before entry into the study, described in the medical history, and that manifest with the same severity, frequency, or duration after IP exposure, will not be recorded as AEs. However, when there is an increase in the severity or duration of a preexisting disease, the event must be described on the AE or Medical History CRF.

[v] For reporting SAEs on the Serious Adverse Event Report (SAER), the categories of possibly and probably related are to be reported as "related."

12.2.8 Untoward Medical Occurrences Not Considered Adverse Events

Each untoward medical occurrence experienced before the second booster vaccination (e.g. from the time of signed informed consent up to but not including the second booster vaccination) – except for any events associated with the procedures of the current study (e.g. blood draw) - will not be documented, since these events will not be considered as AEs.

12.2.9 Assessment of Adverse Events

Each AE from the second booster vaccination until the blood draw 21 - 35 days after the booster vaccination will be described on the AE CRF (i.e. 1 AE per form) using the medical diagnosis (preferred), symptom, or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions (see definition in Section 12.2). Each AE will be evaluated by the Investigator for:

- Seriousness as defined in Section 12.2.2
- Severity as defined in Section 12.2.5
- Causal relationship to IP exposure as defined in Section 12.2.6

For each AE, the outcome (i.e. recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal) and action taken (i.e. dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn), as well as treatment of AE will also be recorded on the AE CRF. Recovering/resolving AEs will be followed until the AE has resolved or the study completion form is completed for the subject, whichever occurs first. Any AE(s) being followed after the subject's last visit in the study (21 – 35 days after the booster vaccination) does not extend the subject's study completion date.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

12.2.10 Sponsor Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

12.3 Medical, Medication, and Non-Drug Therapy History

12.3.1 Medical history

At Visit 1, the subject's medical history will be documented including significant medical events (e.g., events fulfilling SAE criteria) experienced since the last study visit in Study 700401. Medical history will be reviewed / updated at each blood draw visit and at the booster vaccination visit (Visit 4) with regard to significant medical events.

12.3.2 Medication and Non-Drug Therapy

All medications, including non-steroidal antirheumatic drugs, vitamins and minerals for therapeutic use, taken for up to 2 weeks prior to the booster vaccination until the blood draw 21 – 35 days after the booster will be documented in the subject's clinic / hospital and study records using the guidelines set forth by the Sponsor.

The following concomitant medication will be documented in the CRF:

- medication to treat fever or pain after vaccination;
- medication possibly interfering with the immune response (e.g., systemic corticosteroids);
- medication to treat SAEs;

including product name (generic name), total daily dose as well as start and end date of treatment.

Medication to treat SAEs will also be reported to the Sponsor on SAE reports as described in Section 12.2.9.

Any vaccinations given during the entire study period must be documented in the CRF.

In the context of this study, information on non-drug therapy will only be collected in relation to SAEs.

12.4 Physical Examinations

At enrollment and subsequent study visits (as described in Section 10.3), a physical examination will be performed on the following body systems being described as normal or abnormal: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At the yearly blood draw visits (as described in Section 10.3.2.1) and at the Booster Vaccination Visit (Visit 4) (as described in Section 10.3.2.2), if significant medical events (e.g. events fulfilling SAE criteria) are detected, the condition will be described on the medical history CRF. At the Post-booster Visit (Visit 5), if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE CRF.

12.5 Clinical Laboratory Parameters

Apart from urinary pregnancy testing, no safety laboratory testing will be conducted in this study.

12.5.1 Assessment of Abnormal Laboratory Values

In the event of laboratory tests being required for any reason, the Investigator must assess the clinical significance of all abnormal laboratory values as defined by the compendium of normal values for the reference laboratory. The Investigator's assessment of each abnormal laboratory value is to be recorded in the subject's medical records. For each abnormal laboratory value determined between the second booster vaccination and the Post-booster Visit, the Investigator will assess whether the value is also considered an AE (see definition in Section 12.2). If yes, the sign, symptom, or medical diagnosis (including the abnormal laboratory value) will be recorded on the AE CRF.

12.6 Vital Signs

Vital signs will include height (cm), weight (kg), body temperature (°C), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). Weight and height will be measured at the yearly blood draw visits. Body temperature will be measured at the Booster Vaccination Visit (Visit 4) before administration of the vaccine. Blood pressure and pulse rate will be measured before the booster vaccination at the Booster Vaccination Visit (Visit 4) and at the Post-booster Visit (Visit 5), when subjects are in the sitting position. At the Booster Vaccination Visit (Visits 4) pulse rate will also be measured 30 minutes after administration of IP.

Vital sign values are to be recorded on the physical examination CRF. For each vital sign value, the Investigator will determine whether the value is considered an AE (see definition in Section 12.2). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE CRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the Investigator.

12.7 Responsibilities of the DMC

An independent DMC will be utilized for this study. The DMC will consist of 3 individuals who will be selected based upon their knowledge in clinical medicine and their expertise and understanding of TBE vaccines, clinical research and/or skills. A meeting of the DMC may be called at the discretion of the Sponsor, e.g., to address any safety concerns arising during the conduct of the study.

12.7.1 Responsibilities of the DMC

- Upon Sponsor's request, provides independent monitoring of safety issues, which means it reviews and evaluates all SAE reports and study discontinuations for: (i) increases in frequency of SAEs and study discontinuations within the study; and (ii) increases in frequency of SAEs and study discontinuations across studies with the same preparation; and (iii) SAEs in the study sample compared with the population based on what is known from the literature;
- Reviews data produced from the study upon the Sponsor's request to determine whether the conditions on which study design is based have remained the same or have changed. If changed, the DMC will determine whether or not the changes mandate changes to the protocol and suggest a protocol amendment;
- Upon the Sponsor's request, meets for discussion and gives recommendations to the Sponsor as to whether the study should progress unchanged, or the study requires changes, or the study should be terminated prematurely. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate;
- Can propose an unplanned safety analysis of clinical trial data.

13. STATISTICS

The immunogenicity analysis of the ELISA and NT results obtained 38, 46, 58, 70, 82, 94, 106 and 118 months after the first booster vaccination may be carried out separately as soon as the relevant data become available. A final clinical study report including all data will be prepared after completion of the study.

13.1 Sample Size and Power Calculations

A total of 202 subjects who were administered the first booster vaccination in Study 700401 at 3 or 4 years after the third vaccination in Study 209 will be invited to participate in this study. Of these, approximately 175 study participants are expected to return and to provide information on antibody persistence after the first booster vaccination with either FSME-IMMUN 0.25 ml Junior or FSME-IMMUN 0.5 ml. With this sample size, the 95% confidence interval of the seropositivity rate will extend no more than 5.8% from the observed rate assuming the observed rate lies in the region of 90%.

13.2 Datasets and Analysis Cohorts

Per-protocol dataset: Subjects will be included in the "per protocol" dataset if they

- fulfill inclusion/exclusion criteria
- have no major protocol violations
- have available serology data

Modified intent to treat dataset: Subjects will be included in the modified "intent to treat" analysis if they

- have available serology data

13.3 Handling of Missing, Unused, and Spurious Data

Only subjects with available data will be included in the statistical analysis. Missing values for antibody titer at 38 and 46 months will neither be replaced nor estimated. Any missing values at later time points (i.e. 58, 70, 82, 94, 106 and 118 months) will be estimated if at least three data points are available, assuming an exponential decline in antibody titers in time.

13.4 Methods of Analysis

13.4.1 Primary Endpoint

Point estimates and 95% confidence intervals for the seropositivity rate at each time point when blood is drawn (from approximately 38 months to 118 months after the booster vaccination in Study 700401, and separately after the booster vaccination) in this study as measured by NT (according to *Adner et al., 2001*) [1] will be calculated.

The dependence of seropositivity of study participants on demographic factors (age, weight, gender) at yearly intervals from approximately 3 years (38 months) to 10 years (118 months) after the first booster vaccination will be analyzed by logistic regression at the end of the study period.

13.4.2 Secondary Endpoints

The antibody titers as measured by NT (according to *Adner et al., 2001*) [1] and ELISA at yearly intervals from approximately 3 years (38 months) to 10 years (118 months) after the first booster will be used to determine the annual decline rate.

The analysis of immunogenicity before the second booster vaccination will be carried out separately in the three age classes defined previously in Study 209. Subjects will remain in the same age class as they were assigned to at the beginning of Study 209 (1 - 2 years, 3 – 6 years, 7 – 15 years). For the analysis of immunogenicity and safety after the booster vaccination the oldest age class will be further divided into those who received FSME-IMMUN 0.25 ml Junior and those who received FSME-IMMUN 0.5 ml.

The occurrence of fever and the 95% confidence interval of the probability of occurrence will be given. The fever rate after the second booster vaccination will be categorized by severity grade.

Local and systemic reaction rates, other than fever, after the booster vaccination will be provided in tabular format, and the probabilities of the occurrence of the adverse event rates and their 95% confidence intervals will be calculated.

For each symptom queried in the Subject Diary, the number of subjects who experienced the symptom, as well as the probabilities of the occurrence and the 95% confidence interval will be given.

All AEs reported for each subject, including the same event at different time points, will be listed according to Medical Dictionary for Regulatory Activities (MedDRA) terminology.

13.4.3 Exploratory Endpoints

Not applicable.

[redacted]

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the Sponsor or Sponsor's representatives, review by the EC, and inspections by applicable regulatory authorities, as described in the Clinical Study Agreement. If contacted by an applicable regulatory authority, the Investigator will notify the Sponsor of contact, cooperate with the authority, provide the Sponsor with copies of all documents received from the authority, and allow the Sponsor to comment on any responses, as described in the Clinical Study Agreement.

15. QUALITY CONTROL AND QUALITY ASSURANCE

This study will be conducted in accordance with this protocol, the ICH Guideline for Good Clinical Practice and the European Clinical Trial Directive.

The following quality control and quality assurance measures will be taken to ensure the adherence to GCP and applicable regulatory requirements as well as the accuracy and integrity of data obtained from the study:

[redacted]

- The Sponsor will select investigators on the basis of their expertise in the field of vaccinology and the study site's ability to conduct a research study of this nature, given the subject load of the institution;
- Training for study personnel at the sites as well as for monitors will be provided (for more details please refer to Section 15.2);
- Co-monitoring visits will be performed by the Sponsor (at intervals described in the Monitoring Plan). During co-monitoring visits, the Sponsor will check the CRO's monitoring performance as well as the compliance and working procedures of the study site;
- In order to assure integrity and accuracy of study data, selected study sites will be audited by the Sponsor to review subject files and CRFs for consistency and other documentation for compliance with relevant regulations. Discrepancies will be addressed and appropriate corrective action will be implemented;
- The Sponsor will provide the Investigator with a copy of the insurance liability certificate;
- External service providers will be qualified according to the Sponsor's Standard Operating Procedures (SOPs).

15.1 Investigator's Responsibility

The Investigator will comply with the protocol (which has been approved/given favorable opinion by the EC), ICH GCP, and applicable regulatory requirements as described in the Clinical Study Agreement. The Investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the Sponsor. The term "Investigator" as used in this protocol and in study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the Investigator, except where the Investigator's signature is specifically required.

15.1.1 Investigator Report and Final Clinical Study Report

The Investigator, or coordinating investigator(s) for multicenter studies, will sign the clinical study report. The coordinating investigator will be selected before study start.

A summary report by the Investigator must be submitted to the EC and the Sponsor within 30 days after study completion or termination, where required.

15.2 Training

The study monitor will ensure that the Investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator.

Training for study personnel at the sites as well as for monitors will be provided on the correct handling and use of the CRF. Furthermore, monitors will be trained on the Sponsor's SOPs, as applicable. In addition, investigators will also be trained on GCP and Good Documentation Practice (GDP) relevant issues (e.g., via Investigator Meetings).

Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the Investigator and will serve as the liaison between the study site and the Sponsor.

15.3 Monitoring

The study monitor is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The Investigator will permit the study monitor or other authorized representatives to visit the study site at appropriate intervals to observe the progress of the study, review study records/documentation, and ensure that informed consent has been obtained, as described in the Clinical Study Agreement. Monitoring processes specific to the study will be described in the clinical monitoring plan.

15.4 Auditing

The Sponsor and/or Sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The Investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the study will be described in the auditing plan.

15.5 Non-Compliance with the Protocol

The Investigator may deviate from the protocol to eliminate an apparent immediate hazard to the subject or when the change(s) involve(s) only logistical or administrative

aspects of the study (e.g., change of study monitor, change of phone number). In the event(s) of an apparent immediate hazard to the subject, the Investigator will notify the Sponsor immediately by phone and confirm notification to the Sponsor in writing as soon as possible, but within 5 working days after the change is implemented. The Investigator will also notify the EC of the emergency change.

If monitoring and / or auditing identify serious and / or persistent non-compliance with the protocol, the Sponsor may terminate the Investigator's participation. The Sponsor will notify the EC and applicable regulatory authorities of any investigator termination.

15.6 Laboratory and Reader Standardization

Not applicable, a central laboratory will be used for all immunological assessments.

16. ETHICS

16.1 Subject Privacy

The Investigator will comply with applicable subject privacy regulations/guidance as described in the Clinical Study Agreement.

16.2 Ethics Committee and Regulatory Authorities

Before enrollment of healthy volunteers into this study, the protocol, informed consent form, any promotional material/advertisements (as applicable per local EC and regulatory authorities), and any other written information to be provided will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities. The IB and SmPC will be provided for review. The EC's composition or a statement that the EC's composition meets applicable regulatory criteria will be documented. The study will commence only upon the Sponsor's receipt of approval/favorable opinion from the EC and, if required, upon the Sponsor's notification of applicable regulatory authority(ies) approval, as described in the Clinical Study Agreement.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the EC and applicable regulatory authorities, where applicable. The protocol amendment will only be implemented upon the Sponsor's receipt of approval and, if required, upon the Sponsor's notification of applicable regulatory authority(ies) approval.

16.3 Informed Consent

Investigators will choose healthy volunteers for enrollment considering the study eligibility criteria. The Investigator will exercise no selectivity so that no bias is introduced from this source.

All healthy volunteers and/or their parent(s) / legally authorized representative must sign an informed consent form before entering into the study according to applicable regulatory requirements and ICH GCP. An assent form will be provided and should be signed by healthy volunteers less than 18 years of age. Before use, the informed consent form will be reviewed by the Sponsor and approved by the EC and regulatory authority(ies), where applicable (see Section 16.2). The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable

regulatory requirements. Healthy volunteers and/or their parent(s) / legally authorized representative(s) will be allowed sufficient time to consider participation in the study. By signing the informed consent form, healthy volunteers and/or their parent(s) / legally authorized representative(s) agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The Sponsor will provide to the Investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, that have been approved by the applicable EC and regulatory authorities, where applicable, will be provided by the Investigator to the subjects who consented to participate in the study (see Section 16.3 above).

16.4 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The Investigator will comply with the confidentiality policy as described in the Clinical Study Agreement.

17.2 Study Documents and Case Report Forms

The Investigator will maintain complete and accurate study documentation in a separate file. Documentation may include medical records, records detailing the progress of the study for each subject, signed informed consent forms, drug disposition records, correspondence with the EC and the study monitor / Sponsor, enrollment information, CRFs, SAERs, laboratory reports (if applicable), and data clarifications requested by the Sponsor.

The Investigator will comply with the procedures for data recording and reporting. Any corrections to study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry; the use of correction fluid and erasing are prohibited.

17.2.1 Case Report Forms

The Investigator is responsible for the procurement of data and for the quality of data recorded on the CRFs. CRFs will be provided in paper form.

Since paper format CRFs are provided by the Sponsor, all required study data, including corrections, will be clearly and accurately recorded by authorized study site personnel on the CRFs. CRFs will be completed legibly using indelible ink; the use of correction fluid and erasing are prohibited. The CRFs will remain at the site until they are reviewed by the study monitor or Sponsor's representative. All original CRFs will be collected by the study monitor, and an identical copy of the complete set of CRFs for each subject will remain in the Investigator file at the study site in accordance with the document and data retention policy (see Section 17.2 above).

The handling of data by the Sponsor, including data quality assurance, will comply with regulatory guidelines (e.g. ICH GCP) and the standard operating procedures of the Sponsor. Data management and control processes specific to the study will be described in the data management plan.

17.2.2 Investigator File

The Investigator ensures that all documents pertaining to the study are filed in a separate Investigator file provided by the Sponsor or by authorized representative(s) of the Sponsor. These documents include the clinical protocol as well as any amendments, all documentation, the agreement(s) between the Sponsor and the Investigator, and all other documents related to this study. Also included are all documents regarding the coded assignment to the different treatment schemes, if applicable.

17.3 Document and Data Retention

The Investigator will retain study documentation and data (paper forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the Clinical Study Agreement.

18. FINANCING AND INSURANCE

The Investigator will comply with Investigator financing, Investigator / Sponsor insurance, and subject compensation policies, if applicable, as described in the Clinical Study Agreement.

19. PUBLICATION POLICY

The Investigator will comply with the publication policy as described in the Clinical Study Agreement.

20. SUPPLEMENTS

20.1 Study Flow Chart

Figure 20.1-1
Study Design for Pfizer Clinical Study B9371021 (Formerly Baxter 700802)

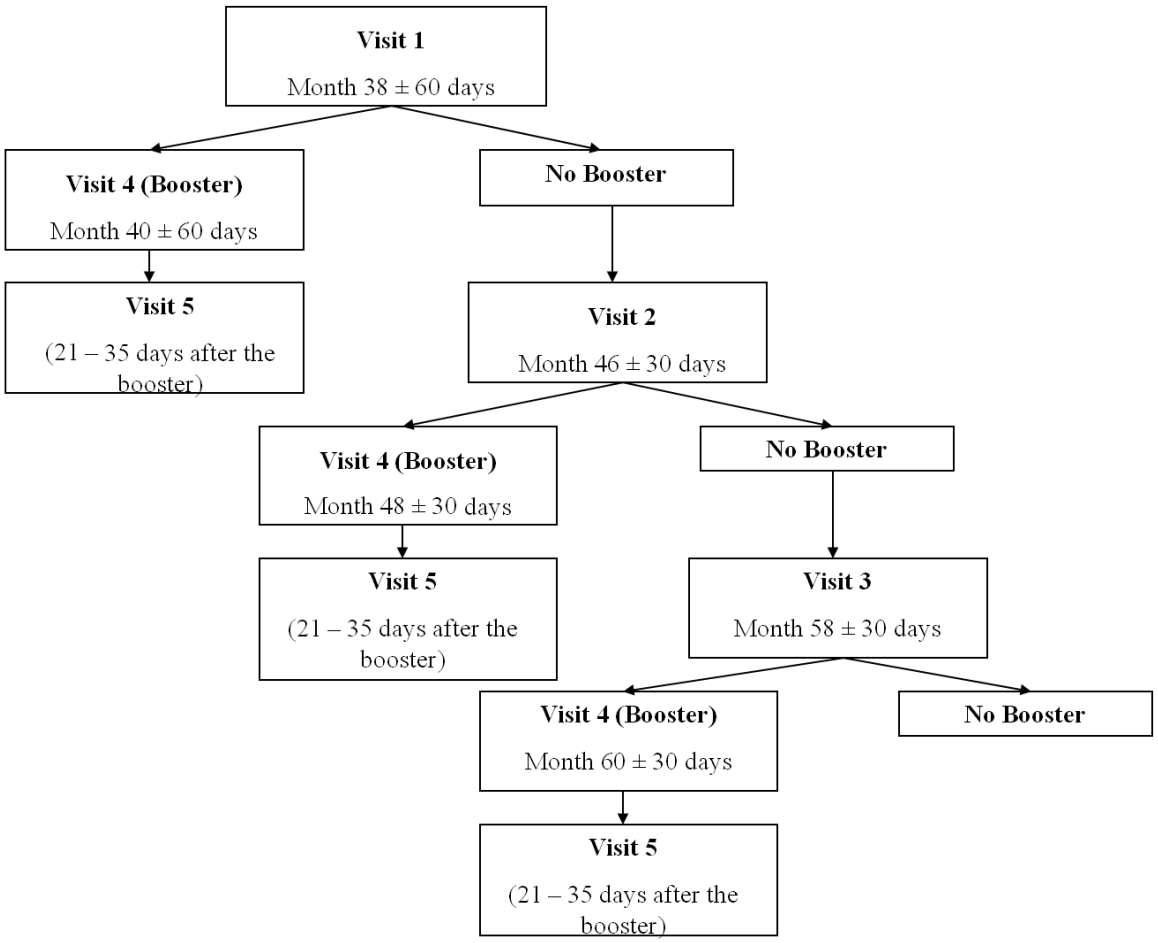
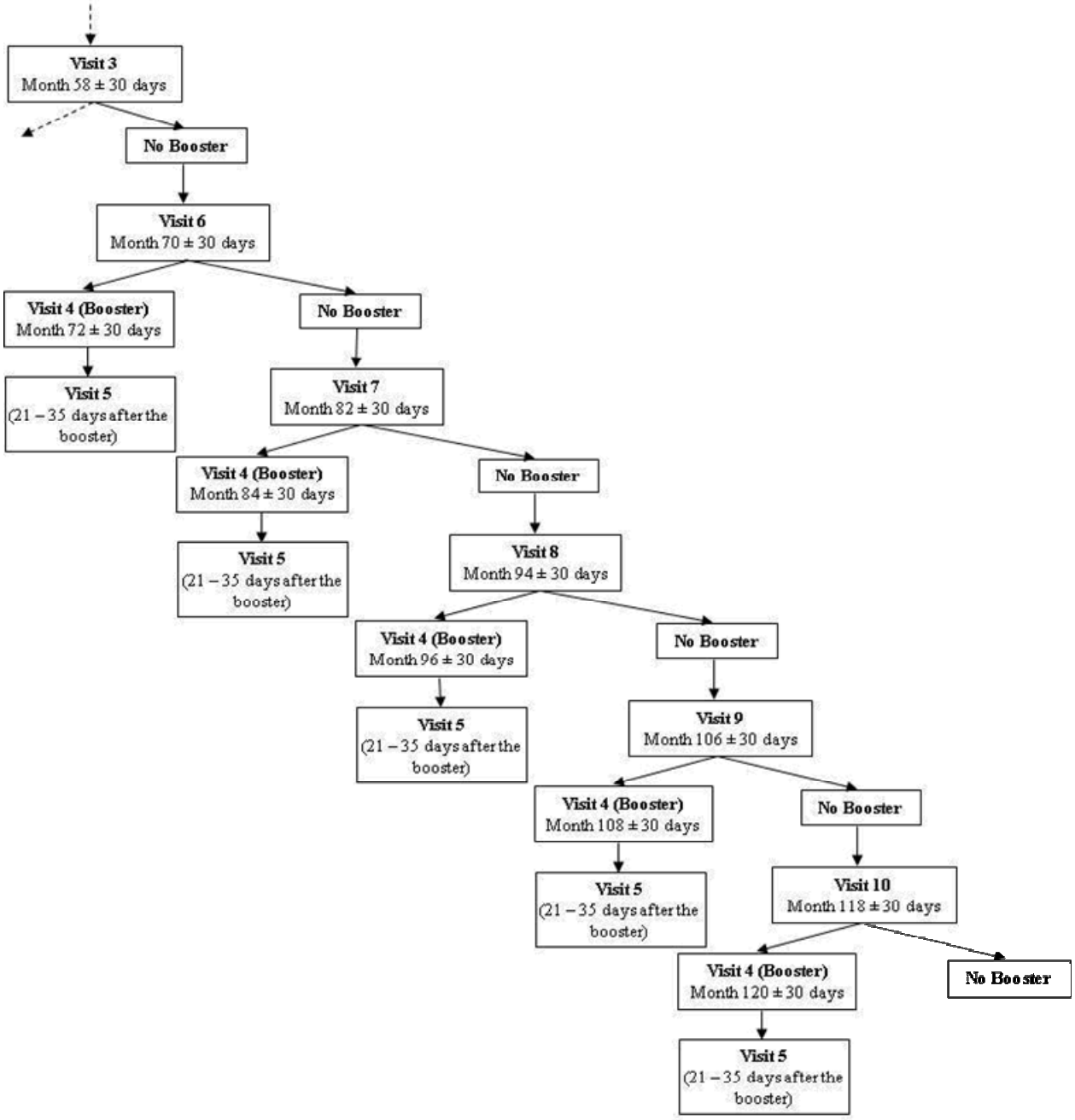


Figure 20.1-2
Study Design for Pfizer Clinical Study B9371021 (Formerly Baxter 700802)



20.2 Schedule of Study Procedures and Assessments

Table 20.2-1
Schedule of Study Procedures and Assessments

Procedure/ Assessment	Visit 1 [a] Month 38 (±60 days)	Visit 2 [b] Month 46 (± 30 days)	Visit 3 [b] Month 58 (± 30 days)	Visit 4 Month 40 (± 60 days) [c] or Month 48 (± 30 days) or Month 60 (± 30 days)	Visit 5 21-35 days after Visit 4
Informed consent	X				
Inclusion/exclusion criteria	X	X (review)	X (review)	X (review)	
Demographic data	X				
Medical history [e]	X	X	X	X	
History of tick bites	X	X	X	X	
Vital signs including:					
Weight	X	X	X		
Height	X	X	X		
Body temperature				X	
Pulse				X	X
Blood pressure				X	X
Physical examination	X	X	X	X	X
Pregnancy test [f]				X	
Blood draw 5 ml	X	X	X		X
Eligibility for vaccination				X	
Delay criteria for vaccination				X	
Vaccination [d]				X	
Subject Diary				Distribute	Collect / Review
AE Assessment	X [g]	X [g]	X [g]	X [h]	X

Table 20.2-1
Schedule of Study Procedures and Assessments

Procedure/ Assessment	Visit 6 [b] Month 70 (± 30 days)	Visit 7 [b] Month 82 (± 30 days)	Visit 8 [b] Month 94 (± 30 days)	Visit 9 [b] Month 106 (± 30 days)	Visit 10 [b] Month 118 (± 30 days)	Visit 4 Month 72, 84, 96, 108 or 120 (± 30 days)	Visit 5 21-35 days after Visit 4
Informed consent							
Inclusion/exclusion criteria	X (review)	X (review)	X (review)	X (review)	X (review)	X (review)	
Demographic data							
Medical history [e]	X	X	X	X	X	X	
History of tick bites	X	X	X	X	X	X	
Vital signs including:							
Weight	X	X	X	X	X		
Height	X	X	X	X	X		
Body temperature						X	
Pulse						X	X
Blood pressure						X	X
Physical examination	X	X	X	X	X	X	X
Pregnancy test [f]						X	
Blood draw 5 ml	X	X	X	X	X		X
Eligibility for vaccination						X	
Delay criteria for vaccination						X	
Vaccination [d]						X	
Subject Diary						Distribute	Collect / Review
AE Assessment	X [g]	X [g]	X [g]	X [g]	X [g]	X [h]	X

Table 20.2-1
Schedule of Study Procedures and Assessments

[a] All subjects who were administered the first booster vaccination in Study 700401 will be invited for this visit.
[b] Visit 2 and Visit 3, and Visit 6 to Visit 10 are applicable for those subjects who did not yet receive the second booster vaccination.
[c] For subjects who received their first booster in Study 700401 at 3 years after the third vaccination and were considered as not protected against TBE after Visit 1 in this study, Visit 4 will be performed at 40 months ± 60 days. If a subject who was administered the first booster vaccination at the 4 year time point in Study 700401 is considered as not protected against TBE after Visit 1 in this study, he/she will proceed to the Booster Visit (Visit 4) at 36 months ± 60 days.
[d] Timing of the booster vaccine will depend on individual TBE antibody levels. Subjects with relatively low TBE serum antibody levels at the preceding visit (NT titer ≤20 and / or ELISA value ≤ 126 VIE U/ml) may not be considered protected against TBE for an entire further tick season and should therefore be scheduled to receive the booster vaccination .
[e] Medical history with particular focus on significant medical events (e.g. events fulfilling SAE criteria) experienced in the time period from the last study visit in Study 700401 until Visit 1 in this study, between the yearly blood draw visits, or between the blood draw visit and the Booster Vaccination Visit (Visit 4), as applicable.
[f] Pregnancy test (urine) will be done in all female subjects capable of bearing children (documentation of first menstruation in medical history).
[g] AE documentation only in association with study procedures.
[h] Any injection site reactions and systemic AEs will be recorded.

20.3 Grading of Adverse Experiences – Vaccine Specific Criteria

Table 20.3-1
Grading of Adverse Events – Vaccine Specific Criteria

	Expedited Report <u>not mandatory</u>			**EXPEDITED REPORT MANDATORY**
	Non-Serious			Serious
Vaccine-specific Criteria	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	
Fever *	≥ 38.0 – 39.0 °C	> 39.0 – 40.0 °C	> 40.0 °C	persistent fever > 40.0 °C over 5 days
Redness, induration or swelling (diameter):	1.0 – 2.5 cm	> 2.5 - 5.0 cm	> 5.0 cm ulceration or superinfection or phlebitis	skin necrosis
Pain or tension	mild, no impairment of arm movement	moderate, impairment of arm movement	severe impairment, arm not functioning	

*as defined in the Common Toxicity Criteria (CTC), Version 3.0, published on December 12, 2003.[39]

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Ref Type: Art Work

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FSME-IMMUN 0.25 ml Junior and

FSME-IMMUN 0.5 ml

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)

PROTOCOL NUMBER: B9371021 (Formerly Baxter 700802)

AMENDMENT 4: 25 JUN 2015 (including non-substantial changes upon sponsorship change)

Replaces Amendment 3: 07 SEP 2011

EUDRACT NUMBER: 2009-009324-36

By signing below, the investigator acknowledges that he/she has read and understands this protocol, and will comply with the requirements for obtaining informed consent from all study subjects prior to initiating any protocol-specific procedures, obtaining written initial and ongoing EC(s) protocol review and approval, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Signature of Principal Investigator Date

Print Name of Principal Investigator Date