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Division / Office	DVRPA/OVRR
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Priority Review	Yes
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Review Completion Date / Stamped Date	
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Applicant	Pfizer Inc.
Established Name	Tick Borne Encephalitis Vaccine (Whole Virus, Inactivated)
(Proposed) Trade Name	Tico Vac
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Each 0.5 mL contains sucrose gradient purified TBE virus antigen (2.4 mg target), 0.35 mg aluminum hydroxide, buffer system containing human serum albumin (HSA, 0.5 mg)
Dosage Form(s) and Route(s) of Administration	Suspension for injection in a 0.25 mL or 0.5 mL single-dose pre-filled syringe
Dosing Regimen	Three doses
Indication(s) and Intended Population(s)	For active immunization to prevent tick-borne encephalitis (TBE) in individuals 1 year of age and older

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## 1. Executive Summary

### 1.1 Introduction

Pfizer, the applicant, submitted the original Biologics License Application (BLA) STN 125740/0 for the Tick-Borne Encephalitis Vaccine FSME-IMMUN on December 15, 2020. The proposed indication for the vaccine is prevention of tick-borne encephalitis (TBE) in individuals 1 year of age and older. Priority review designation was granted for this application.

As of June 2020, FSME-IMMUN has received marketing authorization in 32 countries worldwide and is currently marketed in 28 countries for the 0.5 mL presentation for individuals 16 years of age and older and in 27 countries for the 0.25 mL presentation for individuals 1 through 15 years of age.

The clinical development program for FSME-IMMUN is comprised of 24 completed trials: twelve studies were in adult populations ( $\geq 16$  years of age) and thirteen studies were in pediatric population (one study, B9371038, included both adult and pediatric populations; Tables 1 and 2). The data presented in this submission support the three-dose regimen in both adult and pediatric populations. The antibody persistence results after an initial vaccination series of FSME-IMMUN suggest the timing of the primary booster vaccination; the immune response and antibody persistence after a booster vaccination of FSME-IMMUN were also presented.

### 1.2 Summary Results

Regarding evidence of effectiveness of FSME-IMMUN, since randomized controlled efficacy trials are not available, the review team agrees that licensure of this product would be based on demonstration of an acceptable safety profile and immunogenicity data from available clinical trials, supported by real world effectiveness data. This statistical review focuses on the largest trials: Studies 208/213 and 209. Study 208 evaluated the safety and lot consistency of two vaccinations of FSME-IMMUN 0.5 mL in terms of fever rate with another non-US licensed TBE vaccine, ENCEPUR, serving as the control in healthy subjects aged 16 to 65 years. All subjects continuing into follow-up Study 213 received the third vaccination with FSME-IMMUN 6 months  $\pm$ 28 days after their first vaccination. Study 208 demonstrated that after the first vaccination, the fever rate after administration of FSME-IMMUN (0.8%) was lower than the fever rate after ENCEPUR (5.6%). In addition, all five lots of FSME-IMMUN were shown to be consistent with respect to fever rates. Study 213 showed high seroconversion rates (determined by ELISA and neutralization test (NT)) after the third vaccination among subjects who received FSME-IMMUN and ENCEPUR for the previous two vaccinations (98.8% for FSME-IMMUN only subjects; 98.6% for ENCEPUR + FSME-IMMUN subjects). In Study 209, the immunogenicity of five consecutive lots of FSME-IMMUN 0.25 mL was investigated in healthy children aged 1 to <16 years, although lot consistency equivalence margin was not pre-specified. After the second vaccination, seropositivity rates were similar across five lots, ranging from 92.5% to 97.4%. A total of 362 subjects were included in the immunogenicity analysis after the third vaccination. All

of them were seropositive. With respect to safety, Study 209 demonstrated that frequency of fever was higher among subjects 1 to 2 years of age than in the older age groups after each of the 3 doses administered. In all 3 age groups, fever rates were higher after Dose 1 than after Dose 2 or Dose 3.

### 1.3 Major Statistical Issues and Conclusions

There are no major statistical issues identified.

### 1.4 Conclusion/Recommendation

The immunogenicity data demonstrates high immune responses to the TBE vaccine among adult and pediatric populations. The safety profile of FSME-IMMUN is characterized mainly by local and systemic reactions that are commonly observed after vaccinations, and appears to be acceptable. Overall, from the statistical perspective, the submitted clinical study results support the approval of this application.

## 2. CLINICAL AND REGULATORY BACKGROUND

FSME-IMMUN, the inactivated tick-borne encephalitis virus vaccine developed by IMMUNO in the 1970s, was the first tissue culture-derived TBE vaccine produced commercially. Pfizer acquired the vaccine from Baxter, and the marketing authorizations were transferred from Baxter to Pfizer in 2015.

Various generations of the TBE vaccine, FSME-IMMUN, have been produced over more than forty years. In 1999, a new method of virus propagation for the active substance was developed in which the production virus is obtained from chick embryo cells (CC) instead of mouse brain. The current vaccine for adults  $\geq 16$  years of age (FSME-IMMUN 0.5 mL) is produced using a virus seed obtained from chick embryo fibroblast cell (b) (4) and consists of a sterile suspension of formaldehyde-inactivated and sucrose gradient purified TBE virus (TBEV) antigen (2.4  $\mu\text{g}$  target), bound to an adjuvant (0.35 mg  $\text{Al}(\text{OH})_3$ ) and (b) (4) a buffer system containing human serum albumin (HSA, 0.5 mg). The vaccine contains no preservative (thiomersal).

The current vaccine for children 1 to  $<16$  years of age (FSME-IMMUN 0.25 mL) is identical to FSME-IMMUN 0.5 mL, with the exception that the pediatric presentation contains half the volume and hence half the amount of antigen of the adult dose.

For both adults and children, the vaccine is to be given on the basis of official recommendations regarding the need for and timing of vaccination against TBE. The second dose will be given between 1 and 3 months after the first dose. The third dose will be given between 5 and 12 months after the second vaccination. The first booster dose (i.e., 4th dose) will be given 3 years after the third dose.

On December 21, 2018, Pfizer submitted a Type C meeting request and briefing package to discuss the regulatory package to support future U.S. licensure of FSME-IMMUN.

On March 5, 2019 during the Type C meeting, it was agreed that Pfizer would submit a Type 5 Master File to provide the requested data and information using the relevant sections of the Israeli Marketing Authorization Application (MAA) for FSME-IMMUN.

On March 27, 2020, Pfizer submitted another Type C meeting request to discuss Chemistry, Manufacturing and Controls aspects relevant to the Drug Substance and Drug Product manufacturing facilities and equipment to support a BLA submission for FSME-IMMUN.

### 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

#### 3.1 Submission Quality and Completeness

The quality of the submission was sufficient for a statistical evaluation.

#### 3.2 Compliance with Good Clinical Practices and Data Integrity

No data integrity issues in the pivotal studies (Studies 208/213 and 209) were identified.

### 4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

Deferred to reviewers from other disciplines.

### 5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

#### 5.1 Review Strategy

The statistical review of this BLA comprises two parts: clinical (immunogenicity and safety) data and non-clinical data. This review focus on the clinical data; the review for non-clinical data is documented in a separate statistical memo.

#### 5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

Documents submitted to the following modules were reviewed:

- 125740/0.0 Module 1.14 Labeling
- 125740/0.0 Module 2.5 Clinical Overview
- 125740/0.0 Module 2.7 Clinical Summary
- 125740/0.0 Module 5 Clinical Study Reports

#### 5.3 Table of Studies/Clinical Trials

Tables 1 and 2 provide an overview of the clinical trials providing immunogenicity/safety data for this application.

**Table 1. Overview of Studies in Adults**

<b>Protocol No. (Country)</b>	<b>Study Design and Vaccine Schedule</b>	<b>Study Objectives</b>	<b>Study Population</b>	<b>No. of Subjects (by Treatment Group)</b>
201 (Belgium)	Randomized, double blind, dose-finding, safety and immunogenicity study  Two vaccinations administered 21 to 35 days apart.	To determine whether FSME-IMMUN at a higher dose is at least as safe as FSME-IMMUN at the lowest evaluated dose as determined by fever rates after the first vaccination.	Adults 16 to <65 years of age	Randomized and vaccinated 0.6 µg = 137 1.2 µg = 133 2.4 µg = 135
202 (Belgium)	Open-label follow-up to Study 201; safety and immunogenicity of a third vaccination  One vaccination administered 6 months ±14 days after the first vaccination in Study 201.	To evaluate the safety of a third vaccination of each of the 3 dose levels of FSME-IMMUN based on local and systemic reactions.  To determine the seroconversion rates after the third vaccination.	Subjects who received both vaccinations in Study 201	Enrolled and vaccinated 0.6 µg = 126 1.2 µg = 128 2.4 µg = 118
208 (Poland)	Single-blind, randomized, comparison of the safety and tolerability of 5 consecutive lots of FSME-IMMUN and 2 lots of ENCEPUR  Two vaccinations administered 21 to 35 days apart.	To evaluate the safety and tolerability of FSME-IMMUN compared with ENCEPUR, especially with respect to fever rates after the first vaccination.  To evaluate the lot consistency of 5 lots of FSME-IMMUN.	Adults 16 to <65 years of age	Randomized and vaccinated FSME: 2977 Lot 1 = 570 Lot 2 = 570 Lot 3 = 690 Lot 4 = 578 Lot 5 = 569  ENCEPUR: 989 Lot 1 = 501 Lot 2 = 488
213 (Poland)	Open-label, follow-up to Study 208; safety and immunogenicity of a third TBE Vaccination  One dose of FSME-IMMUN administered 6 months ±28 days after the first vaccination in Study 208.	To evaluate the safety of FSME-IMMUN administered as a third vaccination after 2 vaccinations of FSME-IMMUN or after 2 vaccinations of ENCEPUR.  To evaluate antibody titers and concentrations in a subgroup of subjects after the third TBE vaccination.	Subjects who received both vaccinations in Study 208	3705 subjects were vaccinated: 2790 of these had received FSME-IMMUN in Study 208, and 915 had received ENCEPUR in Study 208.

**Table 1. Overview of Studies in Adults (Continued)**

Protocol No. (Country)	Study Design and Vaccine Schedule	Study Objectives	Subject Population	No. of Subjects (by Treatment Group)
223 (Poland)	Open-label follow-up to Study 213 to assess antibody persistence and to evaluate the response to a booster vaccination of FSME-IMMUN  A booster dose of FSME-IMMUN was given 3 years $\pm$ 28 days after the third TBE vaccination in Study 213.	To assess TBEV antibody persistence at 2 and 3 years after the third TBE vaccination in Study 213.  To assess the TBEV antibody response to a booster vaccination of FSME-IMMUN given 3 years after the third TBE vaccination in Study 213.	Subjects who received a third TBE vaccination in Study 213	347 subjects were enrolled in the study.  328 subjects received the booster vaccination. Of these, 240 had received FSME-IMMUN in Study 208 and 88 had received ENCEPUR in Study 208.
690701 (Poland)	Open-label follow-up to Study 223 to assess antibody persistence and to evaluate the response to a second booster vaccination of FSME-IMMUN  second booster dose of FSME-IMMUN (approximately 2, 3, 4, or 5 years after the first booster in Study 223).	To assess TBEV antibody persistence at approximately 2, 3, 4, and 5 years after the first booster vaccination of FSME-IMMUN in Study 223  To assess the immunogenicity and safety of a second booster vaccination of FSME-IMMUN.	Subjects who had received a booster dose of FSME-IMMUN in Study 223	315 subjects were enrolled in the study.  32 subjects received their second booster vaccination.
691101 (Pfizer Study B9371010)	Open-label follow-up to Studies 223 and 690701 to assess antibody persistence after a first booster and to evaluate the response to a second booster vaccination of FSME-IMMUN  second booster dose of FSME-IMMUN (approximately 84, 96, 108 or 120 months after the first booster in Study 223).	To assess TBEV antibody persistence at approximately 82, 94, 106 and 118 months after the first booster in Study 223.  To assess the immunogenicity and safety of a second booster vaccination of FSME-IMMUN.	Subjects who had received a first booster dose of FSME-IMMUN in Study 223 and did not receive a second booster dose in Study 690701	243 subjects were enrolled in the study.  15 subjects received their second booster vaccination.
225 (Belgium)	Open-label, single arm safety and immunogenicity study  All subjects were to receive 2 doses of FSME-IMMUN administered 12 $\pm$ 2 days apart.	To establish the earliest timepoint at which vaccines could be expected to show seropositive antibody levels after 2 vaccinations with FSME-IMMUN using a rapid immunization schedule.	Adults 16 to <66 years of age	Enrolled: 62  Vaccinated: 60

**Table 1. Overview of Studies in Adults (Continued)**

Protocol No. (Country)	Study Design and Vaccine Schedule	Study Objectives	Subject Population	No. of Subjects (by Treatment Group)
690501 (Belgium)	Open-label follow-up to Study 225; safety and immunogenicity of a third TBE vaccination  A booster dose of FSME-IMMUN was given 12 months after the second vaccination in Study 225.	To evaluate the immunogenicity and safety of a third vaccination of FSME-IMMUN given approximately 12 months after the second vaccination in Study 225.	Subjects who received both vaccinations in Study 225	Enrolled and Vaccinated: 44
690601 (Poland)	Open-label safety and immunogenicity study  All subjects were to receive 3 vaccinations, with the first 2 vaccinations given 12±2 days apart and the third vaccination given approximately 6 months after the first dose.	To evaluate the immunogenicity and safety of FSME-IMMUN in 2 age strata (16-49 years and ≥50 years) when the first and second vaccinations were administered according to a rapid immunization schedule.	Adults ≥16 years of age	Enrolled: 348  340 subjects were vaccinated: 170 subjects aged 16 to 49 years and 170 subjects aged ≥50 years.
B9371038 (Germany)	Open-label catch-up Study  All subjects received a single Booster vaccination with FSME-IMMUN.	To characterize irregularly vaccinated subjects in daily practice with respect to number and time intervals of TBE vaccinations.  To determine TBEV antibody titers before and after a single booster vaccination with FSME-IMMUN in subjects with an irregular TBE vaccination history.  To determine the rate of subjects achieving a putatively seroprotective antibody level after booster vaccination with FSME-IMMUN.	Children and adults ≥6 years of age who had received irregular or incomplete TBE vaccination schedules	Enrolled: 2915  Vaccinated: 2801
WI208682 (Austria)	Open-label, investigator-initiated study  All subjects received a single booster vaccination with FSME-IMMUN (IM or SC).	To compare the immunogenicity and reactogenicity of FSME-IMMUN after intramuscular (IM) versus subcutaneous (SC) vaccination.	Adults 18 to 60 years of age who had completed primary vaccination with FSME-IMMUN and had received at least 1 booster dose at least 3 years prior to study entry	Vaccinated: IM: 58 SC: 58

Source: Adapted from Table 5 in Clinical Overview submitted to BLA 125740/0.0.

**Table 2. Overview of Studies in Children and Adolescents**

Protocol No. (Country)	Study Design and Vaccine Schedule	Study Objectives	Subject Population	No. of Subjects (by Treatment Group)
197 (Austria)	Post-marketing surveillance Observational safety study  All subjects received 1 vaccination of FSME-IMMUN.	To observe the occurrence of fever after the first vaccination with FSME-IMMUN.	Children 6 months to 12 years of age	Enrolled: 1922
198 (Austria)	Open label, single arm, pilot safety and immunogenicity study  Two vaccinations were administered 14 to 32 days apart.	To examine the seroconversion rates after the second vaccination of FSME-IMMUN.  To evaluate the tolerability of the first and second vaccinations of FSME-IMMUN as assessed by body temperature and monitoring of adverse events.	Children 1 to <13 years of age	Vaccinated: 101
215 (Austria)	Open label follow up to Study 198  One vaccination was administered 9 to 10 months after the second vaccination in Study 198.	To investigate the immunogenicity and safety of the third vaccination of FSME-IMMUN.	Children who had received both vaccinations in Study 198	Vaccinated: 99
199 (Germany, Austria)	Randomized, double-blind, dose-finding study  Two vaccinations administered 21 to 35 days apart.	To identify the optimal dose of FSME-IMMUN for children 1 to <6 years of age.  To evaluate the safety and immunogenicity of three different antigen concentrations of the TBE vaccine in healthy children.	Children 1 to <6 years of age	Randomized and Vaccinated: 0.3 µg = 216 0.6 µg = 215 1.2 µg = 208
206 (Germany, Austria)	Double-blind follow-up to Study 199  One vaccination was administered 6 months ±14 days after the first vaccination in Study 199.	To evaluate the safety and immunogenicity of a third vaccination with one of three different antigen concentrations of the TBE vaccine in healthy children.	Children who had received both vaccinations in Study 199	Enrolled: 626 Vaccinated: 625 0.3 µg = 211 0.6 µg = 210 1.2 µg = 204

**Table 2. Overview of Studies in Children and Adolescents (Continued)**

Protocol No. (Country)	Study Design and Vaccine Schedule	Study Objectives	Subject Population	No. of Subjects (by Treatment Group)
205 (Germany)	Randomized, double-blind, dose-finding study  Two vaccinations administered 21 to 35 days apart	To identify the optimal dose of FSME-IMMUN for children 6 to <16 years of age.  To evaluate the safety and immunogenicity of three different antigen concentrations of the TBE vaccine in healthy children.	Children and adolescents 6 to <16 years of age	Randomized: 0.3 µg = 206 0.6 µg = 221 1.2 µg = 212
207 (Germany)	Double-blind follow-up to Study 205  One vaccination was administered 6 months ±14 days after the first vaccination in Study 205.	To evaluate the safety and immunogenicity of a third vaccination with one of three different antigen concentrations of the TBE vaccine in healthy children.	Children who had received both vaccinations in Study 205	Enrolled: 620 Vaccinated: 618  0.3 µg = 196 0.6 µg = 214 1.2 µg = 208
209 (Poland, Germany, Austria)	Open-label, lot consistency study  2 vaccinations administered 21 to 35 days apart; and a third vaccination administered 6 months ±14 days after the first vaccination	To evaluate 5 consecutive lots of FSME-IMMUN with respect to the rate of fever after the first vaccination in 3 age groups (1-2 years, 3-6 years, and 7-15 years).  To evaluate anti-TBE virus antibody concentrations in a subgroup of subjects after the second and third vaccinations.	Children and adolescents 1 to <16 years of age  N by age: 1-2 years: 186 3-6 years: 563 7-15 years: 1668 Total: 2417	Vaccinated FSME: 2417  Lot 1 = 487 Lot 2 = 484 Lot 3 = 483 Lot 4 = 482 Lot 5 = 481
700401 (Poland, Germany, Austria)	Open-label follow-up to Study 209; antibody persistence and booster response  Subjects who had TBE virus antibody concentrations ≤1000 VIE U/mL by ELISA, and NT titers <10, were offered a booster vaccination of FSME-IMMUN at 36 months, 48 months, or 60 months after the third vaccination in Study 209.	To evaluate TBEV antibody persistence 24 and 34 months after the third dose.  To evaluate antibody response to a booster dose administered 36 months after the third vaccination.  To evaluate TBEV antibody persistence 46 and 58 months after the third vaccination with FSME-IMMUN  To evaluate antibody response to a booster vaccination with FSME-IMMUN administered 48 months or 60 months after the third vaccination.	Children and adolescents who had received 3 vaccinations in Study 209	Enrolled: 358  Vaccinated: 205

**Table 2. Overview of Studies in Children and Adolescents (Continued)**

Protocol No. (Country)	Study Design and Vaccine Schedule	Study Objectives	Subject Population	No. of Subjects (by Treatment Group)
700802 (Pfizer B9371021)	Open-label follow-up of Study 700401; antibody persistence after first booster and response to a second booster  A booster dose at either 40, 48, 60, 72, 84, 96, 108, or 120 months after the first booster.	To assess TBE antibody persistence at approximately 38, 46, 58, 70, 82, 94, 106, and 118 months after first booster in Study 700401.  To assess the immunogenicity and safety of a second booster vaccination of FSME-IMMUN.	Children, adolescents, and young adults who received their first TBE booster vaccination in Study 700401	179 subjects were enrolled in the study. 26 subjects received their second booster vaccination
700501 (Austria)	Non-interventional Antibody persistence study	To assess TBEV antibody persistence approximately 3 years after administration of a TBE booster vaccination with FSMEIMMUN 0.25 mL (administered outside of a clinical study).	Children who had received 3 TBE vaccinations in Study IMAG-146A when they were 6 to 47 months of age and had received a booster vaccination	Enrolled: 97
700801 (Czech Republic/Austria)	Randomized, single-blind safety, immunogenicity, and interchangeability of 2 different TBE vaccines after the first vaccination  Two vaccinations administered 28 (±3) days apart, and a third administered 360 (±14) days after the first vaccination.	To assess the immunogenicity, safety and interchangeability of two different TBE vaccines, the first and second vaccination with either FSME-IMMUN 0.25 mL or ENCEPUR Children and the third vaccination with FSME-IMMUN 0.25 mL only, in a standard schedule to children 1 to <12 years of age.	Children 1 to <12 years of age	Stratum A (1 to 2 years of age): FSME-IMMUN: 50 ENCEPUR: 50 Stratum B (3 to 6 years of age): FSME-IMMUN: 51 ENCEPUR: 51 Stratum C (7 to 11 years of age): FSME-IMMUN: 49 ENCEPUR: 51
B9371038 (Germany)	Open-label catchup Study  A single booster vaccination with FSME-IMMUN	To characterize irregularly vaccinated subjects in daily practice with respect to number and time intervals of TBE vaccinations. To determine TBEV antibody titers before and after a single booster vaccination with FSMEIMMUN in subjects with an irregular TBE vaccination history. To determine the rate of subjects achieving a putatively seroprotective antibody level after booster vaccination with FSME-IMMUN.	Children and adults ≥6 years of age who had received irregular or incomplete TBE vaccination schedules	Enrolled 2915  Vaccinated: 2801

Source: Adapted from Table 6 in Clinical Overview submitted to BLA 125740/0.0.

*Reviewer's Comment:*

*The dosing schedule for which the applicant is seeking approval in both adults and children is that the first two doses are to be given at a 1 to 3-month interval and the third dose at 5 to 12 months after the second vaccination. However, none of the clinical trials presented above were according to this schedule. In particular, none of the studies investigated a second dose given three months after the first dose. The clinical team considers it acceptable for the first two doses to be given at a 1 to 3-month interval because this dosing schedule has been adopted in Europe for more than 10 years since the vaccine was approved there. Therefore, giving the second dose 1 to 3 months after the first dose is supported by real-world evidence instead of clinical trial data.*

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Trial #1: Study 208

Single-blind, randomized, multicenter comparison of FSME-IMMUN and ENCEPUR: safety and tolerability of two vaccinations in healthy volunteers aged 16 to 65 years

#### 6.1.1 Objectives

Objective: To investigate the safety of five consecutive lots of FSME-IMMUN in healthy volunteers. The main safety endpoint was fever rate following the first vaccination

#### 6.1.2 Design Overview

Study 208 was a single-blind, randomized, multicenter safety study to compare two TBE vaccines in 3800 healthy volunteers aged 16 to 65 years. The study consisted of 2 vaccinations either with FSME-IMMUN (2.4 µg TBE antigen / dose) or with non-US licensed TBE vaccine ENCEPUR (1.5 µg TBE antigen / dose). Immediately before the first vaccination, volunteers were assigned to receive either FSME-IMMUN or ENCEPUR at a ratio of 3:1 using a blocked randomization with a block size >4. The study period was from October 15, 2001 to January 18, 2002.

#### 6.1.3 Population

Healthy volunteers aged 16 to 65 years

#### 6.1.4 Study Treatments or Agents Mandated by the Protocol

Either 0.5 ml FSME-IMMUN or 0.5 ml ENCEPUR intramuscularly. The following vaccination schedule was used:

- First vaccination: Day 0
- Second vaccination: Day 21-35

#### 6.1.5 Directions for Use

Please refer to clinical reviewer's memo.

#### 6.1.6 Sites and Centers

Fourteen study centers in Poland

### 6.1.7 Surveillance/Monitoring

Please refer to clinical reviewer's memo.

### 6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint:

- Fever rate after the first vaccination

Secondary Endpoints:

- Fever rate after the second vaccination
- Systemic adverse experiences other than fever after the first and second vaccination
- Local reactions after the first and second vaccination

### 6.1.9 Statistical Considerations & Statistical Analysis Plan

Immunogenicity was not assessed during this safety study.

The 95% confidence interval of the difference in fever rates between FSME-IMMUN and ENCEPUR was calculated as described by *Agresti in 1990*<sup>1</sup>. If the upper limit of this confidence interval was not higher than 3%, it was considered that FSME-IMMUN is non-inferior to ENCEPUR with respect to fever rate after the first vaccination.

In order to assess lot consistency of FSME-IMMUN with respect to safety, the probability of occurrence of fever and its 95% confidence interval was calculated separately for FSME-IMMUN and ENCEPUR, as well as for each lot. No success criteria were pre-specified for lot consistency.

A total sample size of 3621 volunteers was sufficient to demonstrate with 83% power that FSME-IMMUN is as safe as ENCEPUR with respect to fever rate after the first vaccination. Taking into account a lost to follow-up rate of approximately 5%, 3800 volunteers needed to be enrolled. Volunteers were randomized at a ratio of 3:1 to receive either FSME-IMMUN or ENCEPUR. According to this randomization, approximately 2850 volunteers were to receive FSME-IMMUN and 950 were to be vaccinated with ENCEPUR.

The analysis populations were defined as follows:

#### Per Protocol Dataset I

This dataset is used for the analysis of fever rate after the first vaccination. It includes volunteers who:

- a) were eligible according to inclusion and exclusion criteria;
- b) had available body temperature measurement after the first vaccination.

#### Per Protocol Dataset II

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<sup>1</sup> Agresti, A. (1990) Categorical Data Analysis. John Wiley and Sons, New York.

This dataset is used for the analysis of fever rate after the second vaccination. It includes volunteers who:

- a) were eligible according to inclusion and exclusion criteria;
- b) had available body temperature measurements after the second vaccination.

**Safety Analysis Set**

Volunteers were included in the analysis of adverse events which occurred after the first or second vaccination if they:

- a) had received the respective vaccinations and
- b) had documented adverse event information (at least) immediately after vaccination.

*6.1.10 Study Population and Disposition*

*6.1.10.1 Populations Enrolled/Analyzed*

The per protocol dataset I (including subjects who had available body temperature measurement after the first vaccination) was comprised of 3922 volunteers, of whom 2947 were in the FSME-IMMUN study group and 975 were in the ENCEPUR study group. Volunteers were evenly distributed by gender in both study groups (Table 3). Other demographic characteristics (age, weight, and height) were generally balanced between the two study groups.

**Table 3. Gender distribution of volunteers included in the per protocol dataset I**

	FSME-IMMUN N (%)	ENCEPUR N (%)	Total
Male	1503 (51.0%)	467 (47.9%)	1970
Female	1444 (49.0%)	508 (52.1%)	1952
Total	2947 (100.0%)	975 (100.0%)	3922

Source: Table 2 in the Clinical Study Report (CSR) for Study 208.

Demographic characteristics were also generally evenly distributed between the two study groups in the other analysis populations (per protocol dataset II, safety analysis sets I and II), too.

*6.1.11 Efficacy and Immunogenicity Analyses*

Efficacy and immunogenicity were not assessed in this study.

*6.1.12 Safety Analyses*

The primary analysis of fever rate after the first vaccination was carried out on the per protocol dataset I. Total fever rate was lower in the FSME IMMUN study group (0.8%) than in the ENCEPUR (5.6%) study group (Table 4). The majority of fever cases were mild. The 95% confidence interval (CI) of the difference in fever rates between FSME-IMMUN and ENCEPUR is (-6.4%, -3.4%), the upper limit of which is below the pre-specified 3% limit. Therefore, the applicant concluded that FSME-IMMUN is non-inferior to ENCEPUR with respect to fever rate after the first vaccination. All five production lots of FSME-IMMUN were found to be consistent with respect to fever occurrence (Table 5).

**Table 4. Occurrence and severity of fever after the first vaccination (per protocol dataset I)**

	No fever	Mild	Moderate	Severe
FSME- IMMUN (N=2947)	2924 (99.2%)	23 (0.8%)	0 (0.0%)	0 (0.0%)
ENCEPUR (N=975)	920 (94.4%)	54 (5.5%)	1 (0.1%)	0 (0.0%)

Source: Table 20 in the CSR for Study 208.

**Table 5. Probability of fever occurrence after the first vaccination by study group and lot number (per protocol dataset I)**

Study group	Lot number	Number of volunteers who experienced fever (n/N)	Probability of fever occurrence (%)	95% CI of the probability of fever occurrence
FSME- IMMUN	370101AA	3/566	0.5%	(0.1%, 1.5%)
FSME- IMMUN	370201AA	3/565	0.5%	(0.1%, 1.5%)
FSME- IMMUN	370301AA	8/683	1.2%	(0.5%, 2.3%)
FSME- IMMUN	370401DA	8/571	1.4%	(0.6%, 2.7%)
FSME- IMMUN	371600KA	1/562	0.2%	(0.0%, 1.0%)
ENCEPUR	201011	12/493	2.4%	(1.3%, 4.2%)
ENCEPUR	205021	43/482	8.9%	(6.5%, 11.8%)

Source: Table 21 in the CSR for Study 208.

The analysis of fever rate after the second vaccination was carried out on the per protocol dataset II, which was comprised of 3891 volunteers (i.e., including subjects who had available body temperature measurement after the second vaccination). Fever occurred at a lower rate after the second vaccination than after the first vaccination and the fever rates in the two study groups were similar (Table 6).

**Table 6. Occurrence and severity of fever after the second vaccination (per protocol dataset II)**

	No fever	Mild	Moderate	Severe
FSME- IMMUN (N=2926)	2910 (99.5%)	15 (0.5%)	1 (0.0%)	0 (0.0%)
ENCEPUR (N=965)	960 (99.5%)	4 (0.4%)	1 (0.1%)	0 (0.0%)

Source: Table 23 in the CSR for Study 208.

The analysis of local reactions after the first vaccination was carried out on the safety analysis set I, which was comprised of 3966 volunteers (i.e., all those who received the

first vaccination in either study group). The majority of local reactions were mild in both study groups (Table 7). The rate of any local reactions was slightly lower in the FSME-IMMUN group (35.6%) than in the ENCEPUR group (44.7%).

**Table 7. Occurrence and severity of local reactions after the first vaccination (safety analysis set I)**

	No reaction	Mild	Moderate	Severe
FSME- IMMUN (N=2977)	1917 (64.4%)	969 (32.5%)	87 (2.9%)	4 (0.1%)
ENCEPUR (N=989)	547 (55.3%)	375 (37.9%)	62 (6.3%)	5 (0.5%)

Source: Table 25 in the CSR for Study 208.

Systemic reactions (excluding fever) occurred with a greater frequency in the ENCEPUR study group than in the FSME-IMMUN group. Mild systemic reactions were most common in both study groups (Table 8).

**Table 8. Occurrence and severity of systemic reactions (excluding fever) after the first vaccination (safety analysis set I)**

	No reaction	Mild	Moderate	Severe
FSME- IMMUN (N=2977)	2573 (86.4%)	347 (11.7%)	56 (1.9%)	1 (0.0%)
ENCEPUR (N=989)	682 (69.0%)	233 (23.6%)	71 (7.2%)	3 (0.3%)

Source: Table 32 in the CSR for Study 208.

The analysis of local reactions after the second vaccination was carried out on the safety analysis set II, which comprised 3927 volunteers (i.e., all those who received the second vaccination in either study group). The rate of local reactions was lower with FSME-IMMUN than with ENCEPUR (Table 9). Table 10 presents the rate of systemic reactions (excluding fever) after the second vaccination. For both study groups, the rates were lower after the second vaccination than after the initial vaccination. In addition, the rates of systemic reactions were similar for the two products.

**Table 9. Occurrence and severity of local reactions after the second vaccination (safety analysis set II)**

	No reaction	Mild	Moderate	Severe
FSME- IMMUN (N=2950)	2016 (68.3%)	834 (28.3%)	95 (3.2%)	5 (0.2%)
ENCEPUR (N=977)	600 (61.4%)	341 (34.9%)	35 (3.6%)	1 (0.1%)

Source: Table 29 in the CSR for Study 208.

**Table 10. Occurrence and severity of systemic reactions (excluding fever) after the second vaccination (safety analysis set II)**

	No reaction	Mild	Moderate	Severe
FSME- IMMUN (N=2950)	2680 (90.8%)	227 (7.7%)	40 (1.4%)	3 (0.1%)
ENCEPUR (N=977)	867 (88.7%)	95 (9.7%)	14 (1.4%)	1 (0.1%)

Source: Table 37 in the CSR for Study 208.

Among the symptoms that were not specifically queried, nasopharyngitis and pharyngitis were the most frequently reported symptoms after both vaccinations. They were all judged to be unrelated to the vaccinations and their rates were similar in both study groups. Other than the specifically queried symptoms, only a small number of adverse events were reported that were judged to be related to vaccination, and their rates were comparable in both study groups.

## 6.2 Trial #2: Study 213

Open-label, multicenter, follow-up, phase III study to investigate the safety of the third vaccination of FSME-IMMUN in volunteers aged 16 to 66 years

### 6.2.1 Objectives

Objectives:

- The safety of the third vaccination with FSME-IMMUN was investigated in all subjects who received both vaccinations in Study 208
- TBE antibody titers and concentrations were investigated in a subgroup of subjects

### 6.2.2 Design Overview

This was an open-label, multi-center, follow-up phase III study. All subjects aged 16 to 66 years who received both vaccinations in Study 208 were invited to participate in the study. As FSME-IMMUN was already on the market in several countries and pharmacovigilance data were available, the study was completed for each subject after the final physical examination, 35-42 days after the third vaccination. The study period was from May 6, 2002 to August 31, 2002.

In order to assess the immunogenicity of a third vaccination with FSME-IMMUN in the present study and to assess TBE-virus antibody persistence in subsequent studies, at least 400 subjects were invited to participate in an immunogenicity subgroup, of whom approximately 300 subjects received FSME-IMMUN and 100 received ENCEPUR for their initial two vaccinations in Study 208.

#### Reviewer's Comment:

*The dataset submitted with Study 213 CSR indicated all subjects were 16 to 64 years of age at the initiation of the study. The only subject aged 65 years in Study 208 did not appear to participate in Study 213.*

### 6.2.3 Population

All subjects who participated in Study 208 were included if they had received two vaccinations during the course of Study 208.

### 6.2.4 Study Treatments or Agents Mandated by the Protocol

All subjects (including those who had previously been vaccinated with ENCEPUR in Study 208) received 0.5 ml FSME-IMMUN approximately six months ( $\pm 28$  days) after the first vaccination had been administered during Study 208.

### 6.2.5 Directions for Use

Please refer to the clinical reviewer's memo.

### 6.2.6 Sites and Centers

Fourteen study centers in Poland

### 6.2.7 Surveillance/Monitoring

Please refer to the clinical reviewer's memo.

### 6.2.8 Endpoints and Criteria for Study Success

Primary Endpoint: Local and systemic reactions after the third vaccination

Secondary Endpoints:

- AEs that occurred between the last visit in Study 208 and the first visit in Study 213
- TBE antibody response assessed before and after the third vaccination in the immunogenicity subgroup subjects

### 6.2.9 Statistical Considerations & Statistical Analysis Plan

#### Determination of Sample size

The maximum sample size for Study 213 was limited by the number of subjects who received two vaccinations in Study 208, i.e., 3927 subjects. Sample size calculation was performed for the number of subjects necessary for the immunogenicity subgroup.

With approximately 300 subjects received FSME-IMMUN and 100 received ENCEPUR for their initial two vaccinations, the seroconversion rate for those who received FSME-IMMUN for all three vaccinations could be calculated with  $\pm 3.4\%$  precision assuming 90% seroconversion and  $\pm 4.5\%$  precision if the seroconversion rate is approximately 80%. For those subjects who received two vaccinations with ENCEPUR and the third one with FSME-IMMUN, the seroconversion rate could be estimated with  $\pm 5.9\%$  and  $\pm 7.8\%$  precision respectively, assuming the seroconversion rates given above.

#### Statistical Hypothesis

No formal statistical hypothesis was formulated.

Statistical Method

Point estimates and 95% CIs for the antibody response, measured before and after the third vaccination, were calculated for the subgroup. Antibody response was assessed separately for those subjects who received FSME-IMMUN and for those who were given ENCEPUR for the first two vaccinations. A subject was considered to be seroconverted if the ELISA value was < 63 VIE U/ml (Vienna Units per milliliter) before entry to Study 208 and > 126 VIE U/ml at the time of assessment (before and/or after the third vaccination in Study 213) and/or if a negative neutralization test (< 1:10) at baseline and a value of ≥ 1:10 at the time of assessment in Study 213 were measured. Seroconversion in subjects with baseline ELISA values between > 63 and < 126 VIE U/ml at entry to Study 208 were defined as a more than 2-fold rise in antibody titers at the time of assessment.

*6.2.10 Study Population and Disposition*

*6.2.10.1 Populations Enrolled/Analyzed*

Subjects included in the immunogenicity dataset were roughly evenly distributed by gender in both study groups, although the ENCEPUR study group consisted of a slightly higher proportion of female subjects (Table 11). Subjects were generally balanced with respect to age, height, and weight in both of the study groups.

**Table 11. Gender distribution of subjects included in the immunogenicity dataset**

	FSME-IMMUN N (%)	ENCEPUR N (%)	Total
Male	186 (44.5%)	57 (38.5%)	243
Female	232 (55.5%)	91 (61.5%)	323
Total	418 (100.0%)	148 (100.0%)	566

*Source: Table 1 in the CSR for Study 213.*

*6.2.11 Immunogenicity Analyses*

ELISA results

The seroconversion rates as determined by ELISA immediately before the third vaccination (compared to baseline) were similar for the FSME-IMMUN only group (43.5%) and ENCEPUR/ FSME-IMMUN (48.6%) groups. The seroconversion rates as determined by ELISA after the third vaccination with FSME-IMMUN (compared to baseline) were high and show no notable difference between the study groups (Table 12).

**Table 12. Seroconversion rates before and after the third vaccination determined by ELISA**

	Before the third vaccination n/N (%) (95% CI)	After the third vaccination n/N (%) (95% CI)
FSME-IMMUN only	182/418 (43.5%) (38.7%, 48.4%)	411/416 (98.8%) (97.2%, 99.6%)
ENCEPUR/ FSME-IMMUN	72/148 (48.6%) (40.4%, 57.0%)	146/148 (98.6%) (95.2%, 99.8%)

Source: Adapted from Tables 7 and 8 in the CSR for Study 213.

Neutralization test (NT) results

The analysis of seroconversion as determined by NT immediately before the third vaccination (compared to baseline) showed a slightly higher rate in the ENCEPUR/FSME-IMMUN group (92.6%) than in the FSME-IMMUN only group (86.5%). The seroconversion rates determined by NT after the third vaccination with FSME-IMMUN (compared to baseline) were identical to the seroconversion rates as determined by ELISA only (Table 13).

**Table 13. Seroconversion rates before and after the third vaccination determined by NT (according to Adner et al., 2001)**

	Before the third vaccination n/N (%) (95% CI)	After the third vaccination n/N (%) (95% CI)
FSME-IMMUN only	360/416 (86.5%) (82.9%, 89.7%)	411/416 (98.8%) (97.2%, 99.6%)
ENCEPUR/ FSME-IMMUN	137/148 (92.6%) (87.1%, 96.2%)	146/148 (98.6%) (95.2%, 99.8%)

Source: Adapted from Tables 9 and 10 in the CSR for Study 213.

Geometric mean concentrations (GMCs) of TBE-virus antibodies determined by ELISA and geometric mean titers (GMTs) determined by NT after the third vaccination

The ELISA GMCs after the third vaccination were higher in the FSME-IMMUN group (Table 14), while the NT GMTs after the third vaccination were higher in the ENCEPUR group (Table 15).

**Table 14. Antibody concentration before and after the third vaccination determined by ELISA**

	Before the third vaccination GMC (95% CI)	After the third vaccination GMC (95% CI)
FSME-IMMUN only (N=416)	111.7 (104.3, 119.6)	1935.7 (1754.3, 2135.9)
ENCEPUR/ FSME-IMMUN (N=418)	115.1 (102.0, 129.9)	1508.7 (1307.4, 1741.1)

Source: Adapted from Table 11 in the CSR for Study 213

**Table 15. Antibody titers before and after the third vaccination determined by NT (according to Adner et al., 2001)**

	Before the third vaccination GMT (95% CI)	After the third vaccination GMT (95% CI)
FSME-IMMUN only (N=416)	22.9 (21.0, 25.0)	259 (235.4, 285.0)
ENCEPUR/ FSME-IMMUN (N=418)	35.5 (30.4, 41.4)	371.4 (324.7, 424.8)

Source: Adapted from Table 12 in the CSR for Study 213.

### 6.2.12 Safety Analyses

Subjects were assessed for safety by means of body temperature measurements and adverse event monitoring. For the determination of local and systemic adverse events (including fever), each subject was provided with a Subject Diary after vaccination. The Subject Diary was returned to the investigator at the following visit.

#### Local reactions

Local reactions after the third vaccination with FSME-IMMUN were similar in both study groups and were predominantly mild in severity (Table 16). Three subjects reported severe local reactions, all of which were injection site pain and in the FSME-IMMUN only group.

**Table 16. Number (%) of subjects reported to have experienced local reactions after the third vaccination (safety dataset I)**

	No reaction	Mild	Moderate	Severe
FSME-IMMUN only (N=2790)	1961 (70.3%)	739 (26.5%)	87 (3.1%)	3 (0.1%)
ENCEPUR/ FSME-IMMUN (N=915)	628 (68.6%)	250 (27.3%)	37 (4.0%)	0 (0.0%)

Source: Table 34 in the CSR for Study 213.

#### Systemic reactions

Systemic reactions (excluding fever) after the third vaccination with FSME-IMMUN were similar in both study groups and were mostly mild in severity (Table 17).

**Table 17. Number (%) of subjects reported to have experienced systemic reactions related to the third vaccination (safety dataset I)**

	No reaction	Mild	Moderate	Severe
FSME-IMMUN only (N=2790)	2500 (89.6%)	247 (8.9%)	42 (1.5%)	1 (0.0%)
ENCEPUR/ FSME-IMMUN (N=915)	797 (87.1%)	97 (10.6%)	21 (2.3%)	0 (0.0%)

Source: Table 36 in the CSR for Study 213.

### Fever

Fever after the third vaccination with FSME-IMMUN occurred at low and comparable rates for both study groups and was mostly mild (Table 18). No severe fever cases occurred after the third vaccination.

**Table 18. Number (%) of subjects reported to have experienced fever after the third vaccination (safety dataset I)**

	No fever	Mild	Moderate	Severe
FSME-IMMUN only (N=2780)	2765 (99.5%)	14 (0.5%)	1 (0.0%)	0 (0.0%)
ENCEPUR/ FSME-IMMUN (N=912)	909 (99.7%)	3 (0.3%)	0 (0.0%)	0 (0.0%)

Source: Table 38 in the CSR for Study 213.

### Secondary endpoint: Analysis of adverse events that occurred between the last visit in Study 208 and the first visit in Study 213

At the beginning of Study 213, two subjects reported moderate systemic AEs that were considered to be related to the second vaccination (administered during Study 208). Table 19 shows that no difference was observed between the study groups in terms of frequency or severity of adverse events (both related and unrelated) reported to have occurred in the period between Studies 208 and 213.

**Table 19. Number of subjects who reported adverse events that occurred in the period between studies 208 and 213 (safety dataset II)**

	No reaction	Mild	Moderate	Severe
FSME-IMMUN only (N=2840)	2613 (92.0%)	126 (4.4%)	99 (3.5%)	2 (0.1%)
ENCEPUR/ FSME-IMMUN (N=937)	861 (91.9%)	33 (3.5%)	42 (4.5%)	1 (0.1%)

Source: Table 41 in the CSR for Study 213.

### 6.3 Trial #3: Study 209

Open-label safety study of FSME-IMMUN NEW in healthy children and adolescents aged 1 to 15 years

### *6.3.1 Objectives*

#### Primary Objective:

- Investigation of the fever rate after the first vaccination in three different age groups (1-2 years, 3-6 years, 7-15 years)

#### Secondary Objectives:

- Anti-TBEV antibody concentrations (determined by ELISA) and NT titers at Visit 4 (21-35 days after the second vaccination) and Visit 6 (35-42 days after the third vaccination) were investigated in a subgroup of subjects at selected centers.

### *6.3.2 Design Overview*

This multicenter, open-label safety study was designed to investigate the safety of three vaccinations with five consecutive vaccine lots of 0.25 ml FSME-IMMUN in 2400 healthy children and adolescents aged 1 to 15 years. The study period was from September 26, 2002 to January 17, 2003.

Safety was assessed by fever and AEs after each vaccination. Immunogenicity was also investigated in a subgroup of 400 subjects (recruited in four study centers), as determined by anti-TBEV antibody concentrations and NT titers from blood drawn at Visit 4 (21-35 days after the second vaccination) and Visit 6 (35-42 days after the third vaccination).

### *6.3.3 Population*

Approximately 2400 healthy children and adolescents 1-15 years of age

### *6.3.4 Study Treatments or Agents Mandated by the Protocol*

The investigational product was provided in pre-filled syringes containing one single dose of 0.25 ml FSME-IMMUN (1.2 µg ± 15 % TBEV antigen). Five consecutive lots were used in this study. The timing of dose for each subject is as follows:

- First vaccination: Day 0
- Second vaccination: Day 21-35
- Third vaccination: Month 6 (± 14 days)

### *6.3.5 Directions for Use*

Please refer to the clinical reviewer's memo.

### *6.3.6 Sites and Centers*

Sixteen study centers in Poland, Austria, and Germany

### *6.3.7 Surveillance/Monitoring*

Please refer to the clinical reviewer's memo.

### *6.3.8 Endpoints and Criteria for Study Success*

Primary Safety Endpoint:

- Fever rate after the first vaccination in three different age groups (1-2 years, 3-6 years, 7-15 years)

Secondary Immunogenicity Endpoints:

- Antibody response after the second and third vaccination measured by ELISA and neutralization test for a subset of subjects
- Fold increase of anti-TBEV antibody concentration and NT titer after the second and third vaccination as compared to baseline measured by ELISA and neutralization test for a subset of subjects
- Seroconversion rate after the second and third vaccination for a subset of subjects

Secondary Safety Endpoints:

- Fever rate after the second and third vaccinations
- Local and systemic reaction rates (other than fever) after each vaccination

*6.3.9 Statistical Considerations & Statistical Analysis Plan*

Sample Size Determination

If 2400 subjects were enrolled into the study, analyzable safety data after the first vaccination on FSME-IMMUN would be expected to be available on at least 2300 subjects. With this sample size, the 95% confidence interval of the rate of severe fever would be within 0.5% from the observed fever rate, assuming a severe fever rate of approximately 1%.

The fever rate was to be analyzed in three different age groups. In the age group of 1-2 years, 200 subjects were expected to be enrolled. With this sample size, the 95% confidence interval of the fever rate would be within 6.3% from the observed rate assuming the latter was 20%. A total of 800 subjects were expected to be enrolled in the 3-6 years old age group. With this sample size the 95% confidence interval of the fever rate would be within 2.3% from the observed rate assuming the latter was 10%. Approximately 1,400 subjects, aged 7-15 years, were expected to be enrolled in the study. In this age group, the confidence interval would be within 1.3% from the observed rate assuming the latter was 5%.

A subset of 400 subjects would be used to analyze antibody responses after the second vaccination. With this sample size the 95% CI of the seroconversion rate after two vaccinations would be within 0.7% from the observed rate assuming the latter was 97%.

Statistical Hypothesis

No formal statistical hypothesis was formulated.

Statistical Method

In order to assess the lot consistency of FSME-IMMUN with respect to safety, the probability of occurrence of fever and its 95% confidence interval were calculated separately for each lot. Only children > 3 years of age were included in the analysis of lot consistency.

As lot consistency equivalence margin was not pre-specified and to assess the lot consistency, point estimates and 95% confidence intervals for the antibody response after the second and third vaccination were calculated separately for each lot for a subset of subjects.

Seroconversion after the second and third vaccination was defined in the same way as Study 213.

The analysis populations were defined as follows:

Immunogenicity Dataset

Subjects who:

- were eligible to participate in the study according to the inclusion/exclusion criteria including informed consent for additional blood draws;
- received the first and second vaccinations;
- had available ELISA and/or NT test results at baseline and after the second vaccination;
- had TBE-antibodies <126 VIE U/ml at baseline;
- received the same lot for the first and second vaccinations.

Per Protocol Dataset I

Subjects who:

- fulfilled exclusion/inclusion criteria,
- received the 1st vaccination,
- have available ELISA test results at baseline (before first vaccination),
- were negative at baseline for TBEV-antibodies, and
- have body temperature measurement available after the first vaccination.

This dataset is used for the analysis of the fever rate after the first vaccination.

Safety Analysis Set I

Subjects are included in the analysis of AEs occurring after the first vaccination if they:

- received the 1st vaccination, and
- have documented AE information at least immediately after the vaccination

Per Protocol Dataset II

Subjects who:

- fulfilled exclusion/inclusion criteria
- received the 2nd vaccination
- have available ELISA test results at baseline

Safety Analysis Set II

Subjects are included in the analysis of adverse experiences occurring after the second vaccination if they:

- received the 2nd vaccination, and
- have documented adverse experience information at least immediately after the vaccination.

### 6.3.10 Study Population and Disposition

#### 6.3.10.1 Populations Enrolled/Analyzed

The subjects included in the analysis of antibody response after the second vaccination were distributed evenly by gender (Table 20).

**Table 20. Gender of subjects included in the Immunogenicity Dataset**

Gender	N (%)
Male	185 (49.6%)
Female	188 (50.4%)
Total	373 (100.0%)

Source: Table 9 in the CSR Part A for Study 209.

In the Per Protocol Dataset I (i.e., subjects who received the first vaccination), subjects were evenly distributed by gender (Table 21). Subjects were generally represented across age groups with numerically higher percentages of subjects in older age groups (Table 22).

**Table 21. Gender of subjects included in the Per Protocol Dataset I**

Gender	N (%)
Male	1215 (51.2%)
Female	1159 (48.8%)
Total	2374 (100.0%)

Source: Table 20 in the CSR Part A for Study 209.

**Table 22. Age distribution of subjects included in the Per Protocol Dataset I**

Age range	N (%)
1-2 years	183 (7.7%)
3-4 years	249 (10.5%)
5-6 years	310 (13.1%)
7-8 years	329 (13.9%)
9-10 years	350 (14.7%)
11-12 years	361 (15.2%)
13-15 years	592 (24.9%)
Total	2374 (100.0%)

Source: Table 21 in the CSR Part A for Study 209.

### 6.3.11 Immunogenicity Analyses

#### 6.3.11.1 Analyses of Primary Endpoints

N/A

#### 6.3.11.2 Analyses of Secondary Endpoints

The seroconversion rates measured by ELISA after the second vaccination for the different production lots were generally similar, with a slightly lower rate in those who received Lot 1 (Table 23). The seroconversion rates measured by NT for the different

production lots were generally similar, with a slight lower seroconversion rate observed in Lot 1 compared to the other lots as well (Table 24).

**Table 23. Seroconversion rate as determined by ELISA after the second vaccination**

Lot	Seroconversion n/N (%)	95% CI
1	63/68 (92.6%)	(83.7%, 97.6%)
2	76/80 (95.0%)	(87.7%, 98.6%)
3	77/79 (97.5%)	(91.2%, 99.7%)
4	75/77 (97.4%)	(90.9%, 99.7%)
5	67/69 (97.1%)	(89.9%, 99.6%)
Total	358/373 (96.0%)	(93.5%, 97.7%)

Source: Table 9 in the CSR Part A for Study 209.

**Table 24. Seroconversion rate as determined by NT (Adner et al. (2001)) after the second vaccination**

Lot	Seroconversion n/N (%)	95% CI
1	62/67 (92.5%)	(83.4%, 97.5%)
2	75/77 (97.4%)	(90.9%, 99.7%)
3	76/79 (96.2%)	(89.3%, 99.2%)
4	73/76 (96.1%)	(88.9%, 99.2%)
5	66/69 (95.7%)	(87.8%, 99.1%)
Total	352/368 (95.7%)	(93.0%, 97.5%)

Source: Table 1 in the CSR Part A Addendum for Study 209.

Antibody response measured by ELISA and NT, in terms of GMC and GMT, respectively, after the second vaccination showed similar results among the study lots, with Lot 1 showing a slightly lower GMC or GMT (Tables 25 and 26). The fold increase in antibody response measured by ELISA after the second vaccination ranged from 57.2 to 71.1, and the fold increase in antibody response measured by NT after the second vaccination ranged from 25.5 to 39.6.

**Table 25. Antibody concentration measured by ELISA and fold increase in antibody concentrations after the second vaccination**

Lot	N	GMC (VIE U/ml) (95% CI)	Geometric mean of fold increase
1	68	1172.0 (842.9, 1629.7)	57.2
2	80	1617.6 (1242.1, 2106.7)	68.1
3	79	1457.9 (1112.1, 1911.4)	62.4
4	77	1546.7 (1197.0, 1998.5)	71.1
5	69	1585.9 (1222.8, 2056.8)	64.7
Total	373	1473.0 (1304.3, 1663.5)	64.7

Source: Adapted from Tables 15 and 16 in the CSR Part A for Study 209.

**Table 26. Antibody concentration measured by NT (Adner et al. (2001)) and fold increase in antibody concentrations after the second vaccination**

Lot	N	GMT (95% CI)	Geometric mean of fold increase
1	67	127.5 (95.1, 170.9)	25.5
2	77	179.4 (142.8, 225.2)	32.9
3	79	138.8 (106.1, 181.6)	26.0
4	76	164.9 (126.4, 215.1)	32.8
5	69	203.6 (153.2, 270.6)	39.6
Total	368	160.5 (142.6, 180.8)	30.9

Source: Adapted from Tables 2 and 3 in the CSR Part A Addendum for Study 209.

All subjects received the third vaccination with either lot 4 or lot 5 due to the later expiration dates of these lots. For the seroconversion rates after the third vaccination, all subjects in the immunogenicity dataset were shown to have seroconverted after the third vaccination compared to baseline as determined by ELISA or NT. One subject seroconverted as determined by NT but not by ELISA (Table 27) and two other subjects seroconverted as determined by ELISA but not by NT (Table 28). For the geometric mean titers as determined by ELISA and NT after the third vaccination, Lot 4 showed slightly higher GMC by ELISA and GMT by NT than Lot 5 (Tables 29 and 30). The fold increase of antibody response measured by ELISA and NT after the third vaccination as compared to baseline were 255.4 and 76.7, respectively.

**Table 27. Seroconversion rate in ELISA after the 3rd vaccination by lot**

Lot	Seroconversion rate n/N (%) (95% CI)
Lot 4	205/205 (100.0%) (98.2%, 100.0%)
Lot 5	156/157 (99.4%) (96.5%, 100.0%)
Total	361/362 (99.7%) (98.5%, 100.0%)

Source: Adapted from Table 14.2.5 in the CSR Part B for Study 209.

**Table 28. Seroconversion rate in NT after the 3rd vaccination by lot**

Lot	Seroconversion rate n/N (%) (95% CI)
Lot 4	204/205 (99.5%) (97.3%, 100.0%)
Lot 5	154/155 (99.4%) (96.5%, 100.0%)
Total	358/360 (99.4%) (98.0%, 99.9%)

Source: Adapted from Table 14.2.6 in the CSR Part B for Study 209.

**Table 29. Antibody concentration measured by ELISA after the 3rd vaccination by lot**

Lot	N	GMT (95% CI)
Lot 4	205	6303.7 (5608.9, 7084.6)
Lot 5	157	5040.0 (4349.4, 5840.3)
Total	362	5720.8 (5216.7, 6273.6)

Source: Adapted from Table 14.2.7 in the CSR Part B for Study 209.

**Table 30. Antibody concentration measured by NT after the 3rd vaccination by lot**

Lot	N	GMT (95% CI)
Lot 4	205	421.6 (378.4, 469.7)
Lot 5	157	334.8 (293.8, 381.7)
Total	362	381.5 (350.8, 414.9)

Source: Adapted from Table 14.2.9 in the CSR Part B for Study 209.

#### 6.3.11.4 Subpopulation Analyses

Antibody concentration measured by ELISA and NT after the third vaccination were reported for different age strata (Table 31). The highest GMT was observed in the 1-2 years old group and the GMT generally decreases as age increases.

**Table 31. Antibody concentration measured by ELISA and NT after the 3rd vaccination by age strata**

Age	N	ELISA GMT (95% CI)	NT GMT (95% CI)
1-2 years	75	9281.4 (8109.6, 10622.5)	567.6 (526.6, 611.8)
3-6 years	76	7991.5 (6700.8, 9530.8)	469.3 (399.2, 551.8)
7-15 years	211	4270.4 (3774.9, 4830.8)	307.4 (272.3, 347.0)

Source: Adapted from Tables 14.2.8 and 14.2.10 in the CSR Part B for Study 209.

### 6.3.11.5 Exploratory and Post Hoc Analyses

N/A

### 6.3.12 Safety Analyses

#### Primary endpoint: fever rate after the first vaccination

Analysis of the primary endpoint (fever after the first vaccination) was performed on the Per Protocol Dataset I, which was comprised of 2374 subjects. Fever occurred more frequently in younger than in older subjects. Among subjects aged 1-2 years, 3-6 years and 7-15 years, the estimated frequencies of fever were 36.1%, 12.9% and 5.6%, respectively (Table 32). As shown in Table 33, the vast majority of fever cases were mild. No severe fever (>40.0°C) was reported in any age category.

**Table 32. Occurrence of fever after the first vaccination by age group**

Age	Number of cases / Total N	Probability of fever (95% CI)
1-2 years	66 / 183	36.1 (29.1, 43.5)
3-6 years	72 / 559	12.9 (10.2, 15.9)
7-15 years	92 / 1632	5.6 (4.6, 6.9)
Total	230 / 2374	9.7 (8.5, 11.0)

Source: Adapted from Table 28 in the CSR Part A for Study 209.

**Table 33. Local reactions after the first vaccination by age group and severity**

Age	No fever	Mild	Moderate	Severe
1-2 years (N = 183)	117 (63.9%)	57 (31.1%)	9 (4.9%)	0 (0.0%)
3-6 years (N = 559)	487 (87.1%)	59 (10.6%)	13 (2.3%)	0 (0.0%)
7-15 years (N = 1632)	1540 (94.4%)	90 (5.5%)	2 (0.1%)	0 (0.0%)
Total (N = 2374)	2144 (90.3%)	206 (8.7%)	24 (1.0%)	0 (0.0%)

Source: Adapted from Table 29 in the CSR Part A for Study 209.

#### Secondary endpoints: local and systemic reactions after the first vaccination

The majority of local reactions were mild (Table 34). The lowest frequency was reported in children aged 1-2 years. The rates of local reactions were similar between the 3-6 years and 7-15 years age groups.

**Table 34. Local reactions after the first vaccination by age group and severity**

Age	No reactions	Mild	Moderate	Severe
1-2 years (N = 186)	161 (86.6%)	22 (11.8%)	3 (1.6%)	0 (0.0%)
3-6 years (N = 563)	434 (77.1%)	113 (20.1%)	16 (2.8%)	0 (0.0%)
7-15 years (N = 1668)	1227 (73.6%)	369 (22.1%)	67 (4.0%)	5 (0.3%)
Total (N = 2471)	1822 (75.4%)	504 (20.9%)	86 (3.6%)	5 (0.2%)

Source: Adapted from Table 36 in the CSR Part A for Study 209.

Table 35 shows an overview of systemic reactions (excluding fever) by age group and severity. In contrast to the trend seen with local reactions, systemic reactions were reported most frequently in children aged 1-2 years. The majority of the cases were mild. There were three cases of severe systemic reactions related to vaccination: one in the 3-6 years age group, and two in the 7-15 years age group.

**Table 35. Systemic reactions (excluding fever) related to first vaccination by age and severity**

Age	No reactions	Mild	Moderate	Severe
1-2 years (N = 186)	134 (72.0%)	46 (24.7%)	6 (3.2%)	0 (0.0%)
3-6 years (N = 563)	457 (81.2%)	86 (15.3%)	19 (3.4%)	1 (0.2%)
7-15 years (N = 1668)	1335 (80.0%)	284 (17.0%)	47 (2.8%)	2 (0.1%)
Total (N = 2471)	1926 (79.7%)	416 (17.2%)	72 (3.0%)	3 (0.1%)

Source: Adapted from Table 40 in the CSR Part A for Study 209.

**Secondary endpoint: fever rate after the second vaccination**

Table 36 shows the analysis results of body temperature measurements after the second vaccination. Fever was mild in all except four cases and occurred more frequently among children aged 1-2 years than in subjects >2 years of age.

**Table 36. Severity of fever after the second vaccination by age**

Age	No fever	Mild	Moderate	Severe
1-2 years (N = 183)	160 (87.4%)	22 (12.0%)	0 (0.0%)	1 (0.5%)
3-6 years (N = 558)	545 (97.7%)	11 (2.0%)	2 (0.4%)	0 (0.0%)
7-15 years (N = 1636)	1617 (98.8%)	18 (1.1%)	1 (0.1%)	0 (0.0%)
Total (N = 2377)	2322 (97.7%)	51 (2.1%)	3 (0.1%)	1 (0.0%)

Source: Adapted from Table 46 in the CSR Part A for Study 209.

**Secondary endpoints: local and systemic reactions after the second vaccination**

The analysis of adverse reactions after the second vaccination shows that local reactions occurred least frequently among children aged 1-2 years (Table 37), while systemic reactions were reported slightly more frequently in this age group than in subjects aged >2 years (Table 38).

**Table 37. Local reactions after the second vaccination**

Age	No reaction	Mild	Moderate	Severe
1-2 years (N = 185)	170 (91.9%)	11 (5.9%)	4 (2.2%)	0 (0.0%)
3-6 years (N = 561)	474 (84.5%)	70 (12.5%)	16 (2.9%)	1 (0.2%)
7-15 years (N = 1664)	1355 (81.4%)	250 (15.0%)	59 (3.5%)	0 (0.0%)
Total (N = 2410)	1999 (82.9%)	331 (13.7%)	79 (3.3%)	1 (0.0%)

Source: Adapted from Table 54 in the CSR Part A for Study 209.

**Table 38. Systemic reactions (excluding fever) after the second vaccination**

Age	No reaction	Mild	Moderate	Severe
1-2 years (N = 185)	164 (88.6%)	17 (9.2%)	4 (2.2%)	0 (0.0%)
3-6 years (N = 561)	523 (93.2%)	29 (5.2%)	9 (1.6%)	0 (0.0%)
7-15 years (N = 1664)	1523 (91.5%)	117 (7.0%)	24 (1.4%)	0 (0.0%)
Total (N = 2410)	2210 (91.7%)	163 (6.8%)	37 (1.5%)	0 (0.0%)

Source: Adapted from Table 55 in the CSR Part A for Study 209.

**Secondary endpoint: fever rate after the third vaccination**

Table 39 shows the analysis results of body temperature measurements after the third vaccination. Fever occurred more frequently among children aged 1-2 years (12.7%) than in subjects >2 years of age (2.7% and 1.2% in subjects aged 3-6 and 7-15, respectively). The majority of fever cases were classified as mild and most cases abated within 2 days.

**Table 39. Severity of fever after the third vaccination by age**

Age	No fever	Mild	Moderate	Severe
1-2 years (N = 181)	158 (87.3%)	21 (11.6%)	2 (1.1%)	0 (0.0%)
3-6 years (N = 554)	539 (97.3%)	11 (2.0%)	3 (0.5%)	1 (0.2%)
7-15 years (N = 1632)	1613 (98.8%)	14 (0.9%)	5 (0.3%)	0 (0.0%)
Total (N = 2367)	2310 (97.6%)	46 (1.9%)	10 (0.4%)	1(0.0%)

Source: Adapted from Table 14.3.2.1 in the CSR Part B for Study 209.

Secondary endpoints: local and systemic reactions after the third vaccination

The analysis of adverse reactions after the third vaccination shows that local reactions occurred least frequently among children aged 1-2 years (Table 40), while systemic reactions were reported slightly more frequently in this age group than in subjects aged >2 years (Table 41).

**Table 40. Local reactions after the third vaccination**

Age	No reaction	Mild	Moderate	Severe
1-2 years (N = 184)	170 (92.4%)	14 (7.6%)	0 (0.0%)	0 (0.0%)
3-6 years (N = 557)	467 (83.8%)	71 (12.7%)	19 (3.4%)	0 (0.0%)
7-15 years (N = 1649)	1310 (79.4%)	277 (16.8%)	60 (3.6%)	2 (0.1%)
Total (N = 2390)	1947 (81.5%)	362 (15.1%)	79 (3.3%)	2 (0.1%)

Source: Adapted from Table 14.3.3.1 in the CSR Part B for Study 209.

**Table 41. Systemic reactions (excluding fever) after the third vaccination**

Age	No reaction	Mild	Moderate	Severe
1-2 years (N = 184)	164 (89.1%)	20 (10.9%)	0 (0.0%)	0 (0.0%)
3-6 years (N = 557)	524 (94.1%)	30 (5.4%)	3 (0.5%)	0 (0.0%)
7-15 years (N = 1649)	1517 (92.0%)	117 (7.1%)	14 (0.8%)	1 (0.1%)
Total (N = 2390)	2205 (92.3%)	167 (7.0%)	17 (0.7%)	1 (0.0%)

Source: Adapted from Table 14.3.3.2 in the CSR Part B for Study 209.

#### 6.4 Supportive Studies

N/A

### 7. INTEGRATED OVERVIEW OF EFFICACY

The immunogenicity of FSME-IMMUN has been investigated in 11 adult clinical studies as listed in Table 1 (Study 208 was a safety study only and did not evaluate immunogenicity). The immunogenicity of FSME-IMMUN was evaluated in 12 clinical studies in children and adolescents 1 to <16 years of age as listed in Table 2 (immunogenicity was not evaluated in the post-marketing surveillance Study 197). Table 42 below summarizes the analysis populations for pooled immunogenicity data for primary vaccinations. Since multiple ELISA and NT assays were used across clinical trials, only studies with the Immunozyg ELISA and the Adner 2001 NT results available were included in the pooled analyses.

For pediatric pooled immunogenicity analyses, a total of 1026 and 1009 subjects were included in the Immunozyg ELISA post dose 2 and post dose 3 analysis populations respectively. For the pooled Adner 2001 NT analyses, a total of 497 and 495 subjects were included in the post dose 2 and post dose 3 analysis populations respectively (Table 43).

For adult pooled immunogenicity analyses, a total of 510 and 883 subjects were included in the Immunozyg ELISA post dose 2 and post dose 3 analysis populations respectively. For the pooled Adner 2001 NT analyses, a total of 370 and 755 subjects were included in the post dose 2 and post dose 3 analysis populations respectively (Table 44).

**Table 42. Immunogenicity Population for Pooled Immunogenicity Data**

<b>Analysis Population</b>	<b>Criteria</b>	<b>Adult Studies (Both Standard Schedule and Rapid Schedule)</b>	<b>Pediatric Studies (Standard Schedule Only)</b>
ELISA (IMMUNOZYM) Post dose 2	Had baseline and post dose 2 ELISA results available  Received at least 2-dose FSME-IMMUN  Baseline ELISA is seronegative (ELISA<=126)	Studies: 201/202, 225/690501, 690601  Standard schedule: 201/202 Rapid schedule: 225/690501, 690601 (Day 21 after dose 2)	Studies: 198/215, 199/206, 205/207, 209, 700801
ELISA (IMMUNOZYM) Post dose 3	Had baseline and post dose 3 ELISA results available  Received all 3-dose FSME-IMMUN  Baseline ELISA is seronegative (ELISA<=126)	Studies: 201/202, 208/213, 225/690501, 690601  Standard schedule: 201/202, 208/213 Rapid schedule: 225/690501, 690601 (Day 21 after dose 3)	Studies: 198/215, 199/206, 205/207, 209, 700801
NT (Adner 2001) Post dose 2	Had baseline and postdose2 NT results available  Received at least 2-dose FSME-IMMUN  Baseline NT is seronegative (NT<10)	Studies: 225/690501, 690601  Rapid schedule: 225/690501, 690601 (Day 21 after dose 2)	Studies: 209, 700801
NT (Adner 2001) Post dose 3	Had baseline and postdose3 NT results available  Received all 3-dose FSME-IMMUN  Baseline NT is seronegative (NT<10)	Studies: 208/213, 225/690501, 690601  Standard schedule: 208/213 Rapid schedule: 225/690501, 690601 (Day 21 after dose 3)	Studies: 209, 700801

Source: Adapted from Table 42 in Clinical Overview submitted to BLA 125740/0.0.

**Table 43. Demographic Characteristics - Pediatric Pooled Immunogenicity Populations**

	ELISA Post dose 2 (N= 1026)	ELISA Post dose 3 (N= 1009)	NT (Adner 2001) Post dose 2 (N= 497)	NT (Adner 2001) Post dose 3 (N= 495)
Age Mean (SD)	6.2 (4.26)	6.2 (4.25)	6.7 (4.23)	6.7 (4.22)
1- 5 Years N (%)	507 (49.4%)	496 (49.2%)	203 (40.8%)	198 (40.0%)
6-15 Years N (%)	519 (50.6%)	513 (50.8%)	294 (59.2%)	297 (60.0%)
Female N (%)	486 (47.4%)	476 (47.2%)	249 (50.1%)	245 (49.5%)
Male N (%)	540 (52.6%)	533 (52.8%)	248 (49.9%)	250 (50.5%)
Study 198/215 N (%)	100 (9.7%)	98 (9.7%)	0	0
Study 199/206 N (%)	202 (19.7%)	199 (19.7%)	0	0
Study 205/207 N (%)	206 (20.1%)	202 (20.0%)	0	0
Study 209 N (%)	375 (36.5%)	369 (36.6%)	368 (74.0%)	367 (74.1%)
Study 700801 N (%)	143 (13.9%)	141 (14.0%)	129 (26.0%)	128 (25.9%)

Source: Adapted from Table 43 in Clinical Overview submitted to BLA 125740/0.0.

**Table 44. Demographic Characteristics - Adult Pooled Immunogenicity Populations**

	ELISA Post dose 2 (N= 510)	ELISA Post dose 3 (N= 883)	NT (Adner 2001) Post dose 2 (N= 370)	NT (Adner 2001) Post dose 3 (N= 755)
Age Mean (SD)	43.5 (14.36)	38.7 (14.02)	45.5 (15.05)	38.7 (14.54)
Rapid immunization: 16-59 Years N (%)	305 (59.8%)	280 (31.7%)	296 (80.0%)	271 (35.9%)
Rapid immunization: ≥60 Years N (%)	73 (14.3%)	69 (7.8%)	74 (20.0%)	70 (9.3%)
Standard schedule: 16-64 Years N (%)	132 (25.9%)	534 (60.5%)	0	414 (54.8%)
Female N (%)	328 (64.3%)	537 (60.8%)	247 (66.8%)	461 (61.1%)
Male N (%)	182 (35.7%)	346 (39.2%)	123 (33.2%)	294 (38.9%)
Study 201/202 N (%)	132 (25.9%)	118 (13.4%)	0	0
Study 208/213 N (%)	0	416 (47.1%)	0	414 (54.8%)
Study 225/690501 N (%)	56 (11.0%)	41 (4.6%)	56 (15.1%)	41 (5.4%)
Study 690601 N (%)	322 (63.1%)	308 (34.9%)	314 (84.9%)	300 (39.7%)

Source: Adapted from Table 44 in Clinical Overview submitted to BLA 125740/0.0.

For the pediatric clinical program, results from Studies 198 and 215 demonstrated that a 3-dose series of FSME-IMMUN 0.25 mL with 1.2 µg antigen was highly immunogenic when administered to children 1 to 12 years of age and the third dose given 9 to 10 months after the second vaccination; seroconversion rates of 99% and 100% after the second and third vaccinations were observed respectively. Dose finding studies evaluated 3 dose levels of TBE antigen (0.3 µg, 0.6 µg, and 1.2 µg) in children 1 to <6 years of age

(Studies 199 and 206) and in children and adolescents 6 to <16 years of age (Studies 205 and 207). Subjects received the first 2 vaccinations 21 to 35 days apart and a third vaccination 6 months after the first vaccination. Results of immunogenicity analyses showed that immune responses to the 1.2 µg TBE-virus antigen dose were higher than those to the lower doses investigated, and that the 1.2 µg dose is optimal in terms of immunogenicity for children and adolescents aged 1 to <16 years. Study 209, conducted in subjects 1 to <16 years of age, showed high overall seropositivity rates after the second (96%) and third (100%) vaccinations as determined by NT. The study also showed similar immunogenicity of FSME-IMMUN 0.25 mL across five production lots. Table 45 below presents pooled seropositivity rates determined by ELISA and NT at 21 days after the second and third vaccinations under the standard schedule (0.25 mL). The seropositivity rates appear to be very high post doses 2 and 3 for both ELISA and NT results.

**Table 45. Standard immunization schedule, pooled seropositivity rates in pediatrics by age group - FSME-IMMUN 0.25 mL**

	ELISA Post dose 2 % (n/N) (95% CI)	ELISA Post dose 3 % (n/N) (95% CI)	NT (Adner 2001) Post dose 2 % (n/N) (95% CI)	NT (Adner 2001) Post dose 3 % (n/N) (95% CI)
1-5 Years	99.4% (504/507) (98.3%, 99.9%)	100.0% (496/496) (99.3%, 100.0%)	98.5% (200/203) (95.7%, 99.7%)	99.5% (197/198) (97.2%, 100.0%)
6-15 Years	96.9% (503/519) (95.0%, 98.2%)	99.8% (512/513) (98.9%, 100.0%)	95.6% (281/294) (92.6%, 97.6%)	99.7% (296/297) (98.1%, 100.0%)
Total	98.1% (1007/1026) (97.1%, 98.9%)	99.9% (1008/1009) (99.4%, 100.0%)	96.8% (481/497) (94.8%, 98.1%)	99.6% (493/495) (98.5%, 100.0%)

*Source: Adapted from Table 45 in Clinical Overview submitted to BLA 125740/0.0.*

For the adult clinical program, dose-ranging Studies 201 and 202 concluded that 3 consecutive vaccinations of the 2.4 µg antigen dose of FSME-IMMUN provided higher immunogenicity as compared with the 1.2 µg or 0.6 µg antigen doses. Results from Study 213 demonstrated that, regardless of which TBE vaccine (FSME-IMMUN or ENCEPUR) was administered for the first 2 vaccinations in the preceding safety study (Study 208), a third vaccination with FSME-IMMUN (in Study 213) induced a strong immune response when administered 6 months (± 28 days) after the first vaccination. Studies 225/690501 and 690601 evaluated a rapid immunization schedule comprising 2 vaccinations with FSME-IMMUN on Days 0 and 12±2. Table 46 below presents pooled seropositivity rates determined by ELISA and NT at 21 days after the second and third vaccinations under the standard and the rapid immunization schedules for adults. The seropositivity rates appear to be very high post dose 3 for both ELISA and NT results.

**Table 46. Standard and Rapid Immunization Schedules, Pooled Seropositivity Rates in adults by Age Group - FSME-IMMUN 0.5 mL**

	ELISA Post dose 2 % (n/N) (95% CI)	ELISA Post dose 3 % (n/N) (95% CI)	NT (Adner 2001) Post dose 2 % (n/N) (95% CI)	NT (Adner 2001) Post dose 3 % (n/N) (95% CI)
Standard schedule: 16- 64 Years	97.0% (128/132) (92.4%, 99.2%)	99.1% (529/534) (97.8%, 99.7%)	N/A	99.3% (411/414) (97.9%, 99.9%)
Rapid immunization: 16-59 Years	82.0% (250/305) (77.2%, 86.1%)	98.9% (277/280) (96.9%, 99.8%)	94.3% (279/296) (91.0%, 96.6%)	99.6% (270/271) (98.0%, 100.0%)
Rapid immunization: ≥60 Years	71.2% (52/73) (59.4%, 81.2%)	94.2% (65/69) (85.8%, 98.4%)	90.5% (67/74) (81.5%, 96.1%)	98.6% (69/70) (92.3%, 100.0%)
Total	84.3% (430/510) (80.9%, 87.4%)	98.6% (871/883) (97.6%, 99.3%)	93.5% (346/370) (90.5%, 95.8%)	99.3% (750/755) (98.5%, 99.8%)

Source: Adapted from Table 46 in Clinical Overview submitted to BLA 125740/0.0.

*Reviewer's Comment:*

*Studies 225/690501 and 690601 evaluated rapid immunization schedule in adults. The majority of the pooled data shown in Table 46 above came from Study 690601, in which subjects were enrolled in two age groups, i.e., 16 to 49 years old and 50 years or older. It is not clear why the applicant summarized the immunogenicity data for the rapid immunization schedule according to different age strata in the pooled analyses, i.e., 16-59 years old and ≥60 years old. At the request of the clinical team, I calculated the pooled immunogenicity results post dose 3 for the rapid immunization schedule according to the planned age strata in the trial and completed the following Table 47. For the standard immunization schedule (i.e., 0 and 28 days, and 6 months in Table 47), immunogenicity results from Studies 202 and 213 were pooled; whereas immunogenicity results from Studies 690501 and 690601 were pooled for the rapid immunization schedule (i.e., 0 and 14 days, and 6 or 12 months in Table 47). The subjects included in the analysis met the following criteria: 1) received all 3-dose FSME IMMUN 0.5 ml; 2) had valid ELISA results available at both baseline and post dose 3; 3) seronegative at baseline.*

**Table 47. Standard and Rapid Immunization Schedules, Pooled Seropositivity Rates in adults by Age Group - FSME-IMMUN 0.5 mL**

Age	Dose Schedule	ELISA Post dose 3 % (n/N)	ELISA Post dose 3 (95% CI)	NT (Adner 2001) Post dose 3 % (n/N)	NT (Adner 2001) Post dose 3 (95% CI)
16-64 years	0 and 28 days, and 6 months	99.1% (529/534)	(97.8, 99.7%)	99.3% (411/414)	(97.9%, 99%)
16-49 years	0 and 14 days, and 6 or 12 months	99.5% (185/186)	(97.0%, 100%)	100% (178/178)	(97.9%, 100%)
≥50 years	0 and 14 and 6 or 12 months	96.3% (157/163)	(92.2%, 98.6%)	98.8% (161/163)	(95.6%, 99.9%)
Total		98.6% (871/883)	(97.6%, 99.3%)	99.3% (750/755)	(98.5%, 99.8%)

Source: Reviewer's analysis based on the data submitted to BLA 125740/0.0.

Regarding persistence of antibody after the first booster, the applicant presented the data shown in Tables 48 and 49. The primary immunogenicity endpoint in Study 700802 in the pediatric population was seropositivity rate measured by NT at approximately 38, 46, 58, 70, 82, 94, 106, and 118 months after the first booster vaccination administered in Study 700401. Table 48 presents the predicted Month 58 immunogenicity data based on annual decline rates for the TBE antibody response measured by NT utilizing all 9 time points from 1 month after the first booster dose to 10 years after the first booster dose. The seropositivity rate appears to be high 5 years after the first booster dose.

Table 49 presents the seropositivity rates among adult population included in Study 690701, which also predicted NT GMT values based on annual decline rate estimated from 1 month until 118 months after the first booster vaccination. The seropositivity rate appears to be high 5 years after the first booster dose.

**Table 48. Seropositivity Rates (NT) 5 Years After First Booster Dose in pediatrics - FSME-IMMUN 0.25 mL**

1-2 years of age		3-6 years of age		7-15 years of age		Total	
% (n/N)	95% CI	% (n/N)	95% CI	% (n/N)	95% CI	% (n/N)	95% CI
96.6 (28/29)	(82.2, 99.9)	100.0 (25/25)	(86.3, 100.0)	100.0 (102/102)	(96.4, 100.0)	99.4 (155/156)	(96.5, 100.0)

Source: Adapted from Table 37 in the Summary of Clinical efficacy submitted to BLA 125740/0.0.

**Table 49. Seropositivity Rates (NT) 5 Years After First Booster Dose in adults - FSME-IMMUN 0.5 mL**

	18-49 years of age		50-60 years of age		>60 years of age	
Visit	% (n/N)	(95% CI)	% (n/N)	(95% CI)	% (n/N)	(95% CI)
Month 34	100.0 (245/245)	(98.5, 100.0)	100.0 (51/51)	(93.0, 100.0)	100.0 (9/9)	(66.4, 100.0)
Month 46	97.6 (239/245)	(94.7, 99.1)	92.2 (47/51)	(81.1, 97.8)	77.8 (7/9)	(40.0, 97.2)
Month 58	96.7 (237/245)	(93.7, 98.6)	92.2 (47/51)	(81.1, 97.8)	75.0 (6/8)	(34.9, 96.8)

Source: Adapted from Table 12 in the Summary of Clinical efficacy submitted to BLA 125740/0.0.

*Reviewer's Comment:*

*The predicted seropositivity rates were slightly lower than that observed in Study 690701. For example, at Month 58 after first booster dose (presented in Table 49), among 304 subjects included in the analysis, 290 subjects (95.4%) are seropositive (NT titer  $\geq 10$ ) based on the extrapolated data. I examined the dataset for Study 690701, in which there are 284 subjects with measured NT titers available at Month 58. All of them were seropositive (i.e., seropositivity rate = 100%), and 264 subjects (93.0%) had NT titers  $\geq 40$  at Month 58.*

8. INTEGRATED OVERVIEW OF SAFETY

No pooled safety analyses were performed.

9. ADDITIONAL STATISTICAL ISSUES

N/A

10. CONCLUSIONS

The immunogenicity data demonstrate high immune responses to the TBE vaccine among adult and pediatric populations. The safety profile of FSME-IMMUN is characterized mainly by local and systemic reactions that are commonly observed after vaccinations, and appears to be acceptable. Overall, from the statistical perspective, the submitted clinical study results support the approval of this application.