BLA Clinical Review Memorandum

Application Type	Original BLA
STN	STN 125740
CBER Received Date	12/15/2020
PDUFA Goal Date	08/15/2021
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Ihid Carneiro Leao, MD, PhD
Review Completion Date / Stamped Date	08/13/2021
Supervisory Concurrence	Meghan Ferris, MD, MPH Team Leader Andrea Hulse, MD Chief, Clinical Review Branch 2
Applicant	Pfizer Ireland Pharmaceuticals
Established Name	Tick-Borne Encephalitis Vaccine
(Proposed) Trade Name	TICOVAC
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	TICOVAC is a sterile suspension of formaldehyde-inactivated and sucrose gradient-purified TBE virus antigen obtained from chick embryo fibroblast (CEF) cells, bound to an adjuvant (aluminum hydroxide) and diluted in a buffer system containing human serum albumin (HSA). TICOVAC is supplied as a 0.5mL single-dose syringe (for use in persons 16 years of age and older) and a 0.25mL single-dose syringe (for use in persons 1 to <16 years of age). Each 0.5 mL dose contains 2.4 micrograms of TBE virus antigen with aluminum hydroxide as an adjuvant. Each 0.25mL dose of TICOVAC contains the same vaccine components in half of the quantities.
Dosage Form(s) and Route(s) of Administration	Suspension for injection in a 0.5 mL or 0.25 mL single-dose pre-filled syringe.
Dosing Regimen	For individuals 16 years of age and older (0.5 mL dose): The second dose is administered 14 days to 3 months after the first dose, and the third dose is administered 5 to 12 months after the second dose. For individuals 1 to <16 years of age (0.25 mL dose): The second dose is administered 1 to 3

	months after the first dose, and the third dose is administered 5 to 12 months after the second dose. **Booster Vaccination**: A booster dose (fourth dose) may be given at least 3 years after completion of the primary immunization series if ongoing exposure or re-exposure to TBEV is expected.
Indication(s) and Intended Population(s)	For active immunization to prevent tick-borne encephalitis (TBE) in individuals 1 year of age and older.
Orphan Designated (Yes/No)	No

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Glossary

AE	adverse event
BIMO	Bioresearch Monitoring
BLA	biologics license application
CBER	Center for Biologics Evaluation and Review
CEF	chick embryo fibroblast
CFR	Code of Federal Regulations
CI	confidence interval
CJD	Creutzfeldt-Jakob disease
CMC	chemistry, manufacturing, and controls
CRO	Clinical Research Organization
CSR	clinical study report
CTC	Common Toxicity Criteria
DMF	Drug Master File
DOD	US Department of Defense
ECDC	European Centre for Disease Prevention and Control
E glycoprotein	envelope glycoprotein
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
FDA	US Food and Drug Administration
FSME-IMMUN	inactivated whole-virus vaccine for tick-borne encephalitis
GMC	geometric mean concentration
GMFI	geometric mean fold increase
GMT	geometric mean titer
HSA	human serum albumin
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IND	investigational new drug
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NCT	National Clinical Trial
NT	neutralization test
PeRC	Pediatric Review Committee
PREA	Pediatric Research Equity Act
SAE	serious adverse event
SC	subcutaneous
TBE	tick-borne encephalitis
TBEV	tick-borne encephalitis virus
US	United States
VIEU/mL	Vienna units per milliliter
WHO	World Health Organization

1. Executive Summary

Under Biologics License Application (BLA) 125740, Pfizer Ireland Pharmaceutics, a subsidiary of Pfizer Inc., submitted immunogenicity and safety data from clinical trials, and vaccine effectiveness data from a field study to support licensure of a vaccine to prevent tick-borne encephalitis (TBE) (Tick-Borne Encephalitis Vaccine, TICOVAC). The US Food and Drug Administration (FDA) granted priority review to this application.

The proposed trade name for the vaccine is TICOVAC. In this review, the vaccine is referred to as TICOVAC, FSME-IMMUN, FSME-IMMUN (CC) without thiomersal and FSME-IMMUN "NEW." The proposed indication for TICOVAC is "for active immunization to prevent tick-borne encephalitis (TBE) in individuals one year of age and older."

The proposed primary vaccination series is three doses administered intramuscularly. For individuals 16 years of age and older ("adults") the three-dose schedule is administered as follows: 0, 14 days to 3 months after dose 1, and 5 to 12 months after dose 2. For individuals 1 to <16 years of age ("children") the schedule is administered as follows: 0, 1 to 3 months after dose 1, and 5 to 12 months after dose 2. The Applicant is also proposing a booster dose to be administered at least 3 years after completion of the primary series. The proposed dosing schedule in adults and children is based on the dosing schedule used in the clinical studies of TICOVAC, on post-marketing safety during decades of use in Europe and on field effectiveness data from Austria.

Currently, there is no licensed vaccine in the United States (US) to prevent TBE, a disease caused by a tick-borne encephalitis virus (TBEV). People who work in or travel to TBEV-endemic regions and engage in warm weather outdoor activities are at highest risk for TBE. Laboratory workers are also at risk of infection due to accidental aerosol exposure while working with the virus (Subcommittee on Arbovirus Laboratory Safety 1980; Avšič-Županc et al. 1995). To protect US military personnel deployed to TBEV-endemic areas, the US Department of Defense (DOD) requested that Pfizer seek licensure for its TBE vaccine in the US. DOD cited Public Law 115-92, which authorizes the DOD to request, and the FDA to take, specific actions to expedite the development and review of medical products reasonably likely to prevent serious or life-threatening risk to US military personnel. The Applicant reports that as of June 2020, TICOVAC (marketed as FSME-IMMUN in some countries) has received marketing authorization in 32 countries and is currently marketed in 28 countries as a 0.5 mL presentation for individuals 16 years of age and older ("adults") and in 27 countries as a 0.25 mL presentation for individuals 1 through 15 years of age ("children"), also referred to as "pediatric dose" in this review memo.

Clinical trials evaluating the safety and effectiveness TICOVAC were not conducted under an FDA Investigational New Drug application (IND). In response to Pfizer's request for advice on the acceptability of the available data to support a licensure application, the FDA advised the manufacturer to submit a Drug Master File (DMF). DMF (b) (4) was submitted in March 2019.

Safety

In clinical studies submitted to the BLA, 4427 adults received at least one 0.5 mL-dose of TICOVAC and 3240 children received at least one 0.25 mL-dose of TICOVAC. In dose-ranging studies, an additional 270 adult subjects received doses of the vaccine containing one-fourth or one-half the amount of TBEV antigen contained in the 0.5mL dose, and an additional 856 children received doses containing one-fourth or one-half the amount of antigen contained in the pediatric dose.

The safety of TICOVAC was investigated in 10 clinical studies in adults >16 years of age (Studies 201/202, 208/213, 223, 690701, 691101, 225/690501 and 690601).[1]

The evaluated schedules of the primary vaccine series in individuals older than 16 years of age were as follows: in Studies 208/213 and 201/202, doses 1 and 2 were administered 21 to 35 days apart and dose 3 was administered 6 months after the first dose; while in Studies 225 and 690601, doses 1 and 2 were administered 12±2 days apart followed by dose 3 at 6 months after dose 1 in Study 690601 and at 12 months after dose 2 in Study 690501 (follow-on of Study 225).

In Study 223, a booster dose was administered 3 years after the third dose of the primary series administered to adults in Study 213. Two follow-on studies (Studies 690701 and 691101) evaluated seropersistence after the booster given in Study 223 and administration of one additional booster dose, (b) (4)

In pediatric subjects, safety was assessed in 11 studies, including one postmarketing surveillance study (Study 197 in children aged 6 months to <13 years) and 10 clinical studies in pediatric subjects 1to <16 years of age (Studies 198/215, 199/206, 205/207, 209/700401, 700802 and 700801). In these studies, most subjects (in Studies 199/206, 205/207, and 209) received 2 doses of TICOVAC 21 to 35 days apart, with the third dose given approximately 6 months after the first dose. In the early pilot studies (198/215), the first two doses were given 14 to 32 days apart. However, the data to support administration of the first two doses 14 days apart in children are insufficient because only five children were vaccinated using that schedule. The third dose in Study 215 was given 9 to 10 months after the second dose; and in Study 700801, which compared TICOVAC and a non-US-licensed TBE vaccine comparator, two doses were given 25 to 31 days apart, with the third dose given approximately 1 year after the first dose. Subjects who received a primary series in Study 209 were evaluated for antibody persistence following the primary series and following a booster (fourth dose) in Studies 700401 and 700802, respectively.

As methods of collecting safety data varied between studies submitted to this BLA, pooling of safety data was limited to reported serious adverse events (SAEs). Among 3240 pediatric subjects (1to <16 years of age) who received TICOVAC (0.25 mL) in clinical trials, serious adverse events and death were reported in 62 subjects and 1 subject respectively. Among 4427 subjects 16 years of age and older who received TICOVAC (0.5mL) in clinical trials, SAEs and deaths were reported in 54 subjects and 2 subjects, respectively. All these events were considered unrelated by the Principal Investigator, except for one SAE which was considered possibly related to the vaccine by the Principal Investigator: a 12-month-old boy had a febrile convulsion 2 days after vaccination in Study 197. Rhinopharyngitis, gastroenteritis, and otitis media were diagnosed and may have contributed to the occurrence of the febrile convulsion.

The most common adverse reactions reported after any dose in the primary series in the three pivotal clinical studies submitted in this application (Studies 208/213 and 209) were as follows:

- Studies 208/213 (adults 16-65 years of age): injection site local tenderness (29.9%), injection site pain (13.2%), fatigue (6.6%), headache (6.3%) and muscle pain (5.1%),

[1] In some TICOVAC studies subjects received only the first 2 doses of the TICOVAC primary series and were then re-enrolled in a follow-up study to receive the third dose. The study numbering for these studies in the review is shown as XXX/XXX.

- Study 209 (children 1-15 years of age): injection site tenderness (18.1%), injection site pain (11.2%), headache (11.1%), fever (9.6%) and restlessness (9.1%). Approximately 36% of children 1-2 years of age experienced fever (≥38ºC) within 4 days after administration of the first dose of TICOVAC.

The cumulative worldwide distribution for TICOVAC from launch in 2001 through January 31, 2020 is estimated to be (b) (4) doses, of which approximately 30% are the 0.25mL pediatric dose of TICOVAC. No safety signals were identified with the use of the vaccine in clinical studies.

Vaccine Effectiveness

Because of the low incidence of TBE (5 cases per 100,000 people/year in areas considered endemic), randomized clinical trials evaluated immunogenicity rather than clinical disease endpoints. Although a correlate or threshold of protection has not been defined for TBE vaccines (WHO 2011b), Tick Borne Encephalitis virus (TBEV) neutralizing antibodies are widely believed to confer protection. In TICOVAC clinical studies response to vaccination was evaluated using a TBE virus neutralization test (NT). A TBEV NT titer of ≥10 was considered seropositive. Although the neutralization assays used were not fully validated as per current standards, they were reviewed and found to be acceptable to measure immune responses induced by vaccination. Of note, immunogenicity data demonstrated an immune response among TICOVAC recipients as measured by NT while placebo recipients had no measurable immune response. In addition, overall field effectiveness of TBE vaccines including FSME-IMMUN (recommended for use in Austria for individuals above one year of age living in endemic area) was above 90% for all vaccinated individuals (refer to Real World Evidence BLA Memorandum). Data from these post-authorization field effectiveness studies together with the immunogenicity data provide evidence of the effectiveness of TICOVAC.

Four clinical studies provided immunogenicity data supporting TICOVAC vaccine effectiveness in adults (202, 213, 690501 and 690601): Studies 202 and 213 enrolled subjects 16-66 years of age. Antibody responses were evaluated 21 to 28 days after the third dose. Seropositivity rates by NT were 94.9% (95% confidence interval [CI] 89.3%, 98.1%) with a geometric mean titer (GMT) of 38.7 (95% CI: 32.5, 46.1) in Study 202 (N=118) and 98.8% (95% CI: 97.2%, 99.6%) with GMT of 259 (95% CI: 235.9, 285) for Study 213 (N=416). The NT data were generated using different methods in Study 202 and 213. Therefore, although the proportion of seropositive (NT titer ≥1:10) subjects is similar in both studies, the GMTs from these two studies cannot be directly compared. In addition, Study 690501 measured immune responses following completion of the three-dose primary series in 41 subjects 16-65 years of age while Study 690601 did the same in 297 subjects ≥16 years of age with no upper age limit. Approximately 9% (31/340) of subjects enrolled in Study 690601 were ≥65 years of age. In both studies, the first 2 doses were administered 12±2 days apart. Seropositivity rates based on NT at Day 7 after the third dose were 100% in Study 690501 and 90.6% in Study 690601. At Day 21 after the third dose, seropositivity remained at 100% in Study 690501 (GMT 360.2; 95% CI: 286, 453.6) and increased to 99.3% in Study 690601 (GMT 145.6; 95% CI: 127.2, 166.8).

Three studies in adults assessed seropersistence after the primary series and booster (fourth) dose (Study 223, 690701 and 691101). Study 223 assessed TBEV antibody persistence 2 and 3 years (±28 days) after the third dose of TICOVAC administered in Study 213 (N=252); the study also evaluated the antibody response to a booster vaccination of TICOVAC administered at 3 years ±28 days after the third dose in Study 213 (N=240). The seropositivity rate 3 years after the third dose was 94.2% (95% CI: 90.4%, 96.8%) and 100% (95% CI: 98.5%, 100%) one

month after the booster dose. Studies 69070/691101 were follow-on studies in subjects who received their primary immunization series in Studies 208/213, their first booster dose in Study 223 and were subsequently followed through 10 years post-first booster dose (i.e., Study 690701 for the initial 5 years and Study 691101 during years 7 through 10). After 10 years of follow-up post-first booster, 84.9% of the subjects who participated in both studies were still considered seropositive as measured by NT.

In the pediatric clinical program, four dose finding studies evaluated three dose levels of TBEV 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). Results of immunogenicity analyses by NT showed that immune responses to the 1.2 µg TBEV antigen dose were higher than those to the lower doses investigated; thus, the 1.2 µg TBEV antigen dose was chosen as optimal for use in children and adolescents 1 to <16 years of age. Two studies provided support for the vaccine effectiveness of the 0.25mL dose (containing 1.2 µg TBEV antigen) of TICOVAC in the pediatric population (Studies 209 and 700801). Study 209 enrolled subjects 1 <16 years of age (N=368) and seropositivity rates by NT 35 to 42 days after the third dose were 99.4% (95% CI: 98%, 99.9%). Study 700801 enrolled children 1 to <12 years of age (N=129) and seropositivity rates by NT 28 to 31 days after the third dose were 100% (95% CI: 97.2%, 100%).

For the pediatric program there were two follow-on studies that evaluated seropersistence after the primary series and the use of booster doses (Studies 700401 and 700802). Study 700401 was a follow-on study in subjects who had received all three doses of the primary series in Study 209. The study was designed to assess the seropersistence of TBEV antibodies (N=358) and to evaluate the response to a booster vaccination (N=175). Seropositivity rates were summarized separately by age group, based on the age of the subjects in Study 209. At 34 months after the third dose in Study 209, seropositivity rates by NT were 100% (95% CI: 95.1%,100%) in the 1 to 2 years age group (N=73); 98.5% (95% CI: 92.1%, 100%) in the 3 to 6 years age group (N=68) and 97.2% (95% CI: 93.9%, 99%) in the 7 to 15 years age group (N=212). Approximately 50% (N=175) of the subjects received the booster three years after the primary series. Study 700802 was a follow-on study in subjects who received three doses in Study 209 and a first booster dose in Study 700401. The study was designed to assess the 10-year seropersistence of TBEV antibodies, and to evaluate the response to a second booster dose given in the study. Seropositivity rates by NT remained at or above 96.6% for all age groups through 5 years and at or above 86.2% through 10 years post-first booster.

In summary, high seropositivity rates (94.9%-100%) were demonstrated in the adult and pediatric populations after the administration of the three-dose primary series of TICOVAC. At three years after completion of the primary series, seropositivity by NT remained high (94.2%-100%). To maintain seropositivity levels, a booster dose can be administered at least 3 years post completion of the primary series. The immunogenicity data together with the vaccine effectiveness estimates from field studies submitted to the BLA (see review memo from Yun Lu, Real World Evidence BLA Memorandum) demonstrate substantial evidence of effectiveness of FSME-IMMUN. There are not enough data from clinical trials to support (b) (4)

Based on multidisciplinary review of the data submitted for licensure, the Center for Biologics Evaluation and Review (CBER) did not identify issues that would have required the input of an independent panel of experts and determined that it was not necessary to refer the application to an FDA advisory committee.

There are some limitations in the submitted data. The vaccine was not evaluated in subjects living in TBEV non-endemic areas who travel to TBEV-endemic areas. Flavivirus-experienced subjects were excluded from protocol participation. It is possible that previous exposure to other flaviviruses may affect immune response to TBE vaccination because of cross-reactive flavivirus antibodies. Likewise, it is possible that co-administration of TBE vaccine with flavivirus vaccines may affect immune responses to either or both vaccines (Kayser et al. 1985; Bradt et al. 2019). These hypotheses have not been formally evaluated in clinical trials.

The Applicant did not investigate the use of vaccine in pregnant or breastfeeding women or in immunocompromised individuals and did not submit studies evaluating safety or effectiveness of TICOVAC when co-administered with other vaccines. Clinical studies of TICOVAC did not include sufficient numbers of subjects ages 65 years and older to determine whether they respond differently from younger subjects.

This BLA submission is subject to the Pediatric Research Equity Act (PREA) because it is an application for a new active ingredient. The assessment of the safety and effectiveness of TICOVAC for the prevention of TBE in the pediatric population 1 to <17 years of age and the request for a partial waiver of the assessment for infants 0 to <12 months of age were presented to the Pediatric Review Committee (PeRC) on July 27, 2021. The PeRC agreed with the Division's decision to grant the partial waiver based on the rationale that studies in children younger than 12 months would be highly impracticable to conduct because: (1) potential immune response interference due to the presence of pre-existing maternal antibodies in infants born in endemic areas and (2) infants in non-endemic areas could not be ethically enrolled in a study from which no prospect of direct benefit exists.

Conclusions

The adult and pediatric safety and effectiveness data submitted in the BLA support a favorable risk-benefit assessment of TICOVAC for active immunization to prevent tick-borne encephalitis (TBE) in individuals 1 year of age and older.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The demographic characteristics for the adult and pediatric safety populations provided below include sex and age. Information regarding race was not collected in the submitted studies. All submitted studies were completed in five countries in Europe (Austria, Belgium, Czech Republic, Germany, and Poland).

In the adult studies, including 4427 adults who received at least one vaccination with the dosage selected for marketing as well as an additional 270 adults who received other dosages, 2252 subjects (48%) were male and 2445 (52%) were female. The tables below present distribution by sex in Studies 201, 208, 213, 225 and 690601. However, the other five clinical studies that contributed to the safety analysis (i.e., Studies 202, 223, 690701, 691101 and 690501) are accounted for in the tables because they were follow-on to the studies included in the tables.

In Studies 201, 225, and 690601, there was a preponderance of females (62.7% to 68.3%) (Table 1). The distribution of subjects by age is shown for five of the adult studies in Table 2 and Table 3.

Table 1. Distribution of Subjects by Sex, All Subjects Who Received at Least 1 Dose of FSME-IMMUN (at Any Dose Level) Adult Studies 201, 208, 213, 225, 690601

Study Number	Male n (%)	Female n (%)	Total N
201	151 (37.3)	254 (62.7)	405
208	1518 (51.0)	1459 (49.0)	2977
213[a]	441 (48.2)	474 (51.8)	915
225	19 (31.7)	41 (68.3)	60
690601	123 (36.2)	217 (63.8)	340
Total	**2252 (48%)**	**2445 (52%)**	**4697**

Source: Summary of Clinical Safety, pages 33, 34
[a] Subjects who received non-US licensed comparator in Study 208

Table 2. Distribution of Subjects Who Received at Least 1 Dose (at Any Dose Level) of FSME-IMMUN by Age Range, Adult Studies 201, 208, 213, and 225

Age Range (Years)	Study 201 n (%)	Study 208 n (%)	Study 213[a] n (%)	Study 225 n (%)
16-25	64 (15.8)	1275 (42.8)	369 (40.3)	11 (18.3)
26-35	97 (23.95)	600 (20.2)	163 (17.8)	7 (11.7)
36-45	115 (28.39)	626 (21.0)	208 (22.7)	22 (36.7)
46-55	90 (22.22)	385 (12.9)	135 (14.8)	11 (18.3)
55-65	39 (9.63)	91 (3.1)	40 (4.4)	9 (15.0)
Total	**405**	**2977**	**915**	**60**

Source: Summary of Clinical Safety, pages 33, 34
[a] Subjects vaccinated with non-US licensed comparator in Study 208 who received FSME-IMMUN in Study 213

Table 3. Distribution of Subjects Who Received FSME-IMMUN by Age Range, Study 690601

Age Range	n	%
16-19 years	16	(4.7%)
20-29 years	41	(12.1%)
30-39 years	52	(15.3%)
40-49 years	61	(17.9%)
50-59 years	97	(28.5%)
60-69 years	63	(18.5%)
70-79 years	10	(2.9%)
80 years or older	0	(0.0%)
Total	**340**	**(100.0%)**

Source: Summary of Clinical Safety, pages 33, 34

In the pediatric studies, including 3240 children who received at least one vaccination with the dosage selected for marketing as well as an additional 856 children who received other dosages, 2118 subjects (51.7%) were male and 1978 (48.3%) were female (Table 4). The distribution of subjects by age is shown for five of the pediatric studies in Table 5, Table 6, and Table 7. The other five pediatric studies not mentioned below were follow-on studies (215, 206, 207,700401 and700802), therefore they do not change the demographic information.

Table 4. Distribution of Subjects by Sex, All Subjects Who Received at Least One Dose of FSME-IMMUN (at Any Dose Level) in the Pediatric Clinical Studies of Safety

Study Number	Male n (%)	Female n (%)	Total N
198	52 (51.5)	49 (48.5)	101
199	334 (52.3)	305 (47.7)	639
205	341 (53.4)	298 (46.6)	639
209	1241 (51.3)	1176 (48.7)	2417
700801 (Dose 1)	73 (48.7)	77 (51.3)	150
700801 (Dose 3)[a]	77 (51.3)	73 (48.7)	150
Total	**2118 (51.7)**	**1978(48.3)**	**4096**

Source: Original BLA, pages 34, 35 of Clinical Safety
[a] Subjects who received non-US licensed TBE vaccine comparator at dose 1 and dose 2 but received FSME-IMMUN for dose 3

Table 5. Distribution of Subjects Who Received FSME-IMMUN (at Any Dose Level) by Age Range, Pediatric Studies 199 and 209

Age Range	Study 199 n (%)	Study 209 n (%)
1-2 years	259 (40.5)	186 (7.7)
3-4 years	266 (41.6)	250 (10.3)
5-6 years	114 (17.8)	313 (12.9)
7-8 years	-	336 (13.9)
9-10 years	-	357 (14.8)
11-12 years	-	371 (15.3)
13-14 years	-	604 (25.0)
Total	**639**	**2417**

Source: Original BLA, pages 34, 35 of Clinical Safety

Table 6. Distribution of Subjects Who Received FSME-IMMUN (at Any Dose Level) by Age Range, Pediatric Studies 198 and 205

Age Range	Study 198 n (%)	Study 209 n (%)
1-3 years	93 (92.1)	-
4-9 years	8 (7.9)	322 (50.4)
10-11 years	-	125 (19.6)
12-13 years	-	117 (18.3)
14-15 years	-	75 (11.7)
Total	**101**	**639**

Source: Original BLA, pages 34, 35 of Clinical Safety

Table 7. Distribution of Subjects Who Received FSME-IMMUN by Age Range, Pediatric Study 700801

Age Range	Number of Subjects (%) FSME-IMMUN	Mean Age (Years) FSME-IMMUN	Number of Subjects (%) Non-US licensed TBE vaccine comparator	Mean Age (Years) Non-US licensed TBE vaccine comparator
1-2 years	50	1.4	50	1.3
3-6 years	51	4.8	51	4.4
7-11 years	49	8.9	51	8.7
Total	**150**		**152**	

Source: Original BLA, pages 34, 35 of Clinical Safety

In Study 197, a postmarketing observational safety study in children who received FSME-IMMUN, 1899 subjects were included in the evaluation of safety; 53.0% were male and 46.6%

were female (0.4% not reported). Age distribution was as follows: 6 months - <1 year, 467 subjects (24.6%); 1 to 3 years, 1198 (63.1%); 4 to 6 years, 143 (7.5%); 7 to 9 years, 55 (2.9%); 10 to 12 years, 36 (1.9%).

1.2 Patient Experience Data

Patient experience data were not submitted as part of this application.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Tick-borne encephalitis virus (TBEV) is a flavivirus transmitted mainly by *Ixodes* tick species and by unpasteurized dairy products, mainly goat milk. TBE is an important infectious disease in areas where there is a reservoir of *Ixodes* ticks, including many parts of central Europe, countries that made up the former Soviet Union, and Asia. There are no reports of TBE occurring in North America, so the risk to residents of the United States (US) is primarily through travel to endemic regions. According to the European Center for Disease Prevention and Control, there were 3246 serologically confirmed notifiable cases of TBE in countries in the European Union in 2019. Notifiable cases are defined as cases with symptoms of inflammation of the CNS (e.g., meningitis, meningoencephalitis, encephalomyelitis and encephaloradiculitis) and are further confirmed as TBE using serological or virological criteria. Cases occurred seasonally (with 95% of cases occurring between May and November) and were reported more frequently among men than women. Rates were highest among adults 45-65 years of age. From 2015 to 2019, European reports of TBE increased from 0.4 to 0.7 cases per 100,000 population. In 2019, as in previous years, the highest notification rates were reported in Lithuania, Czechia and Estonia (ECDC 2019b).

Prior to 2000, only one case of TBE was reported among US travelers. Between 2000 and 2020, 11 cases in US residents were identified, with countries of probable acquisition including Czech Republic, Sweden, Russia, Switzerland, Austria, Finland and China. US military personnel and their family members are at risk of infection with TBEV while stationed in Europe. Mancuso et al. used military health records and laboratory data to identify cases of TBE among US military service members and their dependents between 2006 and 2018 (Mancuso et al. 2019). A total of 8 individuals (5 service members, 3 children) met the case definition for TBE over the 13-year interval. All eight cases occurred in Germany. The authors concluded that, although the case numbers during the 13 years were small, the number of cases during 2017 to 2018 (n=7) greatly exceeded the number from the previous 11 years (n=1), suggesting an increased TBE risk in recent years. Although small numbers of cases in the US military population precluded formal statistical testing, the increase in observed number of cases in 2017 and 2018 was considered consistent with increases reported in the German population, which were statistically significant. The authors concluded that based on a population of approximately 50,000 US military service members and beneficiaries dispersed throughout Germany, approximately 1 case per year of TBEV infection would be expected.

TBEV subtypes are closely related genetically and antigenically. There are three subtypes: the European, also called European/Western subtype (TBEV- Eu, continental Europe and the United Kingdom), the Far Eastern (TBEV- Fe) and the Siberian (TBEV- Sib) subtypes transmitted throughout eastern Europe and Asia, including China and Japan (Hayasaka et al. 2001b). Approximately two-thirds of TBEV infections are asymptomatic, although viremia can be demonstrated. For symptomatic individuals, TBE caused by the Western subtype often has a biphasic course. The first phase is associated with non-specific symptoms (such as fever,

fatigue, headache, myalgia, or nausea). This phase is followed by an afebrile asymptomatic interval that precedes the second phase, when the central nervous system is affected and can present as meningoencephalitis, myelitis, or paralysis. Only 20% to 30% of those infected with TBEV proceed into the second phase of the disease. The clinical manifestations of this second febrile episode include 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. Encephalitic patients may develop stupor, pyramidal tract dysfunction, as well as paralyses that frequently involve muscles of the shoulder region. In up to 40% of encephalitic cases TBE results in permanent central nervous system sequelae, including various neuropsychiatric and cognitive complaints characteristic of the postencephalitic syndrome.

The clinical outcome may depend in part on the infecting TBEV subtype. The Western European subtype is associated with milder disease, mortality rates of 0.5% to 2%, and severe neurologic sequelae in up to 10% of patients. The Far Eastern subtype is associated with monophasic disease and mortality rates up to 35% (ECDC 2019a). The Siberian subtype is associated with a tendency for patients to develop chronic or extremely prolonged infections, and a fatality rate of 1% to 3% (Borde and Zajkowska 2017).

The clinical course and the probability of death or severe neurologic sequelae depend also on the age of the affected person, with severity increasing with age. The disease often takes a more acute course in the elderly population (Logar et al. 2006). Among patients with TBE, those older than 40 years of age were more likely than younger patients to develop the encephalitic form of the disease (Logar et al. 2006). In older patients, especially those older than 60 years of age, TBE can take a severe course, leading to paralysis and sometimes resulting in death. Paralysis occurs in 30% of patients who enter the acute phase of the illness (Krausler 1981; Herzig et al. 2002; Gritsun et al. 2003).

The course of illness is similar in children and adults, with some differences in several clinical and laboratory features, including that disease severity increases with age. In children, meningitis has been noted in 63%-79% of cases, meningoencephalitis in 21%-38%, and meningoencephalomyelitis in 0%-4%. Although TBE in childhood is, in general, a milder illness than TBE in adults, pediatric TBE carries a high risk for residual symptoms (e.g., headache, fatigue, memory problems, irritability, concentration problems), and it can be associated with ongoing or progressive neurodevelopmental and cognitive difficulties. Residual symptoms were seen in approximately 70% of children following the acute phase of the disease. Long-term sequelae of a somatic nature in childhood TBE such as severe neurologic residua (i.e., hemiparesis and epilepsy) have been reported less frequently than in adults (2% and 10%, respectively). Nevertheless, neurologic residua constitute a significant handicap, interfering with quality of life for many years.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently, there are neither effective specific treatments for TBE nor US-licensed vaccines against TBE. TBE clinical treatment is mainly supportive. Moreover, with no specific antiviral therapy licensed or available for TBEV infection, the disease may have serious or life-threatening consequences.

2.3 Safety and Efficacy of Pharmacologically Related Products

There is no US-licensed vaccine to prevent TBE.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

FSME-IMMUN was developed in the 1970s and licensed in Austria in 1976. The antigenic component of the vaccine comes from the European TBEV strain, Neudörfl (Barrett et al. 2003).

For the vaccine marketed in the 1970s through the 1990s, the virus seed inoculum was prepared by passage of the master virus seed into mouse brain (i.e., "mouse chick", [MC]). Other health agencies based their initial recommendations on the use of FSME-IMMUN on studies that used this vaccine formulation. For example, early studies in 1976 showed high seroconversion rates assayed by hemagglutination inhibition test (76%-98%) (Kunz et al. 1976); however, antibodies tended to decline after the second dose. Therefore, a third dose was considered necessary and was administered 9 to 12 months after the first dose. Surveillance of the efficacy of the vaccine in the field showed a protection rate exceeding 99% using the three-dose schedule (Kunz 1980; Kunz et al. 1980).

The immunogenicity profiles of the earlier (MC formulation) and current formulations (produced in chick embryos, referred as FSME-IMMUN-CC) appear to be very similar based on the results of the clinical trial IMAG 062 (discussed in Section 9 of this review). IMAG 062 evaluated the FSME-IMMUN (CC) candidate vaccine with and without thiomersal, in comparison with FSME-IMMUN produced from mouse brain suspension. Immunogenicity and safety results of IMAG-062 supported the decision of Baxter Vaccine AG ("Baxter") to develop FSME-IMMUN (CC) formulations without thiomersal for marketing. The formulation of FSME-IMMUN for which Pfizer is seeking licensure is the same as the formulation (without thimerosal) used in study iIMAG-062.

According to the Applicant, since the launch of the current formulation in 2001, >75 million doses have been administered which includes >50 million doses in adults and >25 million doses in pediatric subjects. Most of the vaccine's clinical development was performed by Baxter Vaccine AG. Pfizer acquired the vaccine from Baxter in 2015. Postmarketing pharmacovigilance data during 2000 to 2020 were provided to the BLA by Pfizer.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Pfizer's key regulatory interactions with the US Food and Drug Administration (FDA) regarding FSME-IMMUN began in mid-2018, after the US Army Medical Research and Material Command asked Pfizer to pursue licensure of FSME-IMMUN in the US. The Department of Defense (DOD) has deemed the vaccine a priority to protect US military personnel deployed to TBEV-endemic areas and has cited Public Law 115-92, which authorizes the DOD to request and FDA to assist in expediting development of products aimed to prevent serious or life-threatening diseases or conditions facing US military personnel. Information regarding the product, completed clinical trials, and field efficacy data in available publications were submitted to a Drug Master File (DMF (b) (4)); regulatory communications occurred in that context.

- On March 5, 2019, a Type C meeting was held, to discuss the Applicant's outlined safety, immunogenicity, and effectiveness data as well as the current chemistry, manufacturing, controls (CMC) information. In support of the Type C meeting, Pfizer submitted a Briefing Document on December 21, 2018. On February 28, 2019, the FDA provided preliminary feedback based on the information provided in this Briefing Document, which Pfizer reviewed and then notified the FDA on March 4, 2019 to proceed with the meeting agenda as planned. Pfizer submitted the following to the FDA as a result of the meeting: a Type V DMF April 12, 2019; Safety Reports May 29, 2019; and Adventitious Agent Report July 30, 2019.

- On September 4, 2019, the FDA provided feedback on the available data from clinical studies and postmarketing use of the vaccine in Europe in support of a BLA.
- On March 13, 2020, FDA sent an information request to Pfizer via email requesting information regarding confirmation that TBE vaccinations administered in Austria during the field effectiveness study period (2000-2006) were FSME-IMMUN.
- FDA granted and scheduled a Type C meeting with Pfizer on June 5, 2020 to discuss the manufacturing facilities at Pfizer, (b) (4) (Drug Substance) and Pfizer, (b) (4) (Drug Product) to support BLA filing for FSME-IMMUN. The background materials were submitted on April 24, 2020. On May 8, 2020, FDA provided feedback via email communication that the source of human serum albumin contained in the candidate vaccine was acceptable to support submission of a BLA.
- Pfizer submitted an initial pediatric study plan on April 28, 2020 and FDA provided comments after presenting the plan to the Pediatric Review Committee (PeRC). FDA sent an Agreed Initial Pediatric Study Plan Confirmation Letter on November 20, 2020.
- Pfizer submitted the BLA on December 15, 2020.

2.6 Other Relevant Background Information

N/A

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

This reviewer identified several issues with the submission during the review and issued information requests to address the BLA deficiencies. These issues did not impact a favorable benefit-risk assessment for FSME-IMMUN. Pfizer submitted safety datasets with solicited adverse reaction data limited to reports of “fever”, “local” and “systemic” adverse reactions, based on datasets transferred from Baxter. In response to an information request to clarify if safety datasets should be used for clinical review, Pfizer reported that they could not exactly reproduce the findings reported in the Baxter’s clinical study reports (CSRs) using the datasets, except for the immunogenicity results.

Reviewer’s Comment: The identified issues with the safety datasets precluded the use of the datasets to perform clinical review activities, including data verification. The Applicant complied with all requests to submit additional information and analyses and to correct deficiencies. (See Section 5.2 of this review for a list of amendments with dates of submission). The postmarketing experience with the product in Europe is supportive of the safety of FSME-IMMUN in both the adult and the pediatric populations.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The Applicant stated that the covered trials were conducted according to all applicable laws and regulations including, but not limited to, the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice, the Code of Federal Regulations (CFR), the ethical principles that have their origin in the Declaration of Helsinki, and applicable privacy laws and the standard practices of Baxter International, Inc.

Reviewer’s Comments: A Bioresearch Monitoring (BIMO) inspection was not feasible for the BLA review since the studies were done more than 10 years ago by Baxter and the data were not anticipated to be available for BIMO inspection at the clinical study sites.

3.3 Financial Disclosures

In module 1.3.4, the Applicant submitted financial disclosure information for the following covered studies, covering the time period from the start of the study through one year after the completion of the study:

- Adult studies: 201, 202, 208, 213, 223, 690701, 691101, 225, 690501, 69601
- Pediatric studies: 198, 215,199, 206, 209, 700802, 205, 207, B9371038
- Adult and pediatric study: WI208682

Reviewer's Comments: Financial disclosure was not submitted for Studies 197, 700401, 700501, 700801 and IMAG-062. However, these studies do not contribute significantly to the safety database for the product and do not directly support any claim of effectiveness. Therefore, they are classified as "not covered" studies.

Certification, using Form FDA 3454, that none of the financial interests or arrangements described in 21 CFR Part 54 exist, is provided for 20 of the 774 clinical investigators who participated in the covered studies. Pfizer Inc. has not identified investigators who were full-time or part-time employees of the Sponsor of the covered studies. Due diligence activities were required for 754 of the clinical investigators. On Form 3454, the Applicant certified that the following statement is correct:

> "As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

Reviewer's Comments: CBER reviewed the documents submitted by Pfizer. We have no indication that any missing information would impact the overall integrity of the data submitted.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

FSME-IMMUN is prepared from tick-borne encephalitis virus propagated in chick embryo fibroblast (CEF) cells. The harvested virus suspension is inactivated by treatment with formaldehyde, purified by sucrose gradient centrifugation and adsorbed onto aluminum hydroxide. FSME-IMMUN is available in a 0.5 mL presentation for use in individuals 16 years of age and older and a 0.25 mL presentation for use in individuals 1 to <16 years of age. Each 0.5 mL dose is formulated to contain 2.4 microgram (µg) TBE inactivated virus, 0.5 mg human serum albumin, 0.35 mg aluminum hydroxide, 3.45 mg sodium chloride, 0.22 mg dibasic sodium phosphate, and 0.045 mg of monobasic potassium phosphate. From the manufacturing process, each 0.5 mL may also contain formaldehyde (≤5 µg), sucrose (≤15 mg), protamine sulfate (≤0.5 µg), and trace amounts of chick protein and DNA from CEF cells, neomycin and gentamicin. The pediatric 0.25 mL dose of FSME-IMMUN contains the same components as the 0.5 mL dose in half of the quantities.

Reviewer's Comments: Please refer to the CMC review for review of the Chemistry, Manufacturing and Controls.

4.2 Assay Validation

There is no established correlate of protection for TBE vaccines (WHO 2011a). In clinical studies, blood samples were analyzed for the presence of TBEV immunoglobulin G (IgG) antibodies by means of an enzyme-linked immunosorbent assay (ELISA) and a confirmatory neutralization test (NT). The ability to rely on serological immunogenicity data to support vaccine dosing and schedule is derived from an understanding of the TBEV antigens and the importance of the envelope (E) glycoprotein as a dominant protective antigen. However, for TBEV, several other antigenically related viruses exist that infect humans, and the potential interference of cross-reactive antibodies in ELISA must be considered. Antibodies to E glycoprotein have been clearly correlated with neutralization of the virus in subjects naïve to other potentially cross-reactive flaviviruses. Therefore, false positive ELISA results caused by cross-reactivity with other flaviviruses have been avoided in the studies discussed in this review by excluding from the immunogenicity analyses subjects with prior evidence of TBEV infection based on serological data (ELISA).

Immunogenicity endpoints in the clinical studies used a combination of ELISA and NT results, with the outcome measure being the seroconversion/seropositivity rate determined by ELISA and/or NT (i.e., the percentage of subjects who had seroconverted/were seropositive based on either their ELISA values or their NT values, or both their ELISA and NT values) after the vaccination of interest. In the absence of a history of other flavivirus infections or vaccination, ELISA IgG antibodies relate well with NT results (b) (4)

ELISA

ELISA is a widely used method for the measurement of immune response to TBE vaccination. The assay used by Baxter for the determination of TBEV-specific IgG antibodies in most of the clinical trials (IMMUNOZYM FSME-IgG, produced by (b) (4) was a three-layer ELISA quantitated in Vienna units per milliliter (VIEU/mL) using a standard human anti-TBEV antiserum (Hofmann et al. 1983). Concentrations >126 are considered positive, values between 63 and 126 VIEU/mL are borderline, and values below 63 VIEU/mL are negative (Kießig et al. 1993). The only two submitted studies that used a different ELISA method were Studies B9371038 and 700801. In these studies, antibody concentrations were determined for at least one of the vaccine groups using a commercial ELISA, Enzygnost Anti-FSME-Virus IgG. These two studies were considered supportive.

Neutralization Test

The use of a NT to determine immune response to TBE vaccination overcomes the potential issue of cross-reactive (but functionally inactive) antibodies (b) (4) In adult Studies 201/202 and 213, as well as in pediatric Studies 198/215, 199/206, and 205/207, NT performed according to (b) (4) . was used in addition to ELISA to confirm the presence of TBEV neutralizing antibodies following vaccination with FSME-IMMUN. Serum samples tested by NT according to (b) (4) in adult Study 213 and pediatric Study 209, the two studies described in this memo in Section 6, were reanalyzed using a NT as described by Adner et al. (Adner et al. 2001) that had shown a correlation with ELISA results in a previous clinical study of FSME-IMMUN in adults (IMAG 062). Other studies that contributed to the immunogenicity data such as supportive Study 690601 also determined the NT titers according to the Adner et al. method.

<u>Reviewer's Comments:</u> Review of the immunogenicity data for this vaccine focused on NT results because NT detects functionally active, neutralizing antibodies. Although a protective

antibody level has not been defined, TBEV-neutralizing antibodies are believed to confer protection (WHO 2011a). Using either NT method, a subject was considered to have seroconverted if the subject had a negative neutralization test at baseline (i.e., NT titer <1:10) and an NT titer ≥1:10 after vaccination. Seropositivity by NT in this review is defined as an NT titer ≥1:10. Please refer to the CMC review for a more detailed description of the assays used to determine the immunogenicity endpoints in the pivotal trials discussed in this review. The NT assays used the Neudörfl TBEV strain (European subtype). Although the assays used in Pfizer's clinical development program were not validated, there are placebo-controlled immunogenicity data through post dose 2 using these assays in the supportive study IMAG-062. Please refer to Section 9 for a discussion of the IMAG-62 Study.

4.3 Nonclinical Pharmacology/Toxicology

The CBER Non-clinical Pharmacology/Toxicology reviewer (Dr. Andrew O'Carroll) did not identify issues with the non-clinical toxicology data submitted that would preclude approval. Please refer to the Pharmacology/Toxicology memo for a discussion of the Nonclinical Pharmacology/Toxicology studies submitted to this application.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

FSME-IMMUN induces an immune response to the E glycoprotein, a protein expressed on the virion surface, that neutralizes live TBEV. Accumulated data from animal studies, clinical trials of FSME-IMMUN and other non-US-licensed TBE vaccines, and human epidemiological studies, suggest that virus neutralizing antibody titers are protective (WHO 2011b). However, a protective antibody level titer has not been defined.

Reviewer's Comments: The clinical data submitted in this application supports FSME IMMUN vaccine effectiveness against the Western subtype. However, there is evidence that FSME-IMMUN may induce protective immunity not only against the homologous subtype but also against the Far Eastern and Siberian subtypes of the virus in preclinical studies in mice (Holzmann et al. 1992) and published serological studies (Hayasaka et al. 2001a; Leonova et al. 2007; Orlinger et al. 2011; WHO 2011b). Sera from people vaccinated with FSME-IMMUN was able to neutralize pseudoviruses with envelopes, not only from the European strain but also from the Siberian and Far Eastern strains, in an in vitro neutralizing assay that we have not reviewed (Orlinger et al. 2011). Based on the similarity between the TBEV strains, cross-protection would be expected (WHO 2011b). Please refer to the CMC review for a more detailed discussion regarding TBEV strain homology and vaccine cross-protection.

4.4.2 Human Pharmacodynamics (PD)

Pharmacodynamic data, comprised of immune response to the vaccine, can be found in the review of clinical studies.

4.4.3 Human Pharmacokinetics (PK)

N/A

4.5 Statistical

The issues related to the safety datasets have been described previously in this memo. The CBER statistical reviewer (Dr. Ruoxuan Xiang) did not identify issues with the immunogenicity data submitted that would preclude approval. Please refer to the statistical memo for details.

4.6 Pharmacovigilance

The Applicant proposes routine pharmacovigilance for all adverse events (AEs). The Applicant does not propose any additional pharmacovigilance activities or postmarketing studies. Please refer to the epidemiology review by Dr. Kerry Welsh for additional information regarding the review of Pharmacovigilance Plan.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

There were 10 clinical studies conducted in adults (i.e., subjects ≥16 years of age) and 10 clinical studies conducted in children and adolescents (i.e., subjects from 1 year to <16 years of age) that we considered as contributing data to support the safety and effectiveness of FSME-IMMUN. Studies 208, 213 and 209 are discussed in Section 6 as these three studies provide the most robust safety and immunogenicity data from clinical studies in support of the three-dose primary series schedule for the adult and pediatric populations, respectively. All the other supportive studies are summarized in Section 9 of this review. Data from these studies were included in the Package Insert (PI). One additional pediatric postmarketing safety study is also discussed in Section 9 because of a report of a possibly related serious adverse event also included in the PI. There were three additional studies submitted, listed below, that were not discussed in Sections 6 or 9 of the review:

- Study WI208682: an investigator-initiated study that evaluated the immunogenicity and reactogenicity of a booster dose administered by either intramuscular (IM) or subcutaneous (SC) injection. (b) (4) .

- Study B9371038: a post-authorization, open-label study to evaluate the immunogenicity of a single booster given to subjects ≥6 years of age who had not completed the three-dose primary series or had completed the primary series according to a different schedule. Vaccine immunogenicity was assessed after the booster dose. Safety surveillance was passive in the study. The immunogenicity data submitted shows that a single vaccination with FSME-IMMUN elicits an anamnestic antibody response in such individuals irrespective of age, and an interruption in the vaccination schedule probably does not require restarting the entire series of vaccinations. However, the immunogenicity data submitted for this study was based only on ELISA results and there is limited information regarding the commercial ELISA test used to draw definitive conclusions regarding the data.

- Study 700501: a non-interventional follow-on study that assessed the persistence of TBEV antibodies approximately 3 years after a booster dose of FSME-IMMUN 0.25 mL, administered outside the scope of a clinical study, in pediatric subjects (6-47 months of age) who had completed the primary series in Study IMAG 146-A (a clinical study not submitted to the BLA). There was no safety analysis for this study since no study

product was administered during Study 700501. Only 18 children in Study 700501, who had received the 0.25 ml dose for their primary series and booster dose, were older than 1 year upon receipt of their first vaccination in Study IMAG-146-A. Seropositivity rate (measured by NT according to Adner et.al. 2001) three years after the first booster for these 18 children was 100%. Data from this study are insufficient to draw conclusions regarding the safety and the need for (b) (4) in children.

There is no integrated summary of efficacy in this review because the different studies supporting the proposed indication used different dose schedules, different assay methods for the quantification of immune response, and collection of blood for immunogenicity assessments occurred at different intervals. There is also no integrated summary of safety because the clinical studies submitted in this BLA used various methods of safety data collection and definitions of adverse events. Therefore, pooling of safety and immunogenicity data was not possible, and data from individual studies are discussed separately.

The safety data provided in this review and in the product package insert is based upon what Baxter reported in the CSR for each study. Limited datasets from the clinical studies were available for our review; therefore, we were unable to verify the safety data using datasets. Excepting fever, reaction terms were not prespecified in the investigational plan. However, our review of the electronic case report forms (eCRFs) suggests that study personnel queried subjects about specific reaction terms that were also queried in the subject diaries (local injection reactions and systemic reactions).

Immunogenicity data from the pivotal studies were verified by the Statistical reviewer using the immunogenicity datasets included in the submission.

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

The following amendments, modules and content were assigned to and reviewed by the clinical reviewer:
Modules 1, 2 and 5

- 125740/0 (received December 15, 2020): Sections 1.3.3 (Debarment Certification), 1.3.4 (Financial Certification and Disclosure), 1.6 (Meetings), 1.2 (Cover Letter for Priority Designation), 1.9 (Pediatric Administrative Information), 1.4 (Labeling), 1.16 (Risk Management Plan), 1.18 (Proprietary Names)
- 125740/5 Response to FDA February 23, 2021 Information Request Regarding Clinical Data (Response to Requests 1, 8 and 9): applicability of the data generated in foreign countries to the US population/medical practice; confirm that Pfizer has submitted all available preclinical and clinical protocols; clarification regarding WHO reference.
- 125740/6 Response to FDA February 23, 2021 Information Request Regarding Clinical Data (Response to Requests 2-7: included submission of CSR with hyperlinks, clarification of submitted data, clarification regarding serious adverse event [SAE] numbers).
- 125740/10 Response to FDA March 26, 2021 Information Request Regarding Clinical and CMC Questions: race/ethnicity of the subjects enrolled in clinical studies and information regarding the vaccine product used in the IMAG-062 study.
- 125740/13 Response to FDA April 5, 2021 Information Request Regarding Clinical Questions concerning the Baxter European Package Insert
- 125740/14 Response to FDA April 30, 2021 FDA IR: Clinical: clarification regarding datasets submitted in the BLA and clarification regarding local and systemic adverse events to be incorporated in the package insert.

- 125740/17 Response to FDA IR: PLL Labeling Update Revisions: clarification regarding data of the use of FSME-IMMUN during pregnancy and lactation
- 125740/23 Response to FDA July 9, 2021 Information Request regarding clarification on data for the geriatric population.

5.3 Table of Studies/Clinical Trials

Table 8. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations for FSME-IMMUN in Subjects Older Than 16 YOA

Trial Identifier	Trial Population	Trial Design	Dose, Regimen and Follow-Up	Primary Endpoints	Non-Primary Endpoints	No. of Subjects Randomized	Countries
Study 208 NCT 00161824	Subjects 16 to <65 YOA	Phase 3, randomized, single blind of 2 doses	0.5 mL[b] FSME-IMMUN Days 0, 21-35 F/U: 4-9 weeks	Fever after dose 1	Fever after dose 2; local and systemic rxns after doses 1, 2	3966[a] (3927 received 2 doses) FSME: 2977	Poland
Study 213 NCT 00161876	Subjects ≥ 16 YOA from Study 208	Phase 3, follow on to 208, open-label, safety; (immuno in subset), Dose 3	0.5 mL[b] FSME-IMMUN 6 mos +/- 28 days F/U: 35-42 days	Local and systemic reactions	Subset: ELISA (GMC), NT (GMT); GMFR, "seroconversion" [NT by (b) (4) , retested by Adner]	3705* for safety of 1 dose; 2790 received FSME-Immun in Study 208 Immunogenicity subset n=567	Poland
Study 225 NCT 00161954	Subjects 16 to <66 YOA	Phase 4, open-label, single arm, safety and immunogenicity, doses 1 and 2	0.5 mL[b] FSME-IMMUN Days 0, 12 F/U: ~60 days	Seropositivity rate for TBEV antibody determined by ELISA at Days 3, 7 and 14 after the second dose	Seropositivity rate for TBEV antibody measured by ELISA at Days 21 and 42 Local and systemic AEs Days 0-4	Enrolled:62 Vaccinated: 60	Belgium
Study 690501 NCT 00163540	Subjects ≥ 16 YOA from Study 225	Phase 4, open-label, safety and immunogenicity of a third TBE vaccination	0.5 mL[b] FSME-IMMUN Month 13-14 F/U: 21 days	Seropositivity rate on Days 3, 7, 14 and 21 post-vaccination, as determined by ELISA.	Seropositivity rate on Days 3, 7, 14 and 21 post-vaccination, as determined by NT	44 (stratified 16-50; 51 - <66)	Belgium
Study 690601 NCT 00460486	Subjects ≥ 16 YOA	Phase 3B, open-label safety and immunogenicity in 2 age strata (Doses 1, 2 and 3)	0.5 mL[b] FSME-IMMUN Days 0, 12; Month 6 F/U: 21 days after 3rd dose	Seropositivity rate as determined by ELISA and NT at Days 7, 14 and 21 after the second dose.	Seropositivity rate as determined by ELISA and NT at Days 7, 14 and 21 after the second dose	340 (170 in each age stratum; aged 16 through 49 years and ≥50 years of age)	Poland

Location in Review: Studies 208 and 213, Section 6; Studies 225, 690501 and 690601, Section 9
Study dates: Study 208: Oct 2001 – Jan 2002, Study 213: May – Aug 2002, Study 225: Mar – May 2004, Study 690501: May – June 2005, Study 690601: Sep 2006 – May 2007
*2790 of these had received FSMEIMMUN in Study 208, and 915 had received non-US licensed TBE vaccine comparator in Study 208
[a] received non-US licensed TBE vaccine comparator: 989; [b] 0.5 mL is the adult dose of FSME-IMMUN and contains 2.4 µg inactivated TBEV antigen
Abbreviations: AE, adverse event; ELISA, enzyme-linked immunosorbent assay; F/U, follow-up duration; NCT, National Clinical Trial; YOA, years of age

Table 9. Tabular Overview of Dose-Finding Studies of FSME-IMMUN in Subjects Older Than 16 YOA

Trial Identifier	Trial Population	Trial Design	Dose Regimen and Follow-Up	Primary Endpoints	Non-Primary Endpoints	No. of Subjects Randomized	Countries
Study 201 NCT unknown	Subjects 16 to < 65 YOA	Phase 2, randomized, double-blind, dose finding, doses 1 and 2	0.6 µg 1.2 µg 2.4 µg[a] Days 0, 21-35 F/U: 21-25 days after second dose	Fever rate after the first dose	Seroconversion rate (ELISA and/or NT) after the second vaccination Local and systemic AEs after the second vaccination	405 (135 received 2.4µg of FSME-IMMUN)	Belgium
Study 202 NCT unknown	Subjects ≥16 YOA from Study 201	Phase 2, follow on to 201, randomized, double-blind, dose finding, dose 3	0.6 µg 1.2 µg 2.4 µg[a] 6 mos +/- 14 days F/U: 25-42 days after vaccination	Local and systemic AEs after the third dose	Seroconversion (ELISA and/or NT) after the third dose Local and systemic AEs that occurred between the last visit of Study 201 and the first visit of Study 202	372 (118 received 2.4 µg of FSME-IMMUN)	Belgium

Location in Review: Section 9
Study dates: Study 201: July 2001 – Nov 2001, Study 202: Jan 2002 – April 2002, IMAG-062 (Part A): May 1994 – July 1995, Study IMAG-062 (Part B): May 1995-May 1996
[a] 2.4 µg is the content of TBEV antigen in the 0.5 mL adult dose
AE: adverse event, ELISA: enzyme-linked immunosorbent assay, F/U: follow-up duration, NCT: National Clinical Trial, YOA: years of age

Table 10. Tabular Overview of Studies of FSME-IMMUN Subjects Older Than 16 YOA (Antibody Persistence and/or Booster, Other*)

Trial Identifier	Trial Population	Trial Design	Dose, Regimen and Follow-Up	Primary Endpoints	Non-Primary Endpoints	No. of Subjects Randomized	Countries
Study 223 NCT 00161785	Subjects ≥18 YOA from Study 213	Phase 4, open-label follow-up to Study 213 to assess antibody persistence at 2, 3 yrs	0.5 mL[a] FSME-IMMUN Boost at 3 years after third dose in Study 213 F/U: 21-35 days after booster	Seropositivity rate[b] 2 and 3 years after the third vaccination in Study 213 and after the booster vaccination in this study	Local and systemic rxns after booster	328 boosted (240 had received FSME-IMMUN in Study 208)[c]	Poland
Study 690701 NCT 00503529	Subjects ≥ 20 YOA from Study 223	Phase 4, open-label follow-up to Study 223 to assess antibody persistence and response to a second booster	0.5 mL[a] FSME-IMMUN Second booster (2,3,4 or years after the first booster in Study 223) F/U: 21-35 days after booster	Seropositivity rate[b] 27, 34, 46 and 58 months after the first booster dose in Study 223 and one month after the second booster dose in this study	Local and systemic rxns after booster Days 0-4	315 enrolled; 32 received 2nd booster	Poland
Study 691101 NCT 01582698	Subjects ≥ 23 YOA from Study 690701	Phase 4, open-label follow-up to 223 and 690701, antibody persistence (7-10 years after 1st booster)	0.5 mL[a] FSME-IMMUN Boost at either 84, 96, 108 or 120 months after first booster in Study 223 F/U: 21-35 days after booster	Seropositivity rate[b] 82, 94, 106 and 118 months after 1st booster dose in Study 223 and after the booster dose in this study.	Seropositivity rate measured by ELISA (and by NT) NT 82, 94, 106 and 118 months after the first booster	243 enrolled; 15 received 2nd booster	Poland
Study WI208682 NCT unknown	Subjects 18 to ≤ 60 YOA	Open-label, immunogenicity of FSME-IMMUN after IM vs SC vaccination of 2.4 µg	0.5 mL[a] FSME-IMMUN (complete primary TBE vaccine series plus at least one booster) 3 years prior to study entry	Immunogenicity and Reactogenicity of FSME-IMMUN after intramuscular (IM) versus subcutaneous vaccination (SC)	NT (with Baxter – unspecified method), other immuno parameters	IM: 58, SC: 58	Austria

*Study B9371038 was a post-authorization open-label catch-up study for irregular or incomplete TBE vaccinations that enrolled subjects older than 6 years of age and it is briefly described in the memo (Section 5.1 but it is not listed in the table of clinical trials.) Study dates: May 2005 – Dec 2006

[a] 0.5 mL is the adult dose of FSME-IMMUN and contains 2.4 µg of TBEV antigen

[b] Seropositivity rate measured by ELISA and/or NT

[c] 240 received FSME-IMMUN as booster; 88 who had received Non-US licensed vaccine comparator in Study 208, received the FSME-IMMUN booster; Location in Review: Studies 223, 690701, 691101 in Section 9 and Study WI208682 is briefly described in Section 5.1.

Study dates: Study 223: June 2004 – July 2005, Study 690701: July 2007 – July 2010, Study 691101: May 2012 – June 2015,

AE: adverse event, ELISA: enzyme-linked immunosorbent assay, F/U: follow-up duration, IM, intramuscular, NCT: National Clinical Trial, SC, subcutaneous YOA: years of age

Table 11. Tabular Overview of Studies of FSME-IMMUN in Subjects 1to <16 YOA (Doses 1, 2 or Dose 3)

Trial Identifier	Trial Population	Trial Design	Dose, Regimen and Follow-Up	Primary Endpoints	Non-Primary Endpoints	No. of Subjects Randomized	Countries
Study 205 NCT 00161798	Subjects 6 to <16 YOA	Phase 2, randomized, double-blind, dose-finding study, two doses	0.3 µg 0.6 µg 1.2 µg[c] Days 0, 21-35 F/U: 21-35 days after second dose	Fever rate after the first dose	Seroconversion rate after two vaccinations (ELISA and/or NT by (b) (4)) Fever rate after dose 2 Local and systemic rxns up to blood draw before dose 2	639; 1.2 µg =212	Germany
Study 207 NCT 00161876	Subjects >6 YOA from Study 205	Phase 2, Follow-up Study 205, third dose	0.3 µg 0.6 µg 1.2 µg[c] Six months after the second immunization F/U: 35-42 days after vaccination	Fever rate after the third immunization	Seroconversion rate 21-28 days after third immunization by ELISA and/or NT by (b) (4) AE after the third vaccination and in between 205 and 207	620 (vaccinated 618); 1.2 µg =208	Germany
Study 209 NCT 00161889	Subjects 1 to < 16 YOA N=2417 1-2 YOA: n=186 3-6 YOA: n=563 7-15 YOA: n=1668	Phase 3, open-label, lot consistency, 3 doses	1.2 µg[c] Days 0, 21-35; Month 6 F/U: 35-42 days after third dose (~7 months)	Fever rate after the first dose in three different age groups (1-2 YOA, 3-6 YOA, 7-15 YOA).	Antibody response after doses 2,3 (ELISA and NT) for a subset of ~373 subjects. Fold increase of anti-TBEV antibody concentration and NT titer after doses 2, 3 as compared to baseline Fever rate after doses 2, 3	2419; Vaccinated:2417 (~480 per lot) (immunogenicity for 366)	Poland, Germany, Austria

Trial Identifier	Trial Population	Trial Design	Dose, Regimen and Follow-Up	Primary Endpoints	Non-Primary Endpoints	No. of Subjects Randomized	Countries
Study 700801[a] NCT 00840801	Subjects 1 to < 12 YOA[b]	Phase 3, single-blind randomized, 3 doses	1.2 µg[c] Part A 0, 28 Part B 12 months after second vaccine F/U: 28±3 days after second vaccination (Part A), 28±3 days after third vaccination	Seropositivity rate as determined by NT 28 days after the second vaccination (Non-inferiority)	Seropositivity rate determined by NT 180 days after first vaccination and 28 days after the third vaccination by age group Local and systemic AE by age stratum	298 FSME-IMMUN =150	Austria, Czech Republic

*Study 197 was a postmarketing surveillance study that enrolled 1922 children 6 months to 12 years of age to assess the rate of fever after administration of half the volume of FSME-IMMUN (adult dose; 1.2 µg TBEV antigen), This study is discussed on Section 9 but not listed in the table of pediatric tables.

Location in Review: Study 209, Section 6, Studies 205, 207, 700801, Section 9, Study dates: Study 205: Sept 2001-Mar 2002, Study 207: Feb-Aug 2002, Study 209: Sept 2002-Jan 2003, Study 700801: Feb-June 2009 Part A, Feb 2009-May 2010 Part B

[a] Non-US licensed Vaccine comparator for first two doses, no control for 3rd dose

[b] Stratum A:1 to 2 YOA =99 (50 FSME), Stratum B: 3 to 6 YOA =100 (51 FSME), Stratum C: 7 to 11 YOA =99 (49 FSME)

[c] 1.2 µg is the content of TBEV antigen in the 0.25 mL pediatric dose.

AE: adverse event, ELISA: enzyme-linked immunosorbent assay, F/U: follow-up duration, NCT: National Clinical Trial, YOA: years of age

Table 12. Tabular Overview of Studies of FSME-IMMUN in Children (Doses 1, 2 or Dose 3)

Trial Identifier	Trial Population	Trial Design	Dose Regimen and Follow-Up	Primary Endpoints	Non-Primary Endpoints	No. of Subjects Randomized	Countries
Study 198 NCT unknown	Subjects 1 to < 13 YOA	Phase 2, open-label, pilot safety and immunogenicity study, doses 1 and 2	1.2 µg[a] Days 0, 14-32 92 subjects received second dose between 14-32 days F/U: 21-35 days after second vaccination	Seroconversion rate after the second immunization by NT (b) (4) or Elisa	Geometric mean of the rise of antibody concentration after the second dose Fever rate after dose 2 Local and systemic rxns	101	Austria
Study 215 NCT unknown	Subjects ≥1 YOA from Study 198	Phase 2, follow-up Study 198, third dose	1.2 µg[a] 9-10 months after the second immunization F/U: 21-35 days after vaccination	Seroconversion rate after the second immunization by NT (b) (4) or Elisa	Antibody response after the third dose by neutralization and ELISA Fever rate after dose 3 Local and systemic rxns	99	Austria
Study 199 NCT 00161772	Subjects 1 to <6 YOA	Phase 2, randomized, double-blind, dose-finding study, doses 1 and 2	0.3 µg 0.6 µg 1.2 µg[a] Days 0, 21-35 F/U: 21-35 days after second dose	Fever rate after the first vaccination	Seroconversion rate after ELISA and/or NT by (b) (4) Fever rate after dose 2. -Local and systemic rxns after dose 2	643 1.2 µg N=208	Germany, Austria
Study 206 NCT 00161850	Subjects ≥1- from Study 199	Phase 2, double-blind, multicenter, follow-up study, third dose	0.3 µg 0.6 µg 1.2 µg[a] 6 months ±14 days F/U: 35-42 days after third dose	Seroconversion rate after third dose by ELISA and/or NT (b) (4) Geometric mean antibody response after the third dose	Local and systemic AEs after third dose AEs between last visit of Study 199 and first visit of Study 206	625 1.2 µg N=204	Germany, Austria

Location in Review: Studies 198, 215, 199 and 206: Section 9,
Study dates: Study 198: April-Aug 2001, Study 215: Feb-May 2002, Study 199: Sep 2001-Mar 2002, Study 206: Feb-Aug 2002
[a]1.2 µg is the content of TBEV antigen in the 0.25 mL pediatric dose.
No comparator was used for Studies 198, 215, 199 and 206
AE: adverse event, ELISA: enzyme-linked immunosorbent assay, F/U: follow-up duration, NCT: National Clinical Trial, YOA: years of age
Study 197 was an observational safety study of the occurrence of fever after the first vaccination with FSME-IMMUN (half the adult dose; 2.4 µg) in children 6 months to 12 years of age. It enrolled 1922 subjects and all subjects received one dose of FSME-IMMUN.

Table 13. Tabular Overview of Studies of FSME-IMMUN in Children (Boosters) and Antibody Persistence

Trial Identifier	Trial Population	Trial Design	Dose Regimen and Follow-Up	Primary Endpoints	Non-Primary Endpoints	No. of Subjects Randomized	Countries
Study 700501 NCT00163618	Subjects ≥ 5 YOA who received 3 doses in Study IMAG-146A and a booster outside of clinical studies	Phase 4, open-label, non-interventional, follow-up, antibody persistence approximately three years after booster	F/U: 3-4 years after the booster dose	Seropositivity rate by ELISA and NT (Adner and (b) (4)	Antibody concentration as measured by ELISA Antibody titer by NT	97	Austria
Study 700401 NCT 00161967	Subjects ≥3 YOA who received 3 doses in Study 209.	Phase 4/3b, open-label follow-up to Study 209; antibody persistence and booster response	1.2 µg[a] (2.4 µg[b] if ≥16 YOA) Single boost at 3, 4, or 5 years after dose 3 in Study 209 F/U: 21-35 days after five-year boost (N=130)	Seropositivity rate measured by ELISA and/or NT at each blood draw after the third dose in Study 209 and separately at each time point after the booster	Antibody concentration by ELISA, antibody titers by NT after the third immunization and after the booster Fever rate after the booster dose; local and systemic rxns after booster	358 boosted 205	Poland, Germany, Austria
Study 700802 NCT 00894686	Subjects (Children, adolescent and young adults) who received FSME-IMMUN in 700401	Open-label follow-up of Study 700401 antibody persistence after first booster and response to a second booster	1.2 µg[a] Booster at either 40, 48, 60, 72, 84, 96, 108, 120 months after first booster F/U: Antibody persistence at yearly intervals from 3 to 10 years after the first booster in 700401	Seropositivity rate measured by ELISA and/or NT		179 Boosted 2	Austria

Location in Review: Studies 700401, 700802: Section 9, Study 700501: Section 5.1.
Study dates: Study 700501: 2005-2006, Study 700401: May 2005-July 2008, Study 700802: April 2009 - May 2017
[a] 1.2 µg is the content of TBEV antigen in the 0.25 mL pediatric dose
[b] 2.4 µg is the content of TBEV antigen in the 0.5 mL adult dose
No comparator was used for Studies 700501, 700401 and 700802
AE: adverse event, ELISA: enzyme-linked immunosorbent assay, F/U: follow-up duration, NCT: National Clinical Trial, YOA: years of age

5.4 Consultations

Pediatric Review Committee (PeRC)

This submission is subject to the Pediatric Research Equity Act (PREA). FDA's Pediatric Review Committee (PeRC) and CBER agreed with the Applicant's request for a waiver of pediatric assessments for children less than 12 months of age as the studies would be highly impracticable to conduct because (1) in endemic regions neonates/infants are expected to have maternal antibodies and early immunization may result in reduced immune responses due to antibody interference and (2) neonates/infants in non-endemic regions could not be ethically enrolled in a study which has no direct prospect of potential benefit (section 505B(a)(5)(B)(i)).

5.4.1 Advisory Committee Meeting

CBER did not identify issues that would have required the input of an independent panel of experts and determined that it was not necessary to publicly present the application at a Vaccine and Related Biologics Product Advisory Committee.

5.4.2 External Consults/Collaborations

N/A

5.5 Literature Reviewed (if applicable)

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6. Discussion of Individual Studies/Clinical Trials

6.1 Trials #1 and #2: Studies 208 and 213: Pivotal Studies on the Safety and Immunogenicity of FSME-IMMUN "NEW" in Adults

Study 208: Single blind, Randomized, Multicenter Comparison of FSME-IMMUN "NEW" and ENCEPUR: Safety and Tolerability of Two Vaccinations in Healthy Volunteers Aged 16 to 65 Years (NCT00161824)
Study Period: October 2001-January 2002 (Poland)

Study 213: Open-label, Multicenter, Follow-up Phase III Study to Investigate the Safety of the Third Vaccination of FSME-IMMUN "NEW" in Volunteers Aged 16 to 66 Years (NCT00161876)
Study Period: May 2002-August 2002 (Poland)

Reviewer's Comments: FSME-IMMUN "NEW" in the title denotes FSME-IMMUN.

6.1.1 Objectives

The main objective for Study 208 was to investigate whether FSME-IMMUN was at least as well tolerated as Encepur with respect to fever rate after the first vaccination. The safety of five consecutive lots of FSME-IMMUN (fever rate following the first vaccination) was also evaluated.

The primary objective for follow-up Study 213 was to determine the safety of the third vaccination with FSME-IMMUN in subjects who received two doses of either FSME IMMUN or the non-US-licensed vaccine comparator, Encepur, in Study 208. In addition, TBEV antibody titers were measured in a subset of subjects.

6.1.2 Design Overview

Study 208 was a single-blind, randomized, multicenter, non-inferiority comparison of the safety of FSME-IMMUN (2.4 µg TBEV antigen) to the safety of Encepur (1.5 µg TBEV antigen) with respect to fever rate after the first vaccination in 3966 healthy subjects aged 16 to < 65 years. Subjects were randomized in a 3:1 ratio using a blocked randomization with block size greater than 4 to receive either FSME-IMMUN or the comparator. The study consisted of two vaccinations either with one of five consecutive lots of FSME-IMMUN or with the TBE vaccine comparator. Subjects received two vaccinations administered 21 to 35 days apart. The study duration was 3 months, with each subject participating for 4 to 9 weeks.

Reviewer's Comments: The clinical development plan for FSME-IMMUN was not conducted under IND. Encepur was licensed in Poland and selected as the active comparator based on the recommendation that an active control "be of established efficacy at the dose used and under the conditions of the study" and "should be a drug acceptable in the region to which the studies would be submitted for the same indication at the dose being studied" (ICH E10: Choice of Control Group in Clinical Trials). Encepur's recommended dose schedule (three doses: time zero, 1 to 3 months after the first dose, and then 9 to 12 months after the second dose) is very similar to that of FSME-IMMUN. As there was "a visible difference between the two products with respect to the syringes", the Applicant assumed that the investigators and other relevant study personnel would be able to recognize the product being administered. Thus, the study

was conducted in a single-blind manner; subjects were not aware whether they had received FSME-IMMUN or the comparator vaccine. No other information exists to clarify whether the visible difference between the products was in the syringe or in the vaccine. The safety data collection for Study 208 was limited to subject follow-up for 7 to 10 days after the second dose with plans for additional follow-up after the third dose to be administered as part of Study 213.

Study 213 was an open-label, follow-on study where all subjects who received their first two doses of vaccine in Study 208 were to receive a single-lot, third dose of FSME-IMMUN "NEW". All subjects from Study 208 were informed of the necessity of returning for a third dose as part of 213. Subjects from two centers (06 and 15) were invited to participate in an immunogenicity subgroup. The data from this subgroup provided post dose 3 immunogenicity data for Study 213 as well as antibody persistence data in subsequent studies (Studies 223, 690701 and 691101). Each subject was followed for 35 to 42 days after the third dose. The overall study duration was approximately 16 weeks.

Reviewer's Comments: Studies 208 and 213 provide safety data for the use of FSME-IMMUN in adults. The subjects were followed until approximately a month after the conclusion of the three-dose primary vaccination schedule. Because there was a six-month interval between the two studies, adverse event reporting may have been prone to reporter bias resulting in underreporting of events. Adverse events that occurred up to 10 days after dose 2 (last visit of Study 208) until enrollment in Study 213 were captured in the first visit of Study 213. There was a small proportion of subjects (N=150) who did not re-enroll in Study 213 (approximately 8%; please refer to Section 6.1.10.1.3). These subjects did not provide information on adverse events that may have occurred after the last visit in Study 208. The limitations surrounding safety data collection are inherent to the study design but were considered acceptable at the time of study conduct because FSME-IMMUN was already licensed in Poland and there were already safety data on the use of similar versions of TBE inactivated vaccines at the time that Studies 208/213 were conducted there.

The Schedules of clinic visits required during Study 208 and 213 are summarized in Table 14 and Table 15 below.

Table 14. Visit Schedule, Study 208

Visit	Time	Action	Tests
Visit 0* Screening	Day -14 to 0	Informed consent Inclusion and exclusion criteria Medical history Physical examination Blood draw (10 mL)	TBEV antibodies
Visit 1*	Day 0	Inclusion and exclusion criteria Physical examination **FIRST VACCINATION** Post-vaccination observation Distribute subject diary	
Visit 2	7-10 days after first vaccination	Check/return subject diary Physical examination	
Visit 3	21-35 days after first vaccination	Physical examination **SECOND VACCINATION** Post-vaccination observation Distribute subject diary	
Visit 4	7-10 days after second vaccination	Check/return subject diary Physical examination	

Source: Original BLA, CSR for Study 208, page 25
*Visit 0 (Screening) and visit 1 may be performed together.

Study 213 consisted of two visits for most individuals and three visits for the individuals who participated in the immunogenicity subgroup. For the immunogenicity subgroup, one additional visit and two additional blood draws, one before and one after the third dose, were necessary to measure antibody titers before and after the third dose.

The schedule of clinic visits required during Study 213 was:

Table 15. Visit Schedule, Study 213

Visit	Time	Action	Tests
Visit 1*	Day 0 (6 months ±14 days after first dose in Study 208)	Informed consent Inclusion and exclusion criteria Medical history Eligibility for vaccination Physical examination Blood draw (10 mL) **THIRD VACCINATION** Post-vaccination observation (30 min) Distribute subject diary	TBEV antibodies
Extra Visit (immunogenicity subgroup only)	21-28 days after third vaccination	Blood draw (10 ml)	TBEV antibodies
Visit 2 Study Termination	35-42 days after third vaccination	Check/return subject diary Final physical examination	

Source: Original BLA, Clinical Study Appendices for Study 213, page 15
*If a subject or his/her parents/legal guardians refused to participate in the follow-up study, the investigator was asked to make a reasonable effort to contact the subject or his/her parents/legal guardian for safety follow-up since the last visit in Study 208.

Amendment 1 (Study 208), December 7, 2001

1. In the protocol, it was stated that subjects should measure and record their body temperature for a total of four days after vaccination (i.e., until Day 3, vaccination day being Day 0), or, if fever occurred after vaccination, until the body temperature returned to normal. However, some subjects recorded the onset of fever on Day 4 or Day 5 after vaccination. It was therefore decided to analyze all fever cases which were reported within seven days of vaccination.
2. It was noted that a typing error had been made in the definition of mild fever in some sections of the protocol, and this was corrected.

Amendment 1 (Study 213), April 26, 2002

1. Due to logistical reasons, some subjects in Study 208 received both vaccinations before the ELISA results of the blood taken at the screening visit were available. TBE vaccination during the course of Study 213 was not recommended for those subjects with an ELISA value greater than 126 VIEU/mL before the first vaccination in Study 208 and, for this reason, an additional sentence was added in the synopsis and eligibility for vaccination to exclude these subjects from Study 213 vaccination.
2. The paragraph detailing the timeframe for SAE reporting was edited to improve clarity: "Any serious adverse event, including death due to any cause, that occurs during this study must be reported within 24 hours of the investigator becoming aware of the SAE, to the sponsor. Additionally, the investigator will forward the SAE information to the IRB/IEC and the appropriate regulatory authorities within the appropriate timeframes."
3. The start of the study was delayed due to internal logistical complications. For this reason, the third vaccination was administered 6 months (+28 days) rather than 6 months (+14 days) after the first vaccination in Study 208. This delay also extended the total study duration.

Reviewer's Comments: Studies 208 and 213 provide safety data for the use of FSME-IMMUN in adults. The subjects were followed until approximately a month after the conclusion of the three-dose primary vaccination schedule. Because there was a six-month interval between the two studies, adverse event reporting may have been prone to reporter bias resulting in underreporting of events. Adverse events that occurred up to 10 days after dose 2 (last visit of Study 208) until enrollment in Study 213 were captured in the first visit of Study 213. There was a small proportion of subjects (N=150) who did not re-enroll in Study 213 (approximately 8%; please refer to Section 6.1.10.1.3). These subjects did not provide information on adverse events that may have occurred after the last visit in Study 208. The limitations surrounding safety data collection are inherent to the study design but were considered acceptable at the time of study conduct because FSME-IMMUN was already licensed in Poland and there were already safety data on the use of similar versions of TBE inactivated vaccines at the time that Studies 208/213 were conducted there.

6.1.3 Population

Study 208 enrolled clinically healthy subjects 16 to < 65 years old, who provided informed consent and agreed to keep a subject diary. Female subjects of childbearing potential had a negative pregnancy test at the first medical examination and had to

agree to employ adequate birth control measures for the duration of the study.
Individuals were excluded from participation in this study if they:

- had a history of any previous TBE vaccination,
- had a history of TBEV infection or showed evidence of "latent" TBEV infection (as demonstrated by screening ELISA >126 VIEU/mL),
- had a history of allergic reactions, in particular to one of the components of the vaccine,
- had previously received volume substitution with a product containing polygeline (stabilizer used in the non-US-licensed comparator vaccine),
- had received antipyretics within 4 hours prior to the first TBE vaccination,
- suffered from chronic, degenerative and/or inflammatory disease of the central nervous system,
- suffered from a disease that could not be effectively treated or stabilized,
- suffered from a disease (e.g., autoimmune disease) or were undergoing any form of treatment that could have been expected to influence immunological functions,
- used any immunosuppressive drugs (e.g., local or systemic corticosteroids, chemotherapeutics),
- had a known or suspected problem with drug or alcohol abuse,
- had donated blood or plasma within one month of study participation,
- had received banked blood or immunoglobulins within one month of the study start,
- were known to be HIV positive (HIV test was not required),
- had been suffering from a febrile illness at study entry,
- had a history of vaccination against yellow fever and/or Japanese encephalitis,
- were participating simultaneously in another clinical trial,
- if female, were pregnant or breast feeding.

Reviewer's Comments: Subjects who were TBEV seropositive by ELISA or who had a history of vaccination against yellow fever and/or Japanese encephalitis were excluded from study participation. The rationale being sequence comparisons of the envelope protein from different flaviviruses have shown similarities which indicate the possibility of cross-reactive, non-neutralizing antibodies being detected by ELISA.

Administration of further doses would be withheld if:

- the volunteer experienced any serious adverse reactions or unacceptable drug-related side-effects,
- after evaluating the results of any physical examination or laboratory profile, the investigator deemed that removal from the study was in the best interest of the subject,
- the subject did not wish to continue with the study vaccinations,
- the subject was lost to vaccination or follow-up.

All subjects who participated in Study 208 were eligible for inclusion in Study 213 if:

- they understood the nature of the study, agreed to its provisions and gave written informed consent or if less than 18 years of age, the parents/legal guardian provided informed consent
- they were considered eligible based on the exclusion criteria detailed above.

Subjects who had a febrile illness (body temperature ≥38.0ºC, measured orally) at the scheduled time of vaccination, were not vaccinated until their body temperature returned to normal. If a subject had received antipyretics within 4 hours prior to the scheduled TBE vaccination, then the vaccination was re-scheduled.

Subjects who had received any other vaccination within 2 weeks prior to visit 1 had their vaccination visit delayed until 2 weeks had passed since the administration of the other vaccine. Subjects who had a tick bite since the last visit in Study 208 were allowed to be vaccinated. However, all tick bites were documented in the eCRF.

Reviewer's Comments: The statistical analysis plan and protocol for Study 213 do not mention any follow-up assessment for individuals who had a tick bite during participation in Studies 208/213. It seems that individuals who experienced tick bites were also not treated differently for the safety and immunogenicity analysis of the Clinical Study.

6.1.4 Study Treatments or Agents Mandated by the Protocol

For Study 208, subjects received either 0.5 mL of FSME-IMMUN "NEW" or 0.5 mL of Encepur intramuscularly. The first dose was provided on Day 0 and the second on Days 21 to 35. Five FSME-IMMUN lots were tested:

- 370101AA
- 370201AA
- 370301AA
- 370401DA
- 371600KA

Encepur (Control): 0.5 mL for adults was administered during the study. The product was purchased in Germany (lot #205021) and Poland (lot #201011) in July 2001 and was identical to the vaccine available for routine medical use in these countries. Encepur was formulated with 1.5 µg of formaldehyde-inactivated K23 TBEV Eu subtype, (b) (4) mg of aluminum hydroxide, maximum of (b) (4) µg of formaldehyde and traces of (b) (4)

For Study 213, all subjects received one vaccination with 0.5 mL FSME-IMMUN "NEW" (lot #370401DA).

Reviewer's Comments: The primary objective of Study 208 was a comparison of the safety of each of five consecutive lots of FSME-IMMUN to a comparator and to each other and for Study 213 was the safety of the third vaccination with FSME-IMMUN. Baxter characterized Study 208 as a lot consistency study. The immunogenicity subset evaluation did not include a formal comparison between lots; therefore, FDA is not reviewing Study 208 as a lot consistency study.

6.1.5 Directions for Use

The test product was administered intramuscularly into the deltoid muscle.

6.1.6 Sites and Centers

Studies 208 and 213 were conducted in 14 study centers in Poland. However, the immunogenicity subgroup for Study 213 was recruited from two (Centers 6 and 15) out of the 14 centers. Please refer to Section 6.1.10 for a list of the Study Centers.

6.1.7 Surveillance/Monitoring

Study Oversight

There is no record that Studies 208/213 had oversight by a Data Safety monitoring Committee.

Reviewer's Comments: Information regarding the study oversight for these two protocols is limited because the protocol for Study 208 was not available for our review (only the CSR) and this information was not clear in the Protocol for Study 213. In the Bias statement, the Applicant states that the validity of the data collected during the study was confirmed by standard monitoring procedures and frequent monitoring of investigator trial sites as outlined in the clinical monitoring plan. However, the clinical monitoring plan is also not available for our review. The CSR for Study 208 provides the dates that the protocol was approved by the ethics committees in the different centers; it states that the study was monitored by the study monitor or other Sponsor representative and that the study (including the study master files, CRO and study centers #7 and #8) was audited by the department of Quality and Regulatory Compliance, Baxter BioScience. For Study 213, a Clinical Research Organization (CRO) monitored the study locally, and the study protocol and informed consent were reviewed by the appropriate Institutional Review Board (IRB).

Safety Assessments

For the determination of local and systemic adverse events (including fever) each subject was provided with a subject diary after each vaccination.

Reviewer's Comments: There was no clear specification of what were to be considered as local or systemic reactions in the protocol or investigational plan for Study 213. The protocol states that subjects were supposed to collect adverse events in diaries for four days after each vaccination. The diaries were not available for our review. However, the protocol for Study 213 states that diaries were the source data for eCRF entries.

The eCRF had the following events as queried (i.e., solicited AEs):

- Injection site reactions: swelling, induration, erythema, injection site pain/local pain, tenderness, ecchymosis, and hematoma.
- Systemic reactions: headache, nausea, vomiting, muscle pain, joint pain, fatigue, malaise, and swelling of the lymph nodes.

The diaries were returned to the investigator in the next visit 7 to 10 days after the first and second vaccination and 35 to 42 days after the third vaccination. During these visits the providers also asked about the occurrence of unexpected adverse events. Investigators monitored adverse events based on subject reports as well as clinical evaluation and assessed each AE for severity and relatedness to study vaccine. The presence and absence of the queried events were captured in the case report forms.

Adverse Event Evaluation

Body temperature was measured orally for a total of 4 days: in the evening after vaccination, morning of the day after vaccination, and evening of the following 3 days after each vaccination. If fever occurred, the body temperature was to be monitored until it returned to normal, and the measurements were recorded in the subject diary. Fever

was categorized by severity grade, according to the Common Toxicity Criteria (CTC) guidelines (National Cancer Institute 1999), as follows:

- Mild: 38.0°C-39.0°C
- Moderate: 39.1°C-40.0°C
- Severe: >40.0°C

Fever cases >39.5°C after vaccination were reported in compliance with the German Protection Against Infection Act (Infektionsschutzgesetz).

AEs were reported by severity according to the following criteria:

- Mild: was a transient discomfort and did not interfere in a significant manner with the subject's normal functioning level. The AE resolved spontaneously or may have required minimal therapeutic intervention.
- Moderate: produced limited impairment of function and could require therapeutic intervention but produced no sequelae.
- Severe: resulted in marked impairment of function and could lead to temporary inability to resume usual life pattern. The AE produced sequelae, which required prolonged therapeutic intervention.

Relationship of Adverse Event:

- Unrelated: may or may not follow a reasonable temporal sequence from administration of the investigational product, does not follow a known response pattern to the investigational product or can be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
- Possibly related: follows a temporal sequence from administration of the investigational product; may follow a known response pattern to the investigational product and may also be reasonably explained by the subject's clinical state or other modes of therapy administered to the subject.
- Probably related: follows a reasonable temporal sequence from administration of the investigational product; may follow a known response pattern to the investigational product and could not be reasonably explained by the subject's clinical state or other modes of therapy administered to the subject; is confirmed by improvement on stopping or slowing administration of the investigational product (de-challenge) and re-emergence of symptoms on further administration of the investigational product (rechallenge), if applicable.

Serious Adverse Events (SAEs)

An SAE was defined as an adverse event that:

- results in persistent or significant disability/incapacity;
- results in or prolongs in patient hospitalization;
- results in congenital anomaly/birth defect;
- is life-threatening,defined as an event in which the volunteer was, in the judgement of the investigator, at immediate risk of death. This does not include an AE that had it occurred in a more serious form, might have caused death;
- is fatal.

The investigator was instructed to report any SAEs, including death due to any cause that occurred during the study.

Volunteers could withdraw from the study for the following reasons:

- Any SAEs or unacceptable drug-related side effects.
- The subject did not wish to continue his/her participation in the study. The reason and date of discharge should be documented in the eCRF.

Stopping rules: the study would be terminated if SAEs or other significant vaccine related side effects occurred or per Sponsor request.

Concomitant medication taken to treat fever up to 7 days after vaccination or an SAE was documented in the eCRF, including the product name (generic name), total daily dose and the start and end date of treatment. Other vaccines were not permitted (other than for emergency reasons, e.g., tetanus or rabies vaccinations). The vaccine used was documented in the eCRF. All other treatments and medications were part of the source data and were not entered in the eCRF.

6.1.8 Endpoints and Criteria for Study Success

In Study 208, the primary and secondary endpoints were:

- 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

In Study 213, the primary and secondary endpoints were:

- 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
    - TBEV antibody response assessed before the third vaccination in the immunogenicity subgroup subjects
    - TBEV antibody response assessed after the third vaccination in the immunogenicity subgroup subjects

6.1.9 Statistical Considerations & Statistical Analysis Plan

For Study 208:

Analysis of the Primary and Secondary Endpoints

The fever rates after the first and second vaccination were categorized by severity. Their 95% CI was calculated separately for each study group (FSME-IMMUN pooled and Encepur) and for each lot of FSME-IMMUN.

Reviewer's Comments: The rate of fever was calculated as described by Agresti in 1990 (Agresti 1990). To assess lot consistency of FSME-IMMUN with respect to safety, the rate of fever and its 95% CI was calculated individually for FSME-IMMUN and Encepur as well as for each lot. If the upper limit of the CI was not higher than 3%, it was considered to be proven that FSME-IMMUN was non-inferior to Encepur. No success criteria were pre-specified for lot consistency. We will not discuss the results of lot

consistency or equivalence of FSME-IMMUN with Encepur since the protocol did not pre-specify formal hypothesis testing and acceptance criteria for concluding lot consistency and Encepur is a non-US licensed comparator.

Local and systemic reaction rates other than fever after the first and second vaccinations were provided in tabular format. For each symptom, the number of subjects who experienced the symptom, as well as the probabilities of the occurrence and the 95% CI, are given. All adverse events of each subject, including the same events at different time points, were listed according to Medical Dictionary for Regulatory Activities (MedDRA) terminology. Adverse events were analyzed separately after each vaccination.

Sample size: sample size calculations were determined based on the numbers needed to compare fever rates between groups. Taking into account anticipated drop-out rates, the overall sample size was chosen based on what would be sufficient to detect an AE with an occurrence of 1:1000 subjects.

Randomization

Subjects were randomized using block randomization with block sizes greater than four at a ratio of 1:3.

Reviewer's Comments: Page 30 of the CSR states that some Encepur syringes were discarded due to the presence of (b) (4) *in the vaccine, and for this reason, some gaps occurred in the sequence of randomization codes.*

Immunogenicity was not assessed during this safety study. No interim analysis was performed. The statistical analyses include only subjects for whom data are available. Missing data were neither replaced nor estimated.

For Study 213:

Analysis of the Primary Endpoint

Local and systemic reactions after the third vaccination

The rates of local and systemic reactions related to the third vaccination were provided in tabular format, and the probabilities of the occurrence of AEs and their 95% CIs are given for the whole study population and also separately for those who previously received either FSME-IMMUN "NEW" or Encepur.

Analysis of the Secondary Endpoint

Safety

The rates of adverse events that occurred between the last visit in Study 208 and the first visit in Study 213 were presented in tabular format by originally assigned treatment group.

Immunogenicity

TBEV antibody response was assessed before and after the third vaccination in the immunogenicity subgroup subjects. Sera were assessed for TBEV antibodies immediately before and 21 to 28 days after the third vaccination by ELISA

(IMMUNOZYM FSME IgG, PROGEN Biotechnik Heidelberg, Germany) and neutralization test (Adner et al., 2001).

A subject was considered to have seroconverted if the ELISA value was <63 VIEU/mL before entry to Study 208 and >126 VIEU/mL at the time of assessment (before and/or after the third vaccination in Study 213) 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 VIEU/mL at entry to Study 208 was defined as a more than 2-fold rise in antibody titers at the time of assessment:

- Geometric mean antibody response before and after the third vaccination, as measured by ELISA and NT.
- Geometric mean fold increase (GMFI) in antibody response before and after the third vaccination as compared to baseline, measured by ELISA and NT.

Reviewer's Comments: NT results are more reliable as indicators of vaccine effectiveness than are ELISA results because NT detects functionally active, neutralizing antibodies which are believed to be protective. Thus, only NT data were included in the Package Insert. However, because different NT methods were used across the clinical studies and in some studies no NT data were available, ELISA data will also be discussed in this review as additional supportive vaccine immunogenicity data.

Missing Values

Missing values were not replaced or estimated.

Sample Size Calculations

The maximum sample size for Study 213 was predefined by the number of subjects (3927) who received two vaccinations in Study 208. Approximately 300 subjects received FSME-IMMUN and 100 received Encepur as their initial two vaccinations. With this sample size, the CSR reports that seroconversion rate for those who received FSME-IMMUN for all three doses was calculated with ±3.4% accuracy assuming 90% seroconversion and ±4.5% accuracy if the seroconversion rate was approximately 80%.

Reviewer's Comments: Please refer to the statistical review of this BLA for a detailed discussion of the statistical methods used in this study.

Changes in the Conduct of the Study or Planned Analyses

Retesting of Sera by NT According to Adner et al., 2001

In the initial proposed immunogenicity assessment, the immunogenicity of a third dose of FSME-IMMUN "NEW" in TBEV-naïve adults was determined by ELISA (IMMUNOZYM FSME IgG, PROGEN Biotechnik Heidelberg, Germany) and neutralization test as described by (b) (4)

Any subjects who showed positive anti-TBEV antibody concentrations by ELISA at screening were excluded from the immunogenicity analyses to avoid possible false positive ELISA results caused by cross-reactivity with other flaviviruses. Thus, positive ELISA values determined after vaccination demonstrated the presence of anti-TBEV

antibodies, and consequently a good correlation was expected between the ELISA and NT results as described by (b) (4) However, a strong antibody response as determined by ELISA post-dose two was not predictive of a strong antibody response as determined by NT: the observed seroconversion rates and fold increases in antibody response as measured by NT were lower than those measured by ELISA after the second dose. The sponsor of this study (Baxter) decided to reanalyze serum samples by NT according to (b) (4) using a different neutralization test (Adner, et al. 2001) that had shown a clear correlation with ELISA results in a previous clinical study with the FSME-IMMUN vaccine (IMAG-062).

Reviewer's Comments: Please refer to the CMC reviewer memo for further discussion regarding the assays used in FSME-IMMUN clinical development program and to Section 9 of this clinical review memo for more information regarding Study IMAG-062.

6.1.10 Study Population and Disposition

A total of 3999 subjects gave informed consent and were screened for Study 208 participation at 14 centers in Poland (Table 16). 3966 subjects satisfied the entry criteria and were randomized in the study.

Table 16. Number of Subjects Enrolled for Screening at Each Study Center

Center Investigator	Center Number	Center Location	N	%
Romaszko	1	Olsztyn	348	(8.7%)
CwinarowicZ-Sliwa	2	Olsztyn	283	(7.1%)
Michalowska	3	Olsztyn	281	(7.0%)
Smukalska	4	Bydgoszcz	279	(7.0%)
Zawada-Skrobisz	5	Tamow	245	(6.1%)
Brzostek	6	Debica	340	(8.5%)
Pomorska	7	Lublin	280	(7.0%)
Dziduch	8	Lubartow	340	(8.5%)
Kozlowska	9	Zamosc	340	(8.5%)
Guzik	10	Krakow	242	(6.1%)
Jurowska	11	Krakow	241	(6.0%)
Patrzaiek	12	Kieice	320	(8.0%)
Sladek	14	Krakow	180	(4.5%)
Konior	15	Krakow	280	(7.0%)

Source: Original BLA, CSR for Study 208, page 26
Total N=3999 (100%)

Reviewer's Comments: Enrollment was evenly distributed amongst the other 14 study centers. Center 13 (not shown in Table 16) was identified as being located in a TBEV non-endemic area; therefore, the local IRB did not approve the study at that center.

All subjects who participated in Study 208 were included in Study 213 if they had received two vaccinations in Study 208. Study 213 was conducted in the same 14 study centers in Poland. However, the immunogenicity subset was limited to subjects from 2 out of 14 centers due to "logistic reasons".

Reviewer's Comments: We are unable to verify if the centers selected for the immunogenicity analysis were representative of the enrolled population based on the data submitted. No corrections for possible center effects were included in the analyses. Of the 620 participants enrolled in Study 208 from Study Centers number 6 and 15, 566

were included in the immunogenicity analysis. We were unable to identify the reasons why 54 subjects enrolled in Centers 6 and 15 did not participate in the immunogenicity analysis.

6.1.10.1 Populations Enrolled/Analyzed

Analysis Population for Study 208

- Per protocol dataset I includes subjects who: a) were eligible according to inclusion and exclusion criteria and b) had available body temperature measurements after the first vaccination. Used for the analysis of fever rate after the first vaccination.

- Per protocol dataset II includes subjects who: a) were eligible according to inclusion and exclusion criteria and b) had available body temperature measurements after the second vaccination. Used for the analysis of fever rate after the second vaccination.

- Safety analysis set includes subjects who have received the respective vaccinations and had documented adverse event information (at least) immediately after vaccination.

Analysis Population for Study 213

- Per protocol dataset I (used to calculate fever rates after third vaccination): includes subjects who:
    - Completed Study 208 according to protocol
    - Were eligible according to the exclusion/inclusion criteria in Study 208
    - Were eligible according to the inclusion criteria in Study 213
    - Received the third vaccination
    - Were negative at baseline (prior to the first vaccination in Study 208) for TBEV antibodies by ELISA
    - Had available body temperature measurements after the third vaccination.
- Safety Dataset I (used for analysis of adverse events that occurred after the third vaccination): includes subjects who:
    - Received the third vaccination
    - Documented adverse event information at least immediately after the third vaccination
- Safety Dataset II (analysis of AEs reported in the period between Study 208 and 213) includes subjects who documented adverse event information for the period between Studies 208 and 213.

6.1.10.1.1 Demographics

A similar proportion of males and females were enrolled in the Study 208 and follow-on Study 213. Approximately 40% of them were 16-25 years old, 20% 26-35 or 36-54 years, 10-15% were 46-55 years old and only a small proportion (5%) was older than 56.

For the immunogenicity set, there was a slightly higher number of female subjects. The majority of the subjects were 16-55 years of age. Fourteen subjects were >55 years of age, and no subject older than 65 was included.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

N/A

6.1.10.1.3 Subject Disposition

From the 3999 subjects enrolled, 33 subjects were not randomized. 27 subjects in the FSME-IMMUN and 12 in the comparator group did not receive the second vaccination. From those subjects, eight subjects (five in the FSME-IMMUN study group and three in the comparator study group) completed visit 2 but did not receive the second vaccination due to reported adverse events. Please refer to Section 6.1.12.7 for more information regarding the adverse events experienced by the subjects in the FSME-IMMUN arm.

Seven subjects were found to be pregnant in Study 208 (four in the FSME-IMMUN arm and three in the comparator arm) but they did not receive the second vaccination, and as described in the CSR "they were removed from protocol participation."

Reviewer's Comments: The CSR for Study 208 provides tables with line listings regarding the events leading to subject exclusion from analyses. We have reviewed the reasons provided and they did not suggest a safety issue (pages 87-93 of the CSR). The CSR for Study 208 states that pregnant subjects would be followed until delivery, but the pregnancy outcomes were not reported in the CSR and CRFs from Study 208 are not available for our review. In Pfizer's response to FDA 25 May 2021 Request for Information, the Applicant states that there is no information on the timeframe of vaccine exposure relative to last menstrual period and/or pregnancy outcomes (including the numbers of spontaneous abortion, stillbirths, pre-term births, term live births, and congenital abnormalities) from clinical trials. A case of a subject who experienced a miscarriage in the 17th week of pregnancy after receipt of FSME-IMMUN is discussed as part of the SAE reports for this study in Section 6.1.12.4.

Protocol Deviations for Study 208

The Applicant reports the following categories of protocol deviations:

- Subjects who entered the study although they did not satisfy entry criteria
  - Due to delays in the determination of ELISA values, it was often not possible to effectively screen subjects for TBEV status prior to study entry and/or vaccination. In the FSME-IMMUN study group, 26 subjects had a positive ELISA value and were removed from the per protocol analysis dataset I and 21 subjects from the per protocol analysis dataset II. For 5 of the 26 subjects, baseline positive ELISA values were reported to the investigator between the first and second vaccination, and consequently they did not receive the second vaccination. Similarly, in the comparator group, ten subjects were removed from both the per protocol analysis datasets I and II.
  - One subject randomized to the comparator study group, was determined as having a latent TBEV infection and was subsequently removed from the per protocol analysis dataset II.
  - A total of seven randomized subjects became pregnant during the study (four subjects in the FSME-IMMUN study group who did not receive the second vaccination and three subjects in the comparator study group who did not receive the second vaccination)
- Subjects who received an excluded concomitant treatment:

- Four subjects (three in the comparator group and one in the FSME-IMMUN "NEW" group) were excluded from the per protocol analysis dataset II after the second vaccination as they had taken antipyretics within four hours prior to vaccination.

The disposition of the subjects enrolled in the safety analysis of Study 213 is shown in Figure 2 below. The disposition of the subjects enrolled in the subgroup immunogenicity analysis are shown below in Figure 3.

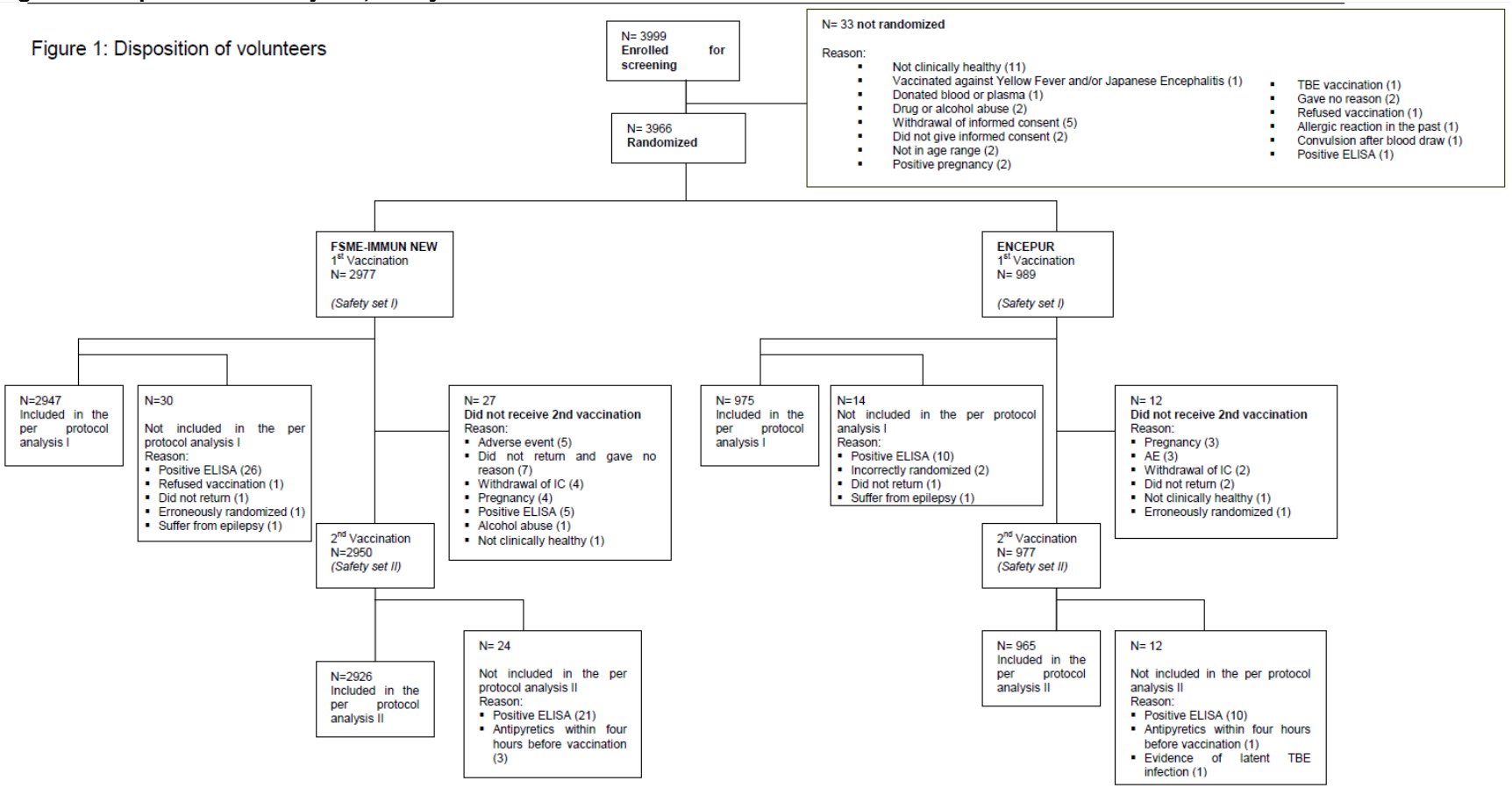
Protocol Deviations for Study 213

One subject (previously vaccinated with the comparator vaccine in Study 208) received the third vaccination but was found to have had a positive ELISA value at baseline in Study 208 and was subsequently excluded from the per protocol analysis.

Reviewer's Comments: The Applicant's description of the events leading to subject exclusion from analyses and protocol deviations not leading to exclusion from analyses were reviewed and no particular protocol deviation/exclusion pattern was noted.

The majority of subjects (559/566; 98.6%) returned for the third vaccination according to the predefined vaccination schedule, i.e., 6 months ±28 days after receiving the first vaccination in Study 208. Only seven subjects had the third vaccination outside the vaccination window and the maximum interval between the first and third vaccinations was 6 months +41 days.

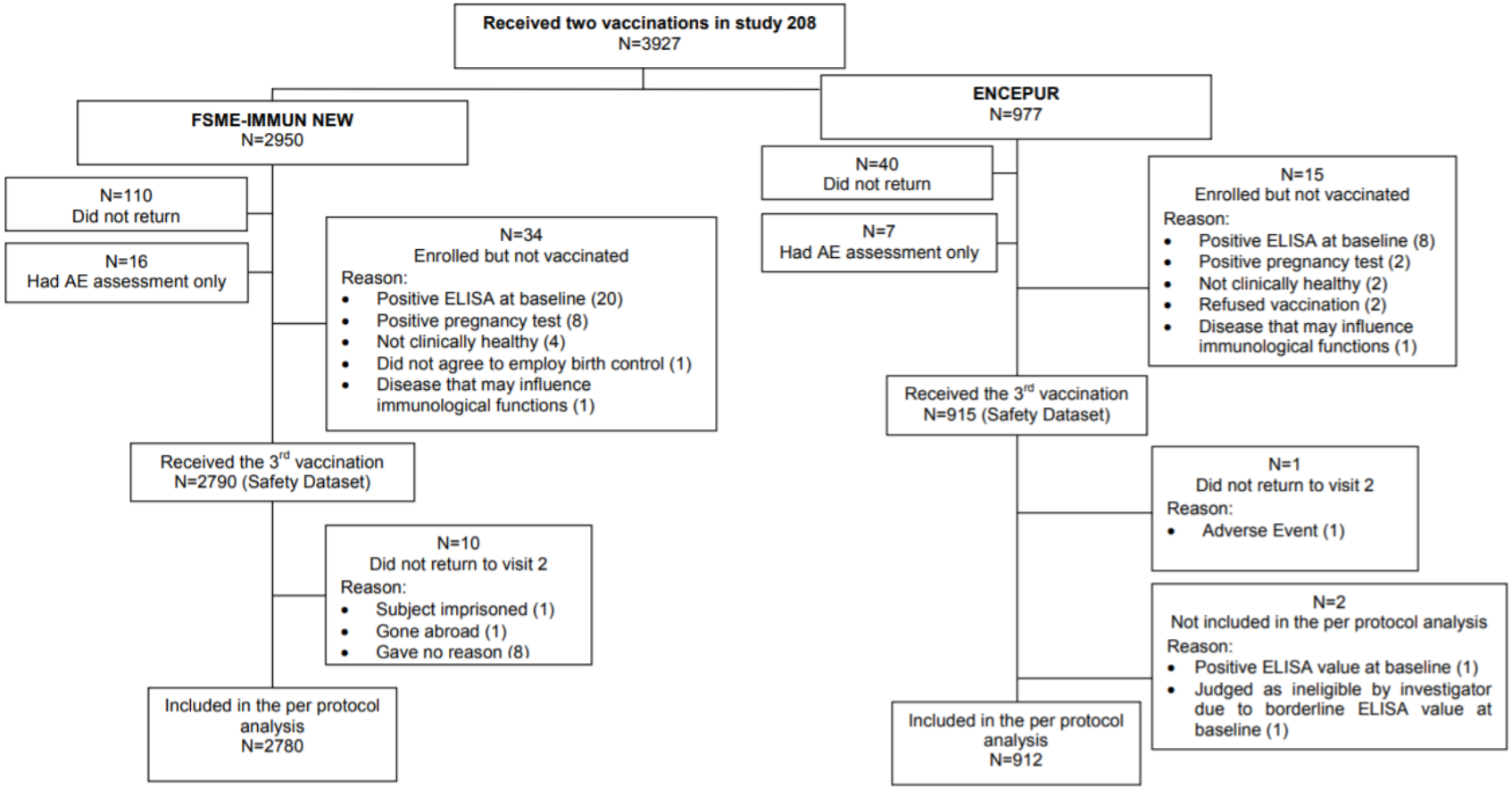
Figure 1. Disposition of Subjects, Study 208



Source: Original BLA CSR for Study 208, page 28.
Encepur is the non-US licensed vaccine comparator

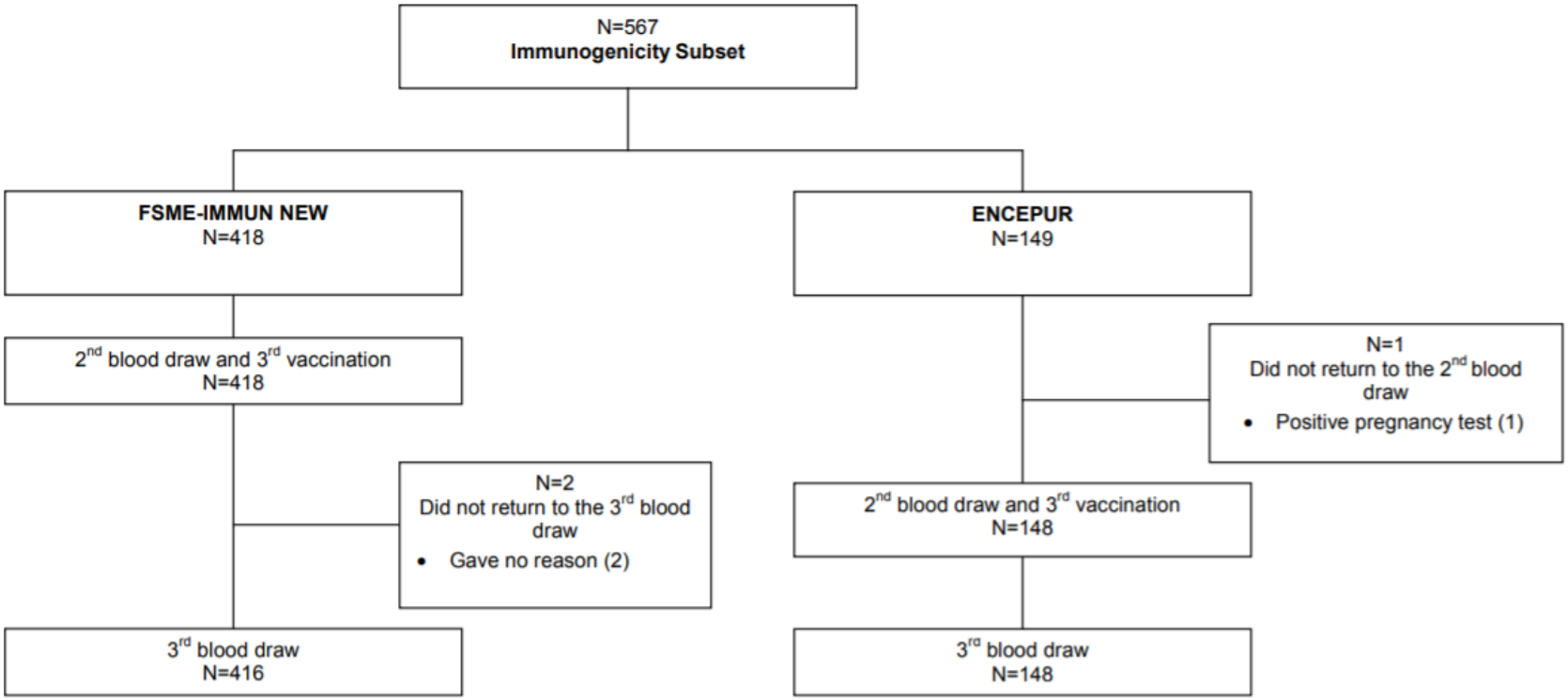
.

Figure 2. Disposition of Subjects, Study 213



Source: Original BLA, CSR for Study 213, page 30.

Figure 3. Disposition, Immunogenicity Subset, Study 213



Source: Original BLA, CSR for Study 213, page 31.

6.1.11 Efficacy Analyses

There were no clinical disease endpoint efficacy analyses for Study 208 and 213. Immunogenicity analyses were performed for Study 213 and are discussed in this section.

6.1.11.1 Analyses of Primary Endpoint(s)

Vaccine immunogenicity was not a primary endpoint in this study.

6.1.11.2 Analyses of Secondary Endpoints

TBEV antibody titers (as measured by NT) and concentrations (ELISA) were evaluated in a subgroup of subjects in Study 213 (N=566). Blood samples were drawn immediately before (6 months ±28 days after the second dose from Study 208) and 21 to 28 days after the third dose; blood samples were also available for these subjects from baseline (before the first dose) in Study 208 for determination of seroconversion. Two subjects did not return for the blood draw after the third vaccination, hence the total number of subjects included in the immunogenicity analysis is 564. The results presented here were determined by ELISA (IMMUNZYM FSME IgG, PROGEN Biotechnik Heidelberg, Germany) and by NT (Adner et al. 2001).

After vaccination with FSME-IMMUN in Study 213, the seroconversion rates (compared to baseline) as determined by ELISA and/or NT were very high among subjects who received FSME-IMMUN for the two previous vaccinations (99.5%) and those who received the non-US-licensed vaccine comparator (99.3%). Similar results were obtained when seroconversion was determined by ELISA or by NT separately (see Table 17 below):

Table 17. Seroconversion Rates Immediately Before and After the Third Vaccination*, as Determined by ELISA and NT in Study 213

		FSME-IMMUN Only		Vaccine Comparator Then FSME-IMMUN	
Method	**Time Point**	**Seroconversion Rate n/N (%)**	**95% CI**	**Seroconversion Rate n/N (%)**	**95% CI**
ELISA and/or NT	Before the third vaccination	362/418 (86.6%)	(83.0, 89.7)	138/148 (93.2%)	(87.9, 96.7)
ELISA and/or NT	After the third vaccination	414/416 (99.5%)	(98.3, 99.9)	147/148 (99.3%)	(96.3, 100.0)
ELISA	Before the third vaccination	182/418 (43.5%)	(38.7, 48.4)	72/148 (48.6%)	(40.4, 57.0)
ELISA	After the third vaccination	411/416 (98.8%)	(97.2, 99.6)	146/148 (98.6%)	(95.2, 99.8)
NT	Before the third vaccination	360/416 (86.5%)	(82.9, 89.7)	137/148 (92.6%)	(87.1, 96.2)
NT	After the third vaccination	411/416 (98.8%)	(97.2, 99.6)	146/148 (98.6%)	(95. 2, 99.8)

*Serconversion rates are relative to the pre-vaccination level of ELISA/NT
Note: NT performed according to Adner et al.
Source: Original BLA, Summary of Clinical Efficacy, page 52 and tables 7,8,9,10 from CSR for Study 213

The geometric mean concentrations (GMCs) of TBEV antibodies as determined by ELISA and the geometric mean titers (GMTs) as determined by NT after the third

vaccination demonstrate a strong immune response in both the FSME-IMMUN "NEW" and the comparator study groups (refer to Table 18 and Table 19 below).

Table 18. Antibody Concentration as Determined by ELISA for Subjects in the Immunogenicity Subset, Study 213

Vaccination in Study 208/Study 213	N	GMC (VIEU/mL)	95% CI of GMC
Baseline			
FSME-IMMUN "new" only	418	17.0	16.1, 17.9
Baseline			
TBE vaccine comparator /FSME-IMMUN "new"	148	17.8	16.2, 19.6
Before the 3rd Vaccination			
FSME-IMMUN "new" only	418	111.7	104.3, 119.6
Before the 3rd Vaccination			
TBE vaccine comparator /FSME-IMMUN "new"	148	115.1	102.0, 129.9
After the 3rd Vaccination			
FSME-IMMUN only	416	1935.7	1754.3, 2135.9
After the 3rd Vaccination			
TBE vaccine comparator /FSME-IMMUN	148	1508.7	1307.4, 1741.1

Source: Original BLA, CSR for Study 213, Table 11, page 52.

Table 19. Antibody Titers as Determined by NT for Subjects in the Immunogenicity Subset, Study 213

Vaccination in Study 208/Study 213	N	GMT	95% CI of GMT
Baseline			
FSME-IMMUN only	416	5	5.0, 5.1
Baseline			
TBE vaccine comparator /FSME-IMMUN "new"	148	5	5.0, 5.1
Before the 3rd Vaccination			
FSME-IMMUN only	416	22.9	21.0, 25.0
Before the 3rd Vaccination			
TBE vaccine comparator /FSME-IMMUN "new"	148	35.5	30.4, 41.4
After the 3rd Vaccination			
FSME-IMMUN "NEW" only	416	259	235.4, 285.0
After the 3rd Vaccination			
TBE vaccine comparator /FSME-IMMUN	148	371.4	324.7, 424.8

Note: NT performed according to Adner et al.
Source: Original BLA, CSR for Study 213, Table 12, page 52.

Reviewer's Comments: Prior to the third vaccination >85% of subjects who had received two doses of FSME-IMMUN met the seroconversion threshold. However, an analysis of NT GMT shows that pre-dose 3 NT titers (GMT 22.9, 95% CI: 21, 25) were at least ten times lower than the values achieved after administration of the third dose (GMT 259, 95% CI: 235.4, 285).

The majority of the subjects participating in Study 208 and 213 had more than a 16-fold increase of antibody response after the third vaccination compared to baseline determined by ELISA (95.7%) and NT (86.5%). For the 416 subjects who received FSME-IMMUN in Study 208, a 51.6-fold (95% CI of geometric mean: 46.8, 56.8) increase in antibody response as determined by NT was observed after the third vaccination compared to baseline. When the antibody response after the third

vaccination is compared with the antibody levels immediately before the third vaccination, an 11.3-fold increase (95% CI of GMFI 10.3, 12.3) was observed.

Reviewer's Comments: There is no correlate of protection for TBE. However, the presence of neutralizing antibodies to the virus (NT titer ≥10) is commonly considered to be associated with protection. Subjects who complete the primary immunization series in this study achieved high levels of seroconversion (i.e., >98%) with neutralization titers significantly above the cut-off value.

6.1.11.3 Subpopulation Analyses

N/A

6.1.11.4 Dropouts and/or Discontinuations

N/A

6.1.11.5 Exploratory and Post Hoc Analyses

N/A

6.1.12 Safety Analyses

6.1.12.1 Methods

Please refer to Section 6.1.7 for details regarding the methods for safety assessment.

6.1.12.2 Overview of Adverse Events

No unexpected AEs or SAEs considered related to FSME-IMMUN were observed. Four SAEs were reported after the first dose, and one SAE was reported after the second dose in the FSME-IMMUN. There were no SAEs reported after the third vaccination in the FSME-IMMUN group. Please refer to Section 6.1.12.4 for additional information regarding the SAEs reported in the two studies.

Reviewer's Comments: The studies submitted to this application were conducted by Baxter, and although queried adverse event data were reported in the CSRs, we are unable to verify the data and calculate rates of events in part because datasets do not support calculation of rate of events. The safety data reported in the review is based on what was reported in the CSRs. We were able to review the information regarding SAEs from the clinical report forms submitted by the Applicant to the BLA.

Fever

In Study 208, fever rate after the first vaccination calculated in the per protocol dataset population was lower in the FSME-IMMUN group (0.8%) than in the Non-US comparator group (5.6%), and fever was mild. Fever after the second (Study 208) and third vaccination (Study 213) occurred at a lower rate and was comparable for both study groups. No cases of fever ≥39.5°C occurred after either vaccination, regardless of study group.

Reviewer's Comment: Per CSR, Subject's oral temperature, local and systemic adverse events after vaccination were recorded in diary cards for four days after each vaccination. Diary cards were expected to be returned to the investigator at the next

study visit. However, after review of source documents, Pfizer clarified that AE reporting occurred outside the planned 4-day diary period. Thus, the data from the tables reported in the CSR may include adverse events that possibly occurred up to 10 days after doses 1 and 2 and up to 42 days after dose 3.

Table 20. Number (%) of Subjects Reporting Fever by Severity in Per Protocol Dataset, Studies 208/213

Vaccination Received	No Fever n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total
First Vaccination FSME-IMMUN	2924 (99.2%)	23 (0.8%)	0 (0.0%)	0 (0.0%)	2947
First Vaccination TBE vaccine comparator	920 (94.4%)	54 (5.5%)	1 (0.1%)	0 (0.0%)	975
Second Vaccination FSME-IMMUN	2910 (99.5%)	15 (0.5%)	1 (0.0%)	0 (0.0%)	2926
Second Vaccination TBE vaccine comparator	960 (99.5%)	4 (0.4%)	1 (0.1%)	0 (0.0%)	965
Third Vaccination FSME-IMMUN only	2765 (99.5%)	14 (0.5%)	1 (0.0%)	0 (0.0%)	2780
Third Vaccination TBE vaccine comparator then FSME-IMMUN	909 (99.7%)	3 (0.3%)	0 (0.0%)	0 (0.0%)	912

Source: Original BLA, Table 17 of the Summary of Clinical Safety, page 40, CSR, pages 57, 60 and 61
n = number of subjects reporting fever

Reviewer's Comments: The severity grade criterion utilized in this study to categorize fever is liberal when compared with recommendations in the FDA Guidance "Toxicity Grading Scale for Healthy Adult and Adolescent Subjects Enrolled in Preventive Vaccine Clinical Trials." Fever, in Studies 208 and 213, was categorized by severity grade according to the CTC guidelines (National Cancer Institute 1999) as follows:

- *Mild: 38.0° C to 39.0° C*
- *Moderate 39.1° C to 40.0° C*
- *Severe >40.0° C*

. Per our guidance, fever would be classified as:

- *Mild (Grade 1): 38.0° C to 38.4° C*
- *Moderate (Grade 2): 38.5° C to 38.9° C*
- *Severe (Grade 3): 39° C to 40° C*
- *Potentially Life Threatening (Grade 4): >40° C*

The oral temperature measurements of subjects who experienced fever after the first and second vaccination were provided in tables in the CSR (Study 208). For the FSME-IMMUN group some cases of mild fever had reported temperatures above 38.4° C, and three cases of fever had temperatures >39° C (grade 3). No cases of fever ≥39.5°C occurred after either vaccination, regardless of study group.

Local Injection Site Reactions

Local injection site reactions after the first dose were reported by 35.6% (1060/2977) of subjects in the FSME-IMMUN group and 44.7% (442/989) in the comparator group.

Local injection site reactions after the second dose were reported by 31.7% (934/2950) of subjects in the FSME-IMMUN group and 38.6% (377/977; CI: 35.5%, 41.7%) in the comparator group.

Local injection site reactions after the third dose were reported by 29.7% (829/2790) of subjects in the FSME-IMMUN group and 31.4% (287/915) of subjects in the group who received TBE vaccine comparator/FSME-IMMUN group.

The majority of local injection site reactions after the first, second and third doses were mild. Please refer to Table 21 below.

Table 21. Number (%) of Subjects Reporting Local Injection Site Reactions by Severity After the First, Second, and Third Vaccination, Studies 208 and 213, Safety Analysis Set

Vaccination Received	No Reaction n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total
First Vaccination FSME-IMMUN	1917 (64.4%)	969 (32.5%)	87 (2.9%)	4 (0.1%)	2977
First Vaccination TBE vaccine comparator	547 (55.3%)	375 (37.9%)	62 (6.3%)	5 (0.5%)	989
Second Vaccination FSME-IMMUN	2016 (68.3%)	834 (28.3%)	95 (3.2)	5 (0.2%)	2950
Second Vaccination TBE vaccine comparator	600 (61.4%)	341 (34.9%)	35 (3.6%)	1 (0.1%)	977
Third Vaccination FSME-IMMUN only	1961 (70.3%)	739 (26.5%)	87 (3.1%)	3 (0.1%	2790
Third Vaccination TBE vaccine comparator then FSME-IMMUN	628 (68.6%)	250 (27.3%)	37 (4%)	0	915

Source: Source: Original BLA, pages 62,64 and 65 of the CSR for Study 208 and page 70 of the CSR for Study 213
n = number of subjects reporting local reaction

The most frequently reported local reactions after each dose were injection site pain and tenderness (greater than 10%, refer to Table 23 below), while the other types of local reactions (such as induration, erythema and swelling) were reported at low frequency (≤0.2%).

Systemic Reactions

Systemic reactions (excluding fever) after first dose occurred at a higher frequency in the comparator study group than in the FSME-IMMUN group. Mild systemic reactions were common (>10%) in both study groups. As expected, the rate of systemic reactions (excluding fever) after the second dose for both study groups was lower than after the first dose. In contrast to systemic reactions after the first dose, the two study products were associated with similar rates of systemic reaction after the second and third dose (Table 22 below). In both vaccine groups and after each dose, the most frequently reported systemic reactions (excluding fever) were headache, muscle pain, fatigue, and malaise.

Table 22. Number (%) of Subjects Reporting Systemic Reactions (Excluding Fever) by Severity, Studies 208 and 213, Safety Analysis Set

Vaccination Received	No Reaction n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total
First Vaccination FSME-IMMUN	2573 (86.4%)	347 (11.7%)	56 (1.9%)	1 (0.0%)	2977
First Vaccination TBE vaccine comparator	682 (69%)	233 (23.6%)	71 (7.2%)	3 (0.3%)	989
Second Vaccination FSME-IMMUN	2680 (90.8%)	227 (7.7%)	40 (1.4)	1 (0.1%)	2950
Second Vaccination TBE vaccine comparator	867 (88.7%)	95 (9.7%)	14 (1.4%)	1 (0.1%)	977
Third Vaccination FSME-IMMUN only	2500 (89.6%)	247 (8.9%)	42 (1.5%)	1 (0%)	2790
Third Vaccination TBE vaccine comparator then FSME-IMMUN	797 (87.1%)	97 (10.6%)	21 (2.3%)	0	915

Source: Original BLA, CSR for Study 208, pages 68, 72 and CSR for Study 213, page 71.
n = number of subjects reporting local reaction

Queried Local and Systemic Symptoms

Local pain and tenderness were the most frequently reported local reactions after vaccination with FSME-IMMUN. The most frequently reported systemic reactions in the two study groups were headache, malaise, fatigue and muscle pain. These events were specifically queried in the CRF. Only a small number of non-queried systemic adverse events (less than 1%) were reported which were judged to be related to vaccination.

Table 23. Incidence Rates of Specifically Queried Local and Systemic Adverse Reactions Within 4 days After Each Dose of FSME-IMMUN (Specified in eCRF, Studies 208/213)

Symptom	Preferred Term	Dose 1 n (%) N=2977	Dose 1 95% CI	Dose 2 n (%) N=2950	Dose 2 95% CI	Dose 3 n (%) N=2790	Dose 3 95% CI
Swelling	Application site edema	2 (0.1)	(0, 0.2)	0 (0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.2)
Induration	Injection site induration	3 (0.1)	(0, 0.3)	0 (0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.2)
Erythema	Application site erythema	0 (0)	(0, 0.1)	1 (0)	(0.0, 0.2)	0 (0)	(0.0, 0.2)
Ecchymosis	Injection site bruising	2 (0.1)	(0, 0.2)	0 (0)	(0.0, 0.1)	1 (0.0)	(0.0, 0.2)
Haematoma	Injection site haemorrhage	2 (0.1)	(0, 0.2)	1 (0.0)	(0.0, 0.2)	4 (0.1)	(0.0, 0.4)
Local Pain	Injection site pain	392 (13.2)	(12, 14.4)	397 (13.5)	(12.3, 14.7)	334 (12.0)	(10.8, 13.2)
Tenderness	Injection site pain	890 (29.9)	(28.3, 31.6.)	808 (27.4)	(25.8, 29.0	718 (25.7)	(24.1, 27.4)
Headache	Headache NOS	171 (5.7)	(4.9, 6.6)	112 (3.8)	(3.1, 4.6)	124 (4.4)	(3.7, 5.3)
Nausea	Nausea	59 (2)	(1.5, 2.6)	26 (0.9)	(0.6, 1.3)	29 (1.0)	(0.7, 1.5)
Vomiting	Vomiting NOS	6 (0.2)	(0.1, 0.4)	3 (0.1)	(0.0, 0.3)	1 (0.0)	(0.0, 0.2)
Muscle pain	Myalgia	144 (4.8)	(4.1, 5.7)	99 (3.6)	(2.7, 4.1)	97 (3.5)	(2.8, 4.2)
Joint pain	Arthralgia	38 (1.3)	(0.9, 1.7)	30 (1.0)	(0.7, 1.5)	38 (1.4)	(1, 1.9)
Fatigue	Fatigue	186 (6.2)	(5.4, 7.2)	113 (3.8)	(3.2, 4.6)	143 (5.1)	(4.3, 6)
Malaise	Malaise	133 (4.5)	(3.8, 5.3)	92 (3.1)	(2.5, 3.8)	92 (3.3)	(2.7, 4)
Swelling of the axillary/inguinal lymph nodes	Lymphadenopathy	17 (0.6)	(0.3; 0.9)	8 (0.3)	(0.1; 0.5)	20(0.7%)	(0.4; 1.1)

Original BLA Tables 41 and 42, CSR for Study 208 pages 76 and 77 and table 39, CSR for Study 213 page 74.

Reviewer's Comments: Some of the incidence rates reported in Table 23 are slightly different from what is reported in Section 6 of the PI. While the source of the data for this table is the CSR for Study 213, the analyses reported in the PI were based on new data analysis performed by Pfizer using the Baxter Core Safety Information that Pfizer received from Baxter during the transfer of the product. Although not identical, the rates are quite similar.

Subject (b) (6), a 22-year-old male, was reported to have experienced severe headache, fatigue, lymphadenopathy, nausea, myalgia, malaise and joint pain. All these symptoms began on the day of the third vaccination and were assessed by the study investigator as being probably related to vaccination. It should be noted that this subject did not experience any local reactions to vaccination and that moderate abdominal pain was also reported to have occurred 2 days after vaccination.

All unsolicited adverse events reported by subjects were assessed as not related to either study vaccine by the study investigator. The overall frequencies of unsolicited events following dose 1 or 2 were balanced between vaccine groups.

6.1.12.3 Deaths

Study 208

One subject death was reported. The SAE was reported as sudden death and considered unrelated to study vaccine by the investigator. The CSR has the following description for this event: Subject (b) (6) a 32-year-old female, died (b) (6) days after receiving the first dose of FSME-IMMUN. The subject lost consciousness while carrying out her daily household routine. The ambulance crew arrived to find the subject in cardiac arrest. After resuscitation (intubation and ventilation, indirect massage and defibrillation) cardiac activity returned and single breaths occurred at a frequency of four per minute. However, during transfer to the hospital, the subject required resuscitation again. The subject was pronounced dead upon arrival at the hospital. Following autopsy, the direct cause of death was attributed to acute respiratory and circulatory insufficiency caused by inflammatory changes in the cardiac muscle (interstitial myocarditis) and lungs (interstitial pneumonia). An underlying congenital heart defect (an abnormal configuration and abnormal ostium of coronary vessels, and arrhythmogenic right ventricular dysplasia) was detected. The etiology of the inflammatory changes in the lungs and heart was most probably viral, but this cannot be unequivocally determined since no detailed tests were carried out. In addition, slight inflammatory changes in the glomeruli of the kidneys were found, which were described by the pathologist as probably resulting from autoimmune processes which had been developing for months, or even years.

Reviewer's Comments: The congenital heart defect is a plausible alternative cause of sudden death. However, the autopsy also revealed inflammatory changes in the heart and lung that contributed to the death and the etiology of this inflammation was not identified. There is not enough information to rule out relatedness of the inflammatory changes in the heart and lung to the FSME-IMMUN vaccine.

Study 213

One death was reported during the study: the murder of a subject. A female subject (b) (6) aged 47 years (at the time of first vaccination in Study 208) was murdered on (b) (6), (b) (6) days after receiving the third vaccination. This death was determined as unrelated to vaccination by the investigator.

Reviewer's Comments: Based on the narrative provided by the Applicant of the death in Study 213, we agree with the Applicant's assessment that this event should be considered not related to the vaccination.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 56 SAEs were reported in 55 subjects in Studies 208/213: 47 of them in the period between Studies 208 and 213; 39 of the SAEs in the FSME-IMMUN group.

Study 208

Non-fatal SAEs were reported for 5 subjects during Study 208; none of these SAEs were considered related to study vaccine by the investigator:

1. Subject (b) (6), a 26-year-old male, was initially diagnosed with a disturbance of electrolyte homeostasis and dehydration after complaining to his general practitioner that he had been vomiting for the previous 7 days (symptoms began 3 days prior to dose 1 of FSME-IMMUN) and had also been suffering from headache and a stiff neck. The general practitioner sent the subject to the hospital for infusion therapy where the headache and stiff neck were quickly resolved following rehydration treatment. Further tests determined that he had a duodenal ulcer, duodenal bulb stenosis, hiatal hernia, and esophagitis. It should be noted that the subject had a 2-year history of gastric complaints.
2. Subject (b) (6), a 16-year-old male, was physically assaulted 16 days after the first vaccination with FSME-IMMUN and sustained a nasal bone fracture and a hematoma of the nasal septum. The subject was hospitalized for repositioning of the nasal bones and insertion of intranasal plates under general anesthetic.
3. Subject (b) (6), an 18-year-old female, complained of severe headache 9 days after the first vaccination with FSME-IMMUN; 12 days later, the headache subsided but she developed vomiting and fever and was hospitalized. Neurological examination determined the presence of marked meningeal symptoms, in the absence of focal damage to the central nervous system, and the subject was diagnosed with viral meningitis. According to the initial report made by the investigator, the SAE was graded as possibly related to vaccination. After obtaining the final diagnosis from the neurological unit of the hospital, the investigator classified the SAE as unrelated to vaccination.
4. Subject (b) (6), a 42-year-old male, was hospitalized 5 days after the second vaccination of FSME-IMMUN for a planned operation of the nasal septum.
5. Subject (b) (6), a 36-year-old male, was diagnosed with chronic sinusitis after receiving FSME-IMMUN. The subject suffered from a headache for which he was hospitalized. During laryngoscopic examination, pansinusitis was diagnosed. The subject recovered without sequelae.

<u>Reviewer's Comments:</u> The SAE of viral meningitis described in item 3 has not been attributed to FSME-IMMUN; however, the limited data provided do not allow this reviewer to rule out the causal relationship to the vaccine because the event occurred 9 days after vaccination and the etiology of the meningitis was not determined. Alternative etiologies are provided for the other four SAEs that occurred in Study 208.

A total of 47 SAEs were reported to have occurred in 46 subjects during the period between Studies 208 and 213, 30 of them in the FSME-IMMUN group (after dose 2 and before dose 3). The SAEs reported between Studies 208 and 213 in the FSME-IMMUN group are listed in Table 24 below:

Table 24. Nonfatal Serious Adverse Events That Occurred During The Period Between Studies 208/213 Among Subjects Who Received FSME-IMMUN

Subject ID	Age	Sex	MedDRA Preferred Term	Onset after Dose 2[a]
(b) (6)	36	M	Cholecystitis, cholelithiasis	152 days
	51	M	Myocardial infarction	154 days
	64	M	Prostatic hypertrophy	47 days
	20	F	Appendicitis	66 days
	17	M	Head Trauma	87 days
	60	M	Degeneration of vertebrae joints, diabetes and hypertension	70 days
	63	M	Tumor right undermandible region	107 days
	55	M	Gastric Ulcer	71 days
	17	F	Cyst of the right maxillary sinus	45 days
	46	M	Deviation of nasal septum	65 days
	34	M	Fracture atebrachium-right	67 days
	41	F	Abortion	185 days
	27	M	Hepatitis Chronic	84 days
	36	F	Varicose veins in lower extremities	105 days
	46	F	Disseminated Peritonitis	127 days
	47	M	Cholelithiasis	80 days
	53	M	Varicose veins lower right extremity	117 days
	22	M	Dermatitis fototoxica	71 days
	16	M	Fractura claviculae	147 days
	21	M	Contusio capitis	154 days
	41	M	Cholecystocholedocholithiasis	136 days
	58	F	Ischias radicularis dex	67 days
	50	F	Pulmonary tuberculosis	131 days
	50	F	Varices crural	159 days
	54	F	Disease Menieri	180 days
	53	M	Subendocardial infarct	85 days
	44	M	Inflammatory infliltration on cutis in neck	128 days
	23	M	Condromalatio epiphysis distalis femoris dx	88 days
	19	F	Miscarriage in 17th week of pregnancy	116 days
	17	F	Appendicitis	116 days

[a] Days after last dose
Original BLA, Table 18, page 30, Additional Responses to FDA Information Request, received on April 30, 2021

Reviewer's Comments: Study 208 enrolled subjects using a 3:1 ratio (number of subjects in the FSME-IMMUN group = 2950 and Encepur = 977). Therefore, even though the SAE numbers reported between studies (interval between dose 2 and 3) are higher for the FSME-IMMUN group (N=30) than in the Encepur group (N=16), there is no significant imbalance in the proportion of subjects reporting SAEs between the two groups (approximately 1% for the FSME-IMMUN group and 1.7% for the Encepur group). In addition, from the SAE listings and narratives provided by the Applicant, we agree with the Applicant's assessment that the SAEs that occurred between the studies were not related to either study vaccine. The SAEs all had an alternative plausible explanation for the pathology or happened more than 30 days after the administration of the vaccine.

One SAE that happened between doses 2 and 3 ((b) (6) days after dose 2) and is discussed further in the CSR was a miscarriage in the seventeenth week of pregnancy. Although considered unrelated to the vaccination by the investigator this SAE was

forwarded to an independent medical expert for further review because of the nature of the SAE. According to the final SAE report, subject (b) (6) experienced a sudden strong pain in the lower abdomen, upon which she went to the obstetrics/gynecological emergency room immediately. An ultrasonographic scan was carried out and fetal death was determined to have occurred. The subject was hospitalized, and an abortion was induced. The subject experienced fever (<39°C) for a number of days after the procedure. In the initial SAE report dated (b) (6), a sub-investigator judged the SAE as being possibly related to vaccination; however, the investigator's final attribution assessment of the SAE on (b) (6) was "unrelated" to vaccination. The independent assessment of this case by a medical expert stated that none of the symptoms reported show any association with a TBEV infection or reaction to the TBE vaccine.

Reviewer's Comment: Based on the information provided, this reviewer agrees with the investigator's assessment of this SAE as not related to FSME-IMMUN. This SAE is discussed individually because the subject may have been exposed to FSME-IMMUN while pregnant.

Study 213

Four SAEs were reported to have occurred after the third vaccination:

1. Subject (b) (6) a female subject aged 49 was hospitalized for 8 days due to abdominal pain which began 22 days after the third vaccination was administered. This pain was diagnosed as being due to gangrenous appendicitis. During the investigation, an ovarian cyst (right side) was also diagnosed. An appendectomy was subsequently performed. The subject recovered without sequelae.
2. Subject (b) (6), a female subject aged 47 years, reported stomach pain, vomiting and diarrhea 14 days after receiving the third vaccination. The subject was hospitalized for 5 days and infectious gastroenteritis was diagnosed. It should also be noted that the subject was reported to have experienced a hepatitis B infection in the past and, as expected, the presence of hepatitis B antibodies was detected in the subject's serum.
3. Subject (b) (6), a male subject aged 52 years, suffered cranial trauma in unknown circumstances 24 days after the third administration. He was unconscious upon arrival at the hospital. Radiographs and computer tomography detected multiple fractures of the skull and an intracranial hematoma. He was hospitalized for 30 days and recovered without sequelae.
4. There was a serious adverse event originally reported between Studies 208 and 213, but ongoing at start of Study 213. Subject (b) (6), a 51-year-old female, was diagnosed as suffering from a breast tumor during the period between Studies 208 and 213. She had received two vaccinations with TBE vaccine comparator during Study 208. The subject was hospitalized from (b) (6) and a tumor in the right breast was surgically removed. The histological examination showed fibroadenoma and benign dysphasia.

<u>Reviewer's Comments:</u> The investigators assessed these SAEs as not related. There is limited information for us to assess causality, but alternative etiologies are provided. The SAEs were diseases that are commonly reported in the adult population. We agree that the Applicant's assessment of these SAEs as not related is reasonable.

6.1.12.5 Adverse Events of Special Interest (AESI)

N/A

6.1.12.6 Clinical Test Results

N/A

6.1.12.7 Dropouts and/or Discontinuations

A total of eight subjects were withdrawn from Study 208 due to adverse events: five subjects who had received FSME-IMMUN and three who had received the non-US comparator. All of these subjects were withdrawn after the first vaccination and did not receive the second vaccination. The five subjects who were withdrawn from Study 208 due to AEs after the first vaccination of FSME-IMMUN were as follows:

1. Subject (b) (6), a 32-year-old female, died as the result of a congenital heart defect, interstitial pneumonia and myocarditis (see description of the event above).
2. Subject (b) (6), a 26-year-old male, was withdrawn from the study due to SAEs of duodenal ulcer and hernia.
3. Subject (b) (6), an 18-year-old female, was withdrawn from the study due to an SAE of viral meningitis.
4. Subject (b) (6), a 54-year-old female, withdrew informed consent after experiencing moderate diarrhea, nausea, malaise, and muscle pain after the first vaccination.
5. Subject (b) (6) an 18-year-old female, was withdrawn from the study due to adverse events of laryngitis and bronchopneumonia.

Reviewer's Comments: The number of subjects who withdrew from each treatment group was small and slightly greater for the comparator group (0.01% for FSME-IMMUN group and 0.03% for the comparator group).

There was one subject who was withdrawn from Study 213 due to an AE after the third dose: this was Subject (b) (6), who was murdered (please refer to Section 6.1.12.3).

6.1.13 Study Summary and Conclusions

Immunogenicity was evaluated in a subgroup of 566 subjects, 416 of whom received FSME-IMMUN for all three doses: sera were assessed for TBEV antibodies immediately before and 21 to 28 days after the third vaccination.

The seroconversion rates in the FSME-IMMUN group (N=416) as determined by ELISA and/or NT after the third dose (compared to baseline) were 99.5% (95% CI: 98.3%, 99.9%). Similar results were obtained when seroconversion was determined by ELISA or by NT (both values: 98.8%, 95% CI: 97.2%, 99.6%). Seroconversion rate before the third dose was above 80%. Among subjects who received 2 doses of FSME-IMMUN in Study 208, >80% met the NT seroconversion threshold prior to the third dose of FSME-IMMUN. The GMT prior to the third dose was 22.9 (95% CI: 21, 25) and administration of a third dose of FSME-IMMUN led to a 10-fold increase in GMT titers (GMT 259, 95% CI: 235.4, 285).

The data from this trial did not raise concerns about the safety profile of FSME-IMMUN. Fever was reported in less than 1% of the subjects and was mostly mild. The severity of

local and systemic reactions was mostly mild and the rates of these reactions were similar after each dose. The most frequently reported adverse reactions were tenderness, local pain, fatigue, headache and muscle pain. All SAEs reported were considered not related to FSME-IMMUN by the Principal Investigator.

6.2 Trial #3: Study 209: Safety Study of FSME-IMMUN NEW in Healthy Children and Adolescents Aged 1 to 15 Years (NCT00161863)

September 2002-January 2003
(Germany, Austria and Poland)

Reviewer's Comments: FSME-IMMUN "NEW" in the title denotes FSME-IMMUN.

6.2.1 Objectives

The objective of this study was to investigate the safety of five consecutive lots of FSME-IMMUN. The main safety objective was the assessment of fever rate after the first vaccination in three different age groups (1-2 years, 3-6 years and 7-15 years).

In addition, anti-TBEV antibody concentrations at baseline, 21 to 35 days after the second vaccination and 35 to 42 days after the third vaccination were investigated by ELISA and NT titers in a subgroup of 400 subjects at selected centers.

6.2.2 Design Overview

Study 209 was a multicenter, open-label study to investigate the safety of three 0.25mL doses of FSME-IMMUN from five consecutive vaccine lots. The study enrolled 2419 healthy children and adolescents aged 1-15 years. Safety was evaluated by assessing fever and adverse event (AE) rates after each vaccination. Immunogenicity was investigated in a subgroup of 427 subjects.

Reviewer's Comments: Study 209 evaluated five lots of FSME-IMMUN. However, we do not consider the study a lot-consistency study because it was not designed to establish immunogenicity equivalence among the different vaccine lots. The study evaluated and compared fever rates and provided a descriptive analysis of immune responses. In addition, only a subset of subjects received the three doses from the same lot (five lots were used for doses 1 and 2 but only two lots for dose 3).

For logistic purposes, the study was divided into two parts (Part A and Part B). The duration of Part A was 6 to 12 weeks (from study start until 21 to 35 days after the second vaccination) while part B lasted 6 to 8 months (from end of part A until 35 to 42 days after the third vaccination). The overall study duration was approximately 15 months. There was no control group.

6.2.3 Population

Male and female infants, children and adolescents were eligible for participation in this study if they were aged 1 to <16 years of age, were clinically healthy and their parents/legal guardians signed the informed consent. Additional written informed consent was given by the subjects themselves if older than 8 years of age in Germany and Austria. Female subjects who had reached sexual maturity at study start were required to test negative for pregnancy before each dose. The exclusion criteria for this protocol, with the exception of the age group eligibility (1 to <16 years of age), are similar

to Study 208. Please refer to Section 6.1.3 of this review for an overview of the eligibility criteria with the following notable exception:

Subjects who had received any other vaccination within 4 weeks prior to visit 1 were temporarily excluded, until 4 weeks had passed (the interval was 2 weeks in Study 208).

6.2.4 Study Treatments or Agents Mandated by the Protocol

The following lots of FSME-IMMUN were used in this study:

- Lot 1:370102AB
- Lot 2 370402CB
- Lot 3 370502DC
- Lot 4:370602EB
- Lot 5 370702EB

Subjects received a total of three doses (Days 0, 21-35 and Month 6±14 days after first dose) provided in pre-filled syringes containing a single 0.25 mL dose.

All medications taken were to be documented in the source data. The following concomitant medications were required to be documented in the eCRF:

- Medication taken to treat fever
- Medication to treat SAEs
- Medication that may possibly interfere with the immune response.

Vaccinations were permitted during the study, provided they were administered at least 4 weeks after the second vaccination in Part A and at least 4 weeks prior to the vaccination in Part B in the study. These vaccinations were to be documented in the eCRF. Emergency vaccinations (e.g., tetanus or rabies) could be administered if needed and documented in the eCRF.

6.2.5 Directions for Use

Mode of administration: intramuscularly into the deltoid muscle or into the upper leg in children up to the age of 18 months and/or according to developmental and nutritional status.

6.2.6 Sites and Centers

The study was conducted in 16 centers: 9 centers in Poland, 5 general practices in Germany and 2 general practices in Austria. According to the country-specific vaccination practices, the majority of children aged 1-2 years were recruited in Austria, and those aged 3-15 years were enrolled in Poland and Germany.

6.2.7 Surveillance/Monitoring

The visit schedule was as follows (Table 25):

Table 25. Visit Schedule, Study 209

Visit	Time	Action	Tests
Visit 0* Screening	Day -14 to 0	Informed consent Inclusion and exclusion criteria Medical history Physical examination Blood draw (1 mL)	TBEV antibodies
Visit 1*	Day 0	Inclusion and exclusion criteria Physical examination **FIRST VACCINATION** Distribute subject diary	
Visit 2	7-10 days after first vaccination	Check/return subject diary Physical examination	
Visit 3	21-35 days after first vaccination	Check/return subject diary Physical examination **SECOND VACCINATION** Distribute subject diary	
Visit 4	21-35 days after second vaccination	Check/return subject diary Physical examination Blood draw (1 mL) subgroup only	TBEV antibodies
Visit 5	6 months ±14 days after first vaccination	Medical history with focus on AEs between visits 4 and 5 Physical examination **THIRD VACCINATION** Distribute subject diary	
Visit 6	35-42 days after third vaccination	Check/return subject diary Physical examination Blood draw (1 mL) subgroup only	TBEV antibodies

Source: Original BLA, CSR for Study 209, page 30
*Visit 0 (Screening) and visit 1 may be performed together.
Part A includes visit 0 through visit 4
Part B begins with completion of visit 4 (and includes visit 5 and visit 6)
If adverse reactions to vaccination occur, an additional optional visit can be held at any time during the study if deemed necessary

Table 26. Study Procedures, Study 209

	PART A					PART B	
	Visit 0	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Procedure	-14-0 days	Day 0	7-10 days after 1st vacc.	21-35 days after 1st vacc.	21-35 days after 2nd vacc.	6 months ±14 days after 1st vacc.	35-42 days after 3rd vacc.
Informed Consent	X						
Medical history	X					X	
Inclusion criteria	X	X					
Exclusion criteria	X	X					
Pregnancy test ***	X			X		X	
Physical examination	X	X	X	X	X	X	X
Blood pressure (only for children aged 3-15 years)		X					
Temperature		X	X	X	X	X	X
Pulse		X* X**	X	X* X**	X	X* X**	X
Lymph nodes general		X*		X*		X*	
Blood draw	X				X subgroup only		X subgroup only
Vaccination		**X**		**X**		**X**	
Lymph nodes auxiliary/ inguinal			X		X		X
AE documentation		X**	X	X**	X	X**	X
Subject diary ****		D	R	D	R	D	R

* Performed before vaccination
**Following vaccination, subject will be observed at least 30 minutes
***Only for female subjects who have reached sexual maturity
****D = distribution, R = return & check
Source: Page 31 of CSR for Study 209

6.2.8 Endpoints and Criteria for Study Success

Primary Endpoint

The primary endpoint was fever rate after the first vaccination in three different age groups (1-2 years, 3-6 years, 7-15 years).

Secondary Endpoint

Safety

- Fever rate after the second and third vaccination
- Local and Systemic AEs other than fever after all three vaccinations

Immunogenicity

- 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.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Calculations

No formal statistical hypothesis was formulated. Sample size calculations were based on the expected fever rate for each age group. Therefore, in the age group 1-2 years, 200 subjects were expected to be enrolled; for the 3-6 years old age group, 800 subjects were expected to be enrolled and approximately 1400 subjects, aged 7-15 years, were expected to be enrolled in the study.

Reviewer's Comments: Please refer to the statistical reviewer's memo for additional statistical considerations for this study.

Protocol Version and Amendments

The final version of the protocol was Version 5.0 (December 15, 2003).

Amendment 1: September 9, 2002:

- Hemorrhagic diathesis was added to the exclusion criteria for study entry at the request of the Polish authorities, one of the lots was changed, the list of investigators was updated and the members of the Oversight Committee were named.

Amendment 2: September 19, 2002

- The measurement of blood pressure at visit 0 was restricted to subjects aged >3 years, as the measurement of blood pressure in infants requires equipment reported in the CSR not usually available to pediatricians.

Amendment 3: December 4, 2002

- An interim analysis of safety data following the first vaccination was added to the study protocol in order to provide requested data to the German health authorities.

Amendment 4: December 17, 2003

- Reanalysis of serum samples post-second vaccination tested by NT according to the method by Holzman using the method by Adner.

Reviewer's Comments: In Amendment 4, Baxter decided to reanalyze serum samples tested by NT according to the method by (b) (4) *using the method by Adner et al, 2001. These additional tests using NT by Adner were used to determine the seropositivity rate and geometric mean titers after the second and third vaccinations reported in this review.*

Methods of Assigning Subjects to Treatment

Five consecutive lots of FSME-IMMUN were used for the first dose. The investigator received the vaccine in packs of five syringes, one from each lot. At the first vaccination, all five syringes were to be used in random order before a new pack was started in order to guarantee even lot distribution. The lot number administered to each subject was recorded in the CRF. The subjects received the same lot for dose 2 and then either lot 4 or 5 for dose 3.

Primary Endpoint

The fever rate after the first vaccination was categorized by severity grade, and the occurrence of fever rates in each category and the 95% CIs were calculated. In addition, the proportion of subjects with fever >39.5°C was provided.

Secondary Endpoint

Safety

The fever rate after the second and third immunization was reported by severity grade. The probability of occurrence of AEs and the respective 95% CIs were provided for each lot. Adverse events were analyzed separately after each. All vaccinated subjects are included in the analysis.

Immunogenicity

- Seroconversion after the second and third vaccination (as defined in protocol 213, refer to Section 6.1.9.)
- Geometric mean antibody response after the second and third vaccination as measured by ELISA and NT
- Geometric mean fold increase in antibody response after the second and third vaccination as compared to baseline measured by ELISA and NT
- Seroconversion by ELISA and NT, GMC and GMT, after the second and third vaccination are calculated separately for each lot for a subset of subjects

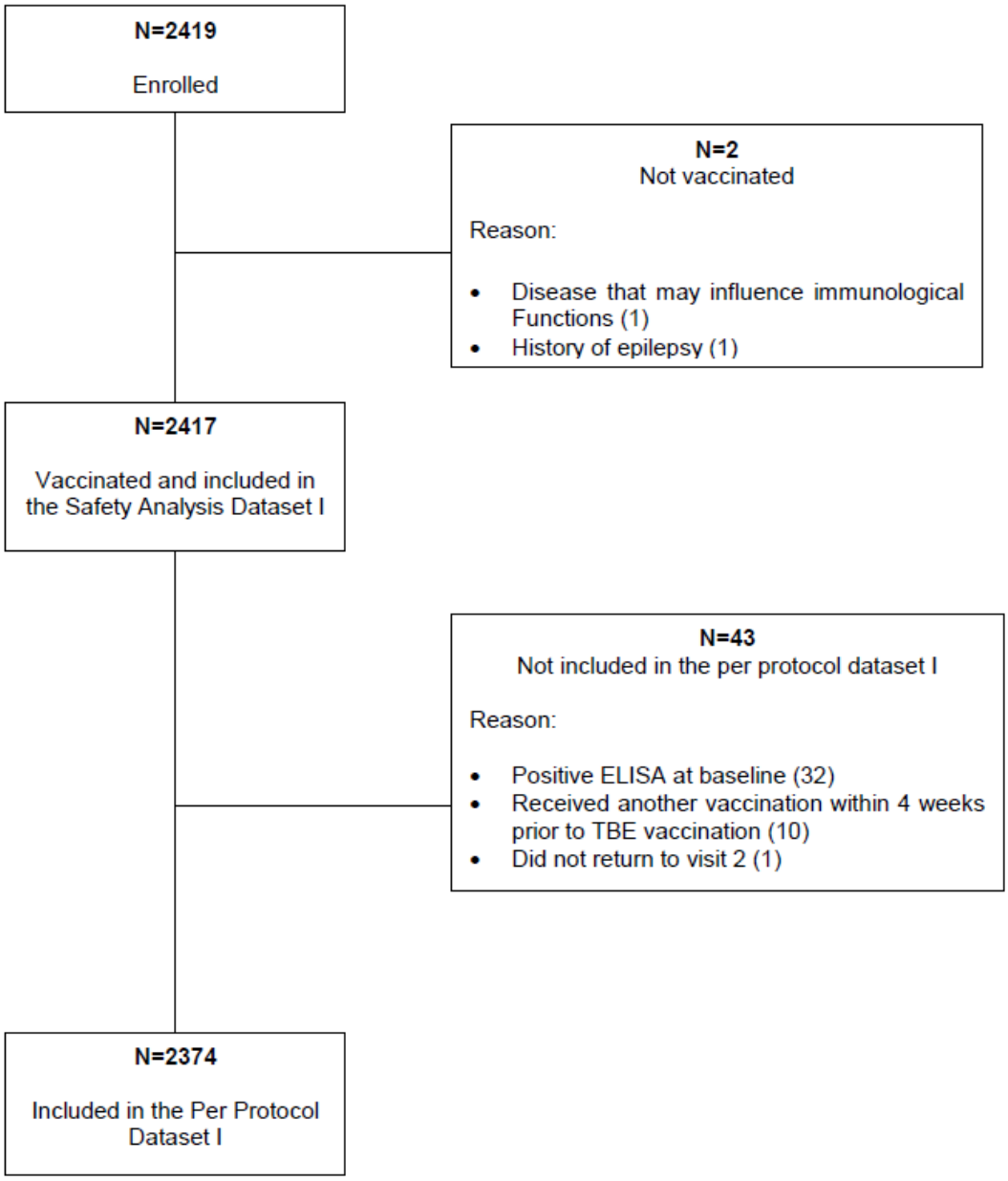
Reviewer's Comments: Study 209 was an uncontrolled clinical study. However, we considered it a pivotal study because it enrolled a substantial number of children from different age groups and provided substantial data regarding the safety and immunogenicity of FSME-IMMUN in different age strata from the pediatric population. This study included 2417 children of the total 3363 children who received FSME-IMMUN (0.25 ml) in the submitted clinical trials.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

A total of 2419 subjects were enrolled in Study 209, and 2417 subjects received the first dose. The diagram below summarizes the population included in the safety and per protocol dataset I population and the reasons for exclusion from analyses. Analysis of fever rate was performed on the per protocol dataset I, which comprised 2374 subjects.

Figure 4. Disposition of Subjects, Part A, Study 209

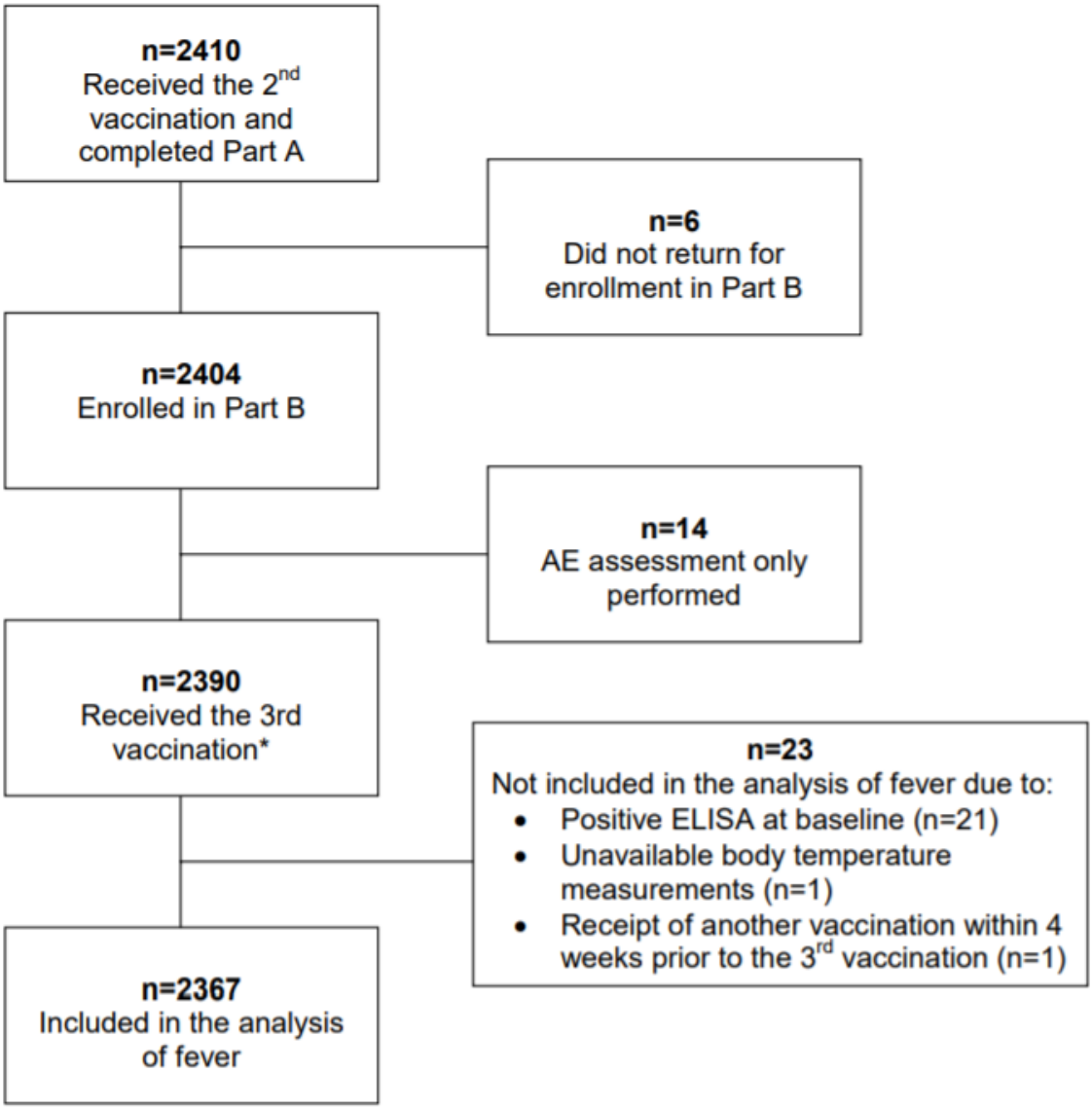


Source: Original BLA, CSR for Study 209 (Part A), page 49

2410 subjects were included in the safety dataset after the second immunization. Of the 2417 included after the first vaccination, one subject did not return for visit 2 and six did not receive the second vaccination. In addition, 33 subjects were not included in the body temperature analysis (32 because of positive ELISA and one because of the lack of body temperature measurement). The per protocol dataset II analysis of body temperature measured after the second vaccination comprised 2377 subjects. Thirty-three subjects were not included in the analysis because they had positive ELISA values at baseline (N=32) or had not taken body temperature measurements (N=1).

Of the 2410 subjects who received two doses and completed Part A of the study, 2404 subjects were enrolled in Part B. Of these, 2390 subjects received the third vaccination, and the remaining 14 subjects were monitored for safety post dose 2. All 2390 subjects who received the third vaccination were included in the analysis of local and systemic reactions after the third vaccination, and 2367 were also included in the analysis of fever. A total of 23 subjects were ineligible for the analysis of fever. The flow-chart below details the information above:

Figure 5. Disposition, Part B, Study 209



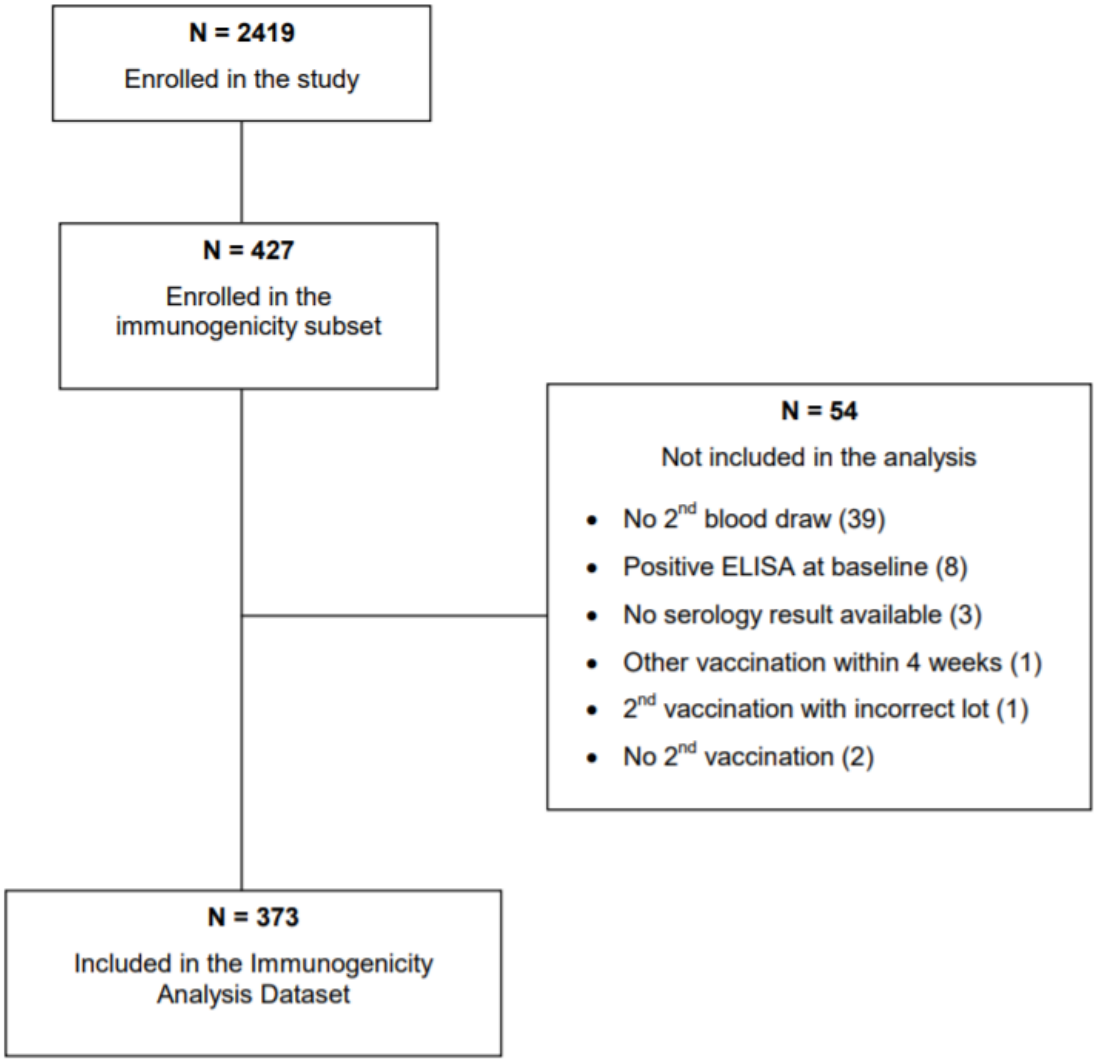
Source: Original BLA, page 52 of the CSR Part B
*For subjects who showed positive TBEV antibody (IgG) concentrations (ELISA) at baseline, sera were reassessed by neutralization test, and the Sponsor's medical director was to determine whether the administration of the third vaccination was appropriate.

A subset of subjects was invited to participate in the assessment of immunogenicity. A total of 427 subjects were enrolled in this subset. In Part A of the study, 386 subjects in the immunogenicity subset received the first two doses and had blood drawn at baseline

and after the second vaccination; of these subjects, 382 were enrolled in Part B of the study and 380 received the third vaccination. A total of 373 were included in the immunogenicity analysis dataset after the second vaccination and 362 were included in the immunogenicity analysis dataset after the third vaccination.

Figure 6 below shows serology analysis of the immunogenicity subset from study start until after the second dose of the vaccine.

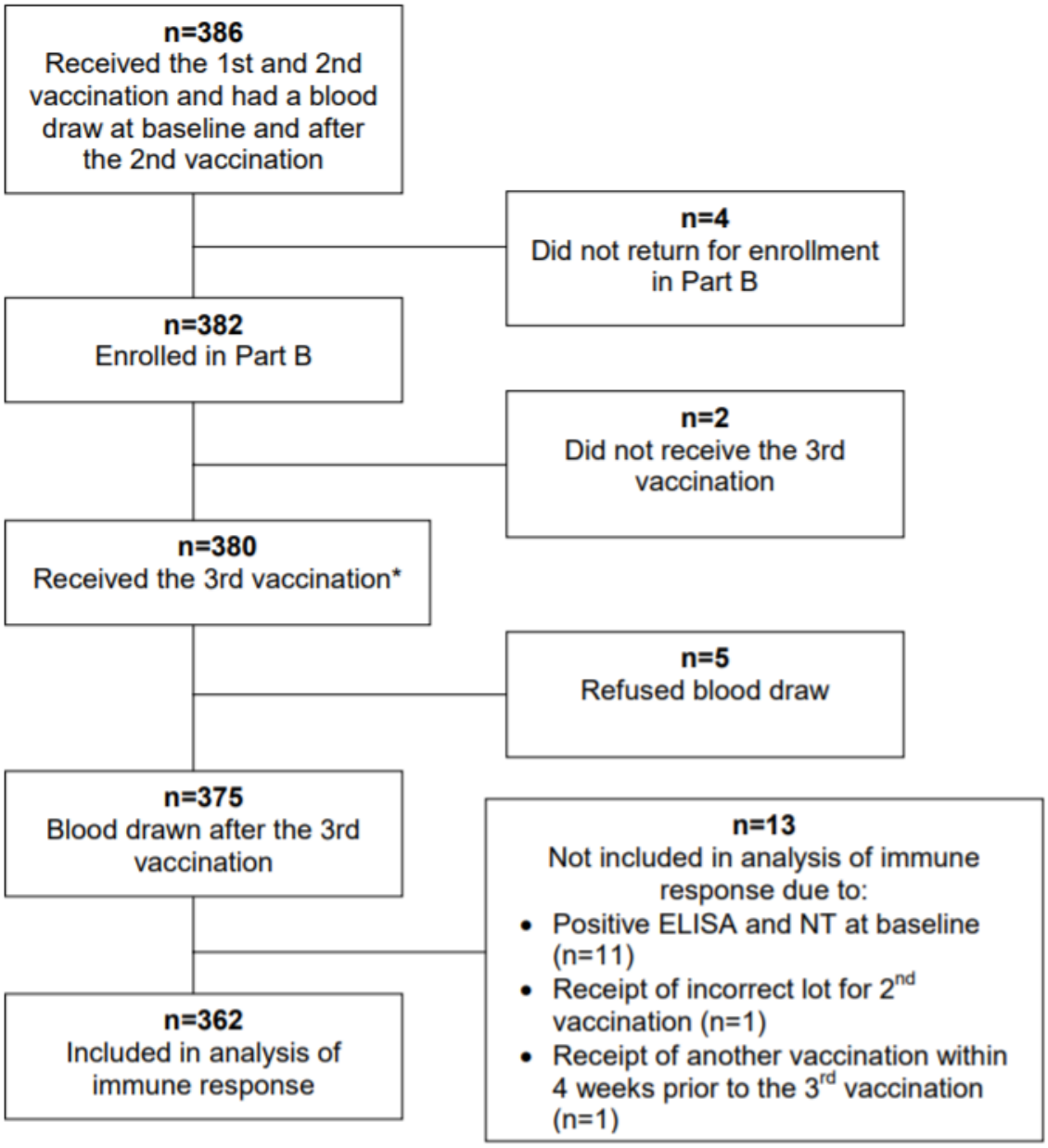
Figure 6. Serology Analysis, Part A, Study 209



Source: Original BLA, page 50 of the CSR for Study 209 (part A)

Figure 7 below shows serology analysis of the immunogenicity subset after the second dose of the vaccine until after third dose of the vaccine.

Figure 7. Serology Analysis, Part B, Study 209



Original BLA, CSR for Study 209, page 53.
*For subjects who showed positive TBEV antibody (IgG) concentrations (ELISA) at baseline, sera were reassessed by neutralization test, and the Sponsor's medical director was to determine whether the administration of the third vaccination was appropriate.

The analysis of the immune response after the third vaccination included a total of 362 subjects who:

- were eligible to participate in the study according to the inclusion/exclusion criteria, including informed consent for additional blood draws;
- had received all three doses;
- had available ELISA and NT results at baseline and after the third vaccination;
- had seronegative levels of TBEV antibodies at baseline as determined by ELISA and NT.

6.2.10.1.1 Demographics

Table 27. Demographic Information, Safety and Immunogenicity Datasets, Post Third Vaccination, Study 209

Characteristic	Safety Dataset	Immunogenicity Dataset
Gender: Male n (%)	1225 (51.3%)	181 (50%)
Gender: Female n (%)	1165 (48.7%)	181 (50%)
Age: 1-2 yrs n (%)	184 (7.7%)	75 (20.7%)
Age: 3-4 yrs n (%)	248 (10.4%)	27 (7.5%)
Age: 5-6 yrs n (%)	309 (12.9%)	49 (13.5%)
Age: 7-8 yrs n (%)	333 (13.9%)	51 (14.1%)
Age: 9-10 yrs n (%)	352 (14.7%)	51 (14.1%)
Age: 11-12 yrs n (%)	368 (15.4%)	60 (16.6%)
Age: 13-15 yrs n (%)	596 (24.9%)	49 (13.5%)
Total	**2390 (100%)**	**362 (100%)**

Source:

Reviewer's Comments: The safety population was balanced by gender. There were fewer children 1-2 years of age (7.7%) compared to all other pediatric age strata (ranging 10.4%-24.9%). The study was designed this way because the primary objective of the study was to assess fever rate in the age groups of 1-2, 3-6 and 7-15 years of age. Fever was anticipated at a higher rate in younger subjects than in older subjects. Consequently, a greater number of older children needed to be enrolled compared to younger children to assess fever rates among the older children. The subjects in the immunogenicity subgroup were evenly distributed by gender and included subjects in each age group.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The analysis of adherence to the visit schedule showed a high level of compliance among subjects included in the immunogenicity dataset. More than 98% of subjects received the third vaccination within the predefined time frame, and 87.8% of subjects had the blood draw within the predefined time frame.

6.2.10.1.3 Subject Disposition

Subject disposition including protocol deviations are reported above in Figure 4 and Figure 5 (Section 6.2.10.1).

6.2.11 Efficacy Analyses

There were no clinical disease endpoint efficacy analyses for Study 209. Immunogenicity was assessed by anti-TBEV antibody concentrations as determined by ELISA and NT titers measured at baseline, 21 to 35 days after the second and 35 to 42 days after the third immunization.

6.2.11.1 Analyses of Primary Endpoint(s)

Vaccine immunogenicity was not a primary endpoint in this study.

6.2.11.2 Analyses of Secondary Endpoints

Although a high seroconversion rate (96%) was observed 21 to 35 days after the second vaccination as determined by ELISA and NT, GMTs after the third immunization were at

least twice the value observed after the second dose. Please refer to Table 28 below that summarizes the immunogenicity data:

Table 28. Immunogenicity Data, Study 209

	Baseline	After Second Dose	After Third Dose
N Seroconverted by ELISA (%, 95%CI)	N/A	358/373 (96%, CI: 93.5, 97.7)	361/362 (99.7%, CI: 98.5, 100)
N Seroconverted by NT (%, 95% CI)	N/A	352/368 (95.7%, CI: 93, 97.5)	358/360 (99.4%, CI: 98, 99.9)
GMC ELISA VIEU/mL (95% CI)	22.4 (21.0; 23.9)	1473 (1304, 1663.5)	5720.8 (5216.7, 6273.6)
GMT NT (95% CI)*	5.2 (5; 5.4)	160.5 (142.6, 180.8)	381.5 (350.8, 414.9)

Source: Page 60 CSR part A, Page 6 CSR addendum A
GMT measured by Adner method.

All subjects in the immunogenicity dataset were shown to have seroconverted after the third vaccination compared to baseline as determined by ELISA and/or NT. One subject (b) (6) seroconverted by NT (titer of 40) but not by ELISA (120 VIEU/mL) after the third vaccination. Two subjects (b) (6) seroconverted as determined by ELISA (336 and 259 VIEU/mL, respectively) but not by NT (titers <5).

Reviewer's Comments: NT detects functionally active neutralizing antibodies which would be expected to be a subset of the antibodies induced by the vaccine; thus, it is not unexpected that there were two subjects who seroconverted as measured by ELISA but not by NT.

The highest GMT was observed in the 1-2 years age group, although immune response was shown in all three age categories. Please refer to Table 29 below:

Table 29. Antibody Concentration Measured by NT, by Age Group*

	Baseline			After 3rd Vaccination		
Age	**N**	**GMT**	**95% CI of GMT**	**N**	**GMT**	**95% CI of GMT**
1-2 years	75	5.0	5.0, 5.1	75	567.6	526.6, 611.8
3-6 years	76	5.0	5.0, 5.0	76	469.3	399.2, 551.8
7-15 years	209	5.0	5.0, 5.0	211	307.4	272.3, 347.0
Total	**360**	**5.0**	**5.0, 5.0**	**362**	**381.5**	**350.8, 414.9**

Source: Original BLA, CSR for Study 209, part B, page 86; * Age at first dose

More than 98% of the subjects had a greater than four-fold increase in neutralizing antibody titer after the third vaccination.

Table 30. Neutralizing Antibody Titers Post Second and Third Vaccination, Study 209

Timing	Geometric Mean by NT n (95% CI)	Geometric Mean Fold Increase by NT <2-fold n (%)	Geometric Mean Fold Increase by NT 2 to 4-fold n (%)	Geometric Mean Fold Increase by NT >4-fold n (%)
After the second vaccination (N=366)	30.9 (27.3, 35)	20 (5.5%)	9 (2.5%)	337 (92%)
After the third vaccination (N=360)	76.7 (70.5, 83.4)	2 (0.55%)	2 (0.55%)	356 (98.9%)

Source: Original BLA, SCR for Study 209, part B, page 86

Reviewer's Comments: All children, regardless of age, demonstrated immune response after completion of the primary series.

6.2.11.3 Subpopulation Analyses

N/A

6.2.11.4 Dropouts and/or Discontinuations

The dropouts and/or discontinuations were discussed in Section 6.2.10 of this clinical review memo (Study Population and Disposition).

6.2.11.5 Exploratory and Post Hoc Analyses

N/A

6.2.12 Safety Analyses

6.2.12.1 Methods

Safety data collection included monitoring for fever, local and systemic AEs (other than fever), and SAEs. Body temperature was to be measured in the evening after each vaccination, the next morning and in the evening for 3 days following each vaccination (4 days total). Temperature was to be measured rectally in children aged <3 years, and orally in children and adolescents aged >3 years. If fever was observed, body temperature was to be measured at least once a day in the evening until the temperature returned to normal. The highest temperature level was used for the evaluation of the fever rate. In accordance with the protocol, body temperature measurements were analyzed in three different age categories: subjects aged 1-2 years, 3-6 years and 7-15 years.

Fever was categorized by severity grade, according to the CTC guidelines (National Cancer Institute 1999), as follows:

- Mild: 38.0°C-39.0°C
- Moderate 39.1°C -40.0°C
- Severe >40.0°C

In addition, the proportion of subjects with fever greater than 39.5° C were also reported.

*Reviewer's Comments: Fever severity was determined using the same scale used in Studies 208/213, and as previously noted, the grading criteria in the CTC grading scale is liberal when compared with recommendations in the FDA Guidance: "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials." We have asked the Applicant for an analysis of fever rates categorized by the highest temperature reported. The data is presented in the next section of this review (*6.2.12.2).

The data documented in the subject diary were assessed for severity and relatedness by the investigator. The AEs were reported on the case report form using standard medical terminology according to MedDRA.

Although the protocols did not pre-specify local or systemic reactions other than fever, the CSR specified that subjects received diaries for recording reactions, and investigators queried subjects regarding adverse events in the following visit and recorded them in the eCRFs. The eCRFs for this study were not available for our review, but for other eCRFs provided (e.g., Study 202 and 213) the queried symptoms described in the protocol are listed in the eCRFs.

Queried symptoms of local and systemic reactions: local pain, tenderness, swelling, induration, erythema, ecchymosis, hematoma, itching, headache, nausea, vomiting, muscle pain, joint pain, swelling of the axillary/inguinal lymph nodes, loss of appetite, changes in sleeping behavior. The following systemic symptoms were queried using different terms in younger and older children, to be age-appropriate:

- Restlessness (children 1-5 years of age)
- Fatigue and Malaise (children 6-15 years of age)

Diary cards were collected 7 to 10 days after dose 1, 21 to 25 days after dose 2 and 35 to 42 days after dose 3. The number of subjects who completed the information in the diary is unknown.

6.2.12.2 Overview of Adverse Events

Fever Rates

Fever occurred more frequently in younger than in older children (please refer to Table 31 below). Fever occurred with higher frequency among younger children (1-2 years of age), the age group most at risk of febrile seizures. In all three age groups, fever rates were higher after dose 1 than subsequent doses.

Table 31. Fever Rates by Severity* Following Doses 1, 2 and 3 of FSME-IMMUN, Study 209

Dose and Age Group	Any Fever n/N(%)	95% CI	No Fever n/N (%)	Mild n/N (%)	Moderate n/N (%)	Severe n/N (%)
Dose 1[a]	66/183		117	57	9	0
1-2 YOA (N=183)	(36.1%)	29.1, 43.5	(63.9%)	(31.1%)	(4.9%)	(0%)
Dose 1	72/559		487	59	13	0
3-6 YOA (N=558)	(12.9%)	10.2, 15.9	(87.1%)	(10.6%)	(2.3%)	(0%)
Dose 1	92/1632		1540	90	2	0
7-15 YOA (N=1632)	(5.6%)	4.6, 6.9	(94.4%)	(5.5%)	(0.1%)	(0%)
Dose 1	230/2374		2144	206	24	0
Total (N=2374)	(9.7%)	8.5, 11	(90.3%)	(8.7%)	(1%)	(0%)

Dose and Age Group	Any Fever n/N(%)	95% CI	No Fever n/N (%)	Mild n/N (%)	Moderate n/N (%)	Severe n/N (%)
Dose 2[a] 1-2 YOA (N=183)	23/183 (12.6%)	8.1, 18.3	160 (87.4%)	22 (12%)	0 (0%)	1 (0.5%)
Dose 2 3-6 YOA (N=558)	13/558 (2.3%)	1.2, 4	545 (97.7%)	11 (2%)	2 (0.4%)	0 (0%)
Dose 2 7-15 YOA (N=1636)	19/1636 (1.2%)	0.7, 1.8	1617 (98.8%)	18 (1.1%)	1 (0.1%)	0 (0%)
Dose 2 Total (N=2377)	55/2377 (2.3%)	1.7, 3	2322 (97.7%	51 (2.1%)	3 (0.1%)	1 (0%)
Dose 3[a] 1-2 YOA (N=183)	23/181 (12.7%)	8.2, 18.5	158 (87.3%)	21 (11.6%)	2 (1.1%)	0 (0%)
Dose 3 3-6 YOA (N=559)	15/554 (2.7%)	1.5, 4.4	539 (97.3%)	11 (2%)	3 (0.5%)	1 (0.2%)
Dose 3 7-15 YOA (N=1632)	19/1632 (1.2%)	0.7, 1.8	1613 (98.8%)	14 (0.9%)	5 (0.3%)	0 (0%)
Dose 3 Total (N=2367)	57/2367 (2.4%)	1.8, 3.1	2310 (97.6)	46 (1.9%)	10 (0.4%)	1 (0%)

[a] Dose 1, 2 and 3 of FSME-IMMUN
Source: Original BLA, page 72, 86, 91,92 of CSR for Study 209 part A (tables 28, 29, 46, 51,53) and pages 90, 93 of CSR for Study 209 part B (tables 14.3.2.1 and 14.3.2.7)
*Severity grade according to CTC guidelines (Common Toxicity Criteria, Version 2, April 1999 (mild: 38.0°C-39.0°C, moderate: 39.1°C-40.0°C, severe: >40 0°C))
YOA = years of age

The majority of fever associated with the first dose was between 38.0°C and 38.5°C. No fever over 40.0°C was observed. More than 75% of all fever subsided within 24 hours. There were no differences related to age in the rate of fever lasting one day or more.

The overall fever rate after the second vaccination was 2.3%. There were three cases of moderate and one case of severe fever after the second vaccination as shown in Table 31 above.

Fever occurred less frequently after the third vaccination with an overall rate of occurrence of 2.4%. The rate of occurrence was higher among subjects aged 1-2 years at study entry (12.7%) than in older subjects (2.7% and 1.2% in subjects aged 3-6 and 7-15, respectively). The majority of fever cases were classified as mild. There were ten cases of moderate fever and one of severe fever after the third dose. Fever cases >39.5°C were reported after the third immunization in approximately 0.3% of the subjects. In most cases fever abated within two days.

The information for the two cases of severe fever in this study is shown below:

- Subject (b) (6) had fever on the second day after the second vaccination with the maximum body temperature (40.1°C) being recorded on Day 5 after vaccination. This fever case was deemed by the investigator as being unrelated to vaccination, it was attributed to concurrent otitis media.
- Subject (b) (6) had a severe fever which began one day after the third vaccination and lasted 3 days, with a maximum body temperature of 40.1°C. The subject also reported acute tonsillitis beginning 1 day after vaccination. The fever and concomitant tonsillitis were judged by the investigator as being unrelated to vaccination.

Reviewer's Comments: Per our request, the Applicant performed a post hoc analysis of fever rates within 4 days after each dose using the severity grading scale recommended

in the FDA Guidance: "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials": The data is as follows:

Table 32. Fever Rates Within 4 Days After Each Dose of TICOVAC by Age Group

Dose	Percentage (%) of Subjects			
Age Group	38.0-38.4°C	38.5-38.9°C	39.0-40.0°C	>40°C
Dose 1				
1-2 Years of Age (N=186)	23.7	5.9	5.9	0
3-6 Years of Age (N=563)	4.6	5.0	3.0	0
7-15 Years of Age (N=1668)	3.4	2.0	0.3	0
Total (N=2417)	5.2	3.0	1.4	0
Dose 2				
1-2 Years of Age (N=185)	9.2	2.2	0.5	0.5
3-4 Years of Age (N=561)	1.2	0.4	0.5	0
7-15 Years of Age (N=1664)	0.8	0.4	<0.1	0
Total (N=2410)	1.6	0.5	0.2	<0.1
Dose 3				
1-2 Years of Age (N=184)	7.1	3.8	1.6	0
3-4 Years of Age (N=557)	1.4	0.4	0.7	0.2
7-15 Years of Age (N=1649)	0.6	0.3	0.2	0
Total (N=2390)	1.3	0.6	0.5	<0.1

Local Reactions

Local reaction rates after the first, second and third doses were 24.6% (22.9%-26.4%), 17.1% (15.6%-18.6%) and 18.5% (17%-20.2%), respectively. Systemic reaction rates after the first, second and third vaccination were 20.3% (18.7%-22%), 8.3% (7.2%-9.5%) and 7.7% (6.7%-8.9%), respectively. The most common related AEs (excluding fever) any dose were local pain and tenderness, restlessness (in children 1-5 years) and headache.

After the first vaccination, reporting rates for any local reaction were lower among subjects 1-2 years of age (13.4%) than among those 3-6 years (22.9%) or 7-15 years of age (26.4%). This same pattern of response by age group was observed after dose 2 (8.1%, 15.5%, and 18.6%, respectively) and after dose 3 (7.6%, 16.2%, 20.6%). The most local reactions were reported to be mild; <4% of subjects in any age group reported a local reaction of moderate severity. Severe local reactions were reported for 5 subjects (7-15 years of age) after dose 1, 1 subject (3-6 years of age) after dose 2, and 2 subjects (7-15 years of age) after dose 3. Among all subjects, after any dose the most frequent adverse reactions were injection site pain (reported for 7.9% to 11.3% of subjects across doses) and tenderness (reported for 12.9% to 18.1% of subjects); other types of local reactions were reported for <2.1% of subjects after any dose.

Systemic Reactions

After the first vaccination, 18.8% to 28.0% of subjects in the 3 age groups reported one or more systemic reactions; most reports of systemic reactions were mild, with moderate reactions reported for ≤3.4% of subjects in any age group, and severe systemic reactions reported for a total of 3 subjects.

For the three cases of severe systemic reactions related to vaccination: there was one individual with generalized urticaria that lasted 3 days, one case of headache and one case of arthralgia, both of which abated within 1 day. The subject with arthralgia was

subsequently hospitalized for diagnostic evaluation, and Lyme disease was diagnosed. Therefore, while the case of severe arthritis was considered related to the vaccination, the SAE/hospitalization was classified as not related.

Reviewer's Comments: Pfizer was queried, and no additional information exists for the three cases of severe systemic reactions.

The frequencies of any systemic reaction were somewhat lower after dose 2 and dose 3, ranging from 5.9% to 11.4% across age groups, with moderate systemic reactions reported for ≤2.2% of subjects in any age group after either dose. No subjects reported a severe systemic reaction after dose 2, one subject reported a severe systemic reaction after dose 3 (7-15 years age group). As with local reactions, the frequency and intensity of systemic reactions were similar across the 5 production lots. The most frequently reported types of systemic reactions after the first vaccination were headache (10.8% among all subjects) and restlessness (9.1%; in subjects 1-5 years of age), also queried to subjects ≥6 years of age as "fatigue, malaise" (5.6% and 4.2%, respectively). Reporting rates for systemic reactions were lower after dose 2 and dose 3 than after dose 1; headache and restlessness were each reported in 3.6% of subjects queried for these events, and all other types of systemic reactions were reported for ≤2.1% of subjects after either dose 2 or dose 3. Please refer to Table 33 and Table 34 below that summarize all adverse events experienced by subjects after the first, second and third dose.

Table 33. Queried Signs and Symptoms Within Four Days After Each Vaccination, Study 209

Symptom	Preferred Term	Dose 1 n (%) N=2417	Dose 1 95% CI	Dose 2 n (%) N=2410	Dose 2 95% CI	Dose 3 n (%) N=2390	Dose 3 95% CI
Local Pain	Injection site pain	272 (11.3)	(10.0, 12.6)	190 (7.9)	(6.8, 9.0)	231 (9.7)	(8.5, 10.9)
Tenderness	Injection site pain	438 (18.1)	(16.6, 19.7)	310 (12.9)	(11.6, 14.3)	319 (13.3)	(12.0, 14.8)
Swelling	Injection site swelling	34 (1.4)	(1.0, 2.0)	23 (1.0)	(0.6, 1.4)	48 (2.0)	(1.5, 2.7)
Induration	Injection site induration	38 (1.6)	(1.1, 2.2)	23 (1.0)	(0.6, 1.4)	35 (1.5)	(1.0, 2.0)
Erythema	Injection site erythema	51 (2.1)	(1.6, 2.8)	32 (1.3)	(0.9, 1.9)	47 (2.0)	(1.4, 2.6)
Ecchymosis	Injection site bruising	0 (0.0)	(0.0, 0.2)	0 (0.0)	(0.0, 0.2)	1 (0.0)	(0.0, 0.2)
Haematoma	Injection site haemorrhage	1 (0.0)	(0.0, 0.2)	0 (0.0)	(0.0, 0.2)	0 (0.0)	(0.0, 0.2)
Itching	Injection site pruritis	1 (0.0)	(0.0, 0.2)	1 (0.0)	(0.0, 0.2)	0 (0.0)	(0.0, 0.2)
Headache	Headache NOS	261 (10.8)	(9.6, 12.1)	87 (3.6)	(2.9, 4.4)	79 (3.3)	(2.6, 4.1)
Nausea	Nausea	76 (3.1)	(2.5, 4.3)	23 (1.0)	(0.6, 1.4)	17 (0.7)	(0.4, 1.2)
Vomiting	Vomiting NOS	33 (1.4)	(0.9, 1.9)	15 (0.6)	(0.3, 1.0)	4 (0.2)	(0.0, 0.4)
Muscle Pain	Myalgia	85 (3.5)	(2.8, 4.3)	46 (1.9)	(1.4, 2.5)	41 (1.7)	(1.2, 2.3)
Joint Pain	Arthralgia	29 (1.2)	(0.8, 1.7)	11 (0.5)	(0.2, 0.8)	11 (0.5)	(0.2, 0.8)
Swelling of the axillary/inguinal lymph nodes	Lymphadenopathy	11 (0.5)	(0.2, 0.8)	10 (0.4)	(0.2, 0.8)	4 (0.2)	(0.0, 0.4)
Loss of appetite	Anorexia	71 (2.9)	(2.3, 3.7)	31 (1.3)	(0.9, 1.8)	23 (1.0)	(0.6, 1.4)
Changes in sleeping behaviour	Circadian rhythm sleep disorder	66 (2.7)	(2.1, 3.5)	24 (1.0)	(0.6, 1.5)	18 (0.8)	(0.4, 1.2)

Source Original BLA, page 84 of CSR for Study 209 part A, Original BLA, Part A of CSR for Study 209, page 99 and Original BLA, CSR for Study 209, part B page 103

Reviewer's Comments: Some of the incidence rates reported in Table 33 are slightly different from what is reported in Section 6 of the PI. While the source of the data for this table is the CSR for Study 209, the analyses reported in the PI were based on new data analysis performed by Pfizer using the Baxter Core Safety Information that Pfizer received from Baxter during the transfer of the product. Although not identical, the rates are quite similar.

Table 34. Queried Local and Systemic Reactions Related to Vaccination, Study 209

Symptom	Preferred Term	Dose 1 n (%) N	Dose 1 95% CI	Dose 2 n (%) N	Dose 2 95% CI	Dose 3 n (%) N	Dose 3 95% CI
Restlessness[a]	Restlessness	53 (9.1%) 584	(6.9, 11.7)	21 (3.6%) 581	(2.3, 5.5)	17 (3.0%) 576	(1.7, 4.7)
Fatigue[a]	Fatigue	102 (5.6%) 1833	(4.6, 6.7)	39 (2.1%) 1829	(1.5, 2.9)	39 (2.1%) 1814	(1.5, 2.9)
Malaise[a]	Malaise	76 (4.2%) 1833	(3.3, 5.2)	25 (1.4%) 1829	(0.9, 2.0)	32 (1.8%) 1814	(1.2, 2.5)

Source Original BLA, CSR Study 209, Part B, Page 103, Part A of CSR, Study 209, Pages 85, 99 and 104
[a]Specific Age groups: Restlessness, only children aged 1-5 years, Fatigue and Malaise, only children aged 6-15 years
Vaccination 1: Ages 1-5, N=584, Ages 6-15 N=1833
Vaccination 2: Ages 1-5, N=581, Ages 6-15 N=1829
Vaccination 3: Ages 1-5, N=576, Ages 6-15 N=1814

6.2.12.3 Deaths

No deaths occurred in subjects of Study 209.

6.2.12.4 Nonfatal Serious Adverse Events

A total of 42 SAEs were experienced by 37 subjects. Five SAEs were reported after dose 1, 33 SAEs after dose 2 and 4 SAEs after dose 3. No SAE was considered related to the investigational product by the Principal Investigator, and SAE listings were provided for our review.

Table 35. Nonfatal Serious Adverse Event Timing, Study 209

Subject ID	Age	Sex	MedDRA Preferred Term	Onset[a]	Duration
(b) (6)	11	F	Removal of internal fixation	65 days after dose 2	5 days
	4	M	Gastroenteritis	62 days after dose 2	4 days
	10	M	Gastroenteritis	73 days after dose 2	4 days
	8	M	Otitis Media	86 days after dose 2	17 days
	6	M	Talipes	112 days after dose 2	5 days
	14	M	Torsion of the appendix of the left testis. Varices of the left spermatic cord.	158 days after dose 2	8 days
	13	M	Hydronephrosis; nephrolithiasis; kidney duplex	53 days after dose 2	91 days
	13	M	Renal Colic. Surgery of hydronephrosis and nephrolithiasis	5 days after dose 3	2 days
	15	M	Testicular torsion	139 days after dose 2	8 days
	9	M	Monoarthritis	59 days after dose 2	14 days
	5	M	Laryngitis	150 days after dose 2	4 days
	9	M	Acute sinusitis; asthma	63 days after dose 2	17 days
	3	M	Coxitis dextra	90 days after dose 2	9 days
	8	M	Concussion	27 days after dose 2	369 days
	11	M	Lyme Disease	14 days after dose 2	12 days
	8	F	Diarrhoea	97 days after dose 2	5 days
	10	M	Infectious mononucleosis	14 days after dose 1	12 days
	5	F	Carbon monoxide poisoning; Convulsion	52 days after dose 2	12 days
	14	F	Central nervous system neoplasm	110 days after dose 2	17 days
	7	M	Head injury; syncope; urticaria	90 days after dose 2	5 days
	6	M	Gastroenteritis	66 days after dose 2	5 days
	11	M	Testicular torsion	21 days after dose 1	2 days
	4	M	Cryptorchism	71 days after dose 1	2 days
	1	M	Laryngitis; Rhinitis	45 days after dose 2	5 days
	1	M	Dermatitis; Gastroenteritis; Hypospadias	93 days after dose 2	9 days
	1	M	Dermatitis diaper; gastroenteritis; upper respiratory infection	117 days after dose 2	10 days
	5	M	Abdominal pain; Enuresis; hypospadias; weight below normal	29 days after dose 3	9 days
	5	M	Abdominal pain; Enuresis; hypospadias; weight below normal	87 days after dose 2	6 days
	1	M	Pharyngitis; rhinitis	78 days after dose 2	8 days
	2	M	Mastoiditis NOS; Bronchitis NOS; Otitis media NOS	5 days after dose 2	13 days

Subject ID	Age	Sex	MedDRA Preferred Term	Onset[a]	Duration
(b) (6)	1	M	Otitis media NOS; gastroenteritis NOS	10 days after dose 1	3 days
	2	M	Congenital atrial septal defect	35 days after dose 2	3 days
	2	M	Correction operation with patch sinus-venosus defect	151 days after dose 2	16 days
	5	M	Pneumonia; pyrexia	27 days after dose 2	11 days
	5	M	Gas poisoning	30 days after dose 2	2 days
	2	M	Febrile convulsion	30 days after dose 2	2 days
	15	M	Abdominal pain NOS; vomiting NOS	14 days after dose 2	4 days
	11	M	Wrist fracture	142 days after dose 2	30 days
	3	M	Tonsilitis	10 days after dose 3	13 days
	2	M	Febrile convulsion (third)	28 days after dose 1	1 day
	14	M	Scrotal varicose veins; testicular torsion	158 days after dose 2	8 days

[a] Days after last dose
Original BLA, Table 5, page 35, Additional Responses to FDA Information Request, received on May 12, 2021

Reviewer's Comments: SAEs reported were consistent with diseases expected to occur in the respective pediatric age group. Therefore, we agree with the Applicant's assessment that the events were unrelated.

Due to its relevance for the safety characterization of FSME-IMMUN for the pediatric population, the details of the two SAEs of febrile convulsion are discussed below:

- Subject (b) (6), a 2-year-old male, had one febrile virus infection with convulsion with duration of 5 minutes at a temperature of 38.3ºC, 28 days after the first dose. The child was reported to have had two previous episodes of convulsions, both in association with viral infection. The subject was reported as having recovered fully, but there is a report of an abnormal electroencephalogram after the third convulsion. He continued study participation and received the two other doses of FSME.
- Subject (b) (6), a 2-year-old male, had a febrile convulsion 66 days after the second vaccination in association with viral infection and exanthema. He recovered fully and received the third dose per protocol.

Reviewer's Comments: Both cases of febrile seizures occurred more than 25 days after vaccination and had other associated infectious disease. From the information provided to us regarding these SAEs, the Principal Investigator's assessment of the causality of these SAEs as not related seems reasonable.

6.2.12.5 Adverse Events of Special Interest (AESI)

N/A

6.2.12.6 Clinical Test Results

N/A

6.2.12.7 Dropouts and/or Discontinuations

N/A

6.2.13 Study Summary and Conclusions

In Study 209 the most frequently reported AEs were fever, headache, restlessness (in children aged 1-5 years only), local pain and tenderness. Following three doses of FSME-IMMUN, 99.4% of children 1 to <16 years of age seroconverted (based on neutralization data).

Approximately 9.7% of the children 1 to <16 years of age experienced fever after the first vaccination. The majority of fever cases reported after the first vaccination (68.3%) had temperatures between 38.0°C and 38.5°C, and 10% of the subjects had fevers above 39°C. However, no fever over 40.0°C was observed after the first vaccination. More than 75% of all fever post dose 1 subsided within 24 hours. In all age groups the highest rates of fever were observed after the first dose of FSME-IMMUN and were highest among children 1-2 years (36%). Among children 3-6 and 7-15 years, fever after the first dose was reported by 13.1% and 5.6%, respectively. Within each age group the rates of fever following the second and third dose were similar: among children 1-2 years (12.6% post dose 2 and 12.7% post dose 3); among children 3-6 years (2.3% reported fever post dose 2 and 2.7% post dose 3); among children 7-15 years (1.2% reported fever post dose 2 and post dose 3). Across all doses and age groups most cases of fever met the protocol definition of mild (38°C-39°C). Across all age groups and doses two subjects reported fever >40°C (protocol definition of severe): One case was reported post dose 2 in a subject 1 year old who also had otitis media and the other post dose 3 in a subject 5 years of age who also had tonsilitis. There were two febrile seizures reported as SAEs in this study. However, none of these events was considered related to the vaccination by this reviewer.

The most commonly reported local reactions after any vaccination were local pain and tenderness. The lowest frequency of local reactions was reported in children aged 1-2 years. The frequency of occurrence of any local reaction was comparable between children aged 3-6 years and those aged 7-15 years. The most frequently reported systemic reactions (excluding fever) related to any vaccination were headache among all age groups and restlessness among children aged 1-5 years. The majority of systemic reactions were reported to be mild.

The seroconversion rates after the third vaccination as determined by ELISA and NT separately were 99.7% and 99.4%, respectively. The assessment of ELISA GMCs and NT GMTs after the third vaccination by age group showed a clear age dependence, although a strong immune response was demonstrated in all age groups. The GMCs and GMTs were 9281.4 VIEU/mL (95% CI: 8109.6 VIEU/mL, 10622.5 VIEU/mL) and 567.6 (95% CI: 526.6, 611.8) in the 1-2 years age group, 7991.5 VIEU/mL (95%CI: 6700.8 VIEU/mL, 9530.8 VIEU/mL) and 469.3 (95% CI: 399.2, 551.8) in the 3-6 years age group and 4270.4 VIEU/mL (95% CI: 3774.9 VIEU/mL, 4830.8 VIEU/mL) and 307.4 (95% CI: 272.3, 347.0) in the 7-15 years age group.

These results provide safety and immunogenicity to support use of FSME-IMMUN (1.2 µg, 0.25 mL) in children and adolescents aged 1 to <16 years.

7. Integrated Overview of Efficacy

The studies supporting the proposed indication used different dose schedules and assay methods for the quantification of the immune response, and collection of blood for immunogenicity assessments occurred at different intervals. Therefore, the integration of

immunogenicity data was not presented in this review. The immunogenicity data for the studies not discussed in Section 6 are reviewed separately in Section 9 of this review.

8. Integrated Overview of Safety

The clinical studies submitted in this BLA had various methods of safety data collection and definitions of adverse events. Therefore, we determined that the safety data should not be integrated. The safety data are reviewed separately for each study in Sections 6 and 9 of this review.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

As pregnant women were excluded from clinical trials, human data on use of FSME-IMMUN during pregnancy are limited. There were five cases of pregnancy reported during clinical trials (four pregnancies in Study 208/213 and one pregnancy in Study 690601); the outcomes of these pregnancies are unknown. The Applicant provided in the BLA a cumulative review and summary of relevant cases reported in Pfizer's pharmacovigilance (Safety) database from the time of drug product development through August 31, 2020.

Reviewer's Comments: Available data are not sufficient to assess the presence or absence of vaccine-associated risk during pregnancy. Please refer to the Pharmacovigilance Original BLA Memorandum for details of the postmarketing experience on the cases of vaccine exposure during pregnancy.

9.1.2 Use During Lactation

Reviewer's Comments: Available data are not sufficient to assess the effects of the vaccine during breastfeeding. Please refer to the Pharmacovigilance Original BLA Memorandum for details of the postmarketing experience on the cases of vaccine exposure through breastfeeding.

9.1.3 Pediatric Use and PREA Considerations

Under the Pediatric Research Equity Act of 2007 (21 U.S.C. 355c), all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived, deferred, or inapplicable. The Applicant requested a partial waiver for children <1 year of age. The reason for waiving pediatric assessment requirements for this age group was that studies are impossible or highly impractical (section 505B(a)(5)(B)(i)) because (1) in TBEV-endemic regions neonates and infants are expected to have maternal antibodies and early immunization may result in reduced immune responses due to antibody interference and (2) neonates and infants in non-endemic regions could not be ethically enrolled in a study from which they could not expect any potential benefit. The Division and PeRC agreed with the Applicant's request for the waiver.

9.1.4 Immunocompromised Patients

Immunocompromised individuals were excluded from clinical trial participation. There are no specific clinical data regarding the use of the vaccine in immunocompromised patients reported in the clinical trials submitted in this BLA.

Reviewer's Comment's: Immunocompromised subjects were excluded from trial participation in the studies supporting this BLA. Please refer to the Pharmacovigilance Original BLA Memorandum for a discussion on the cumulative analysis of the risk of using FSME-IMMUN in patients with impaired immune system. The analysis is based on postmarketing safety reports submitted in the BLA. There are also some published papers reporting the use of FSME-IMMUN in this population (Zielinski et al. 1986; Wolf et al. 1992; Panasiuk et al. 2003; Prelog et al. 2008).

9.1.5 Geriatric Use

Clinical Studies of FSME-IMMUN did not include sufficient numbers of subjects age 65 and over to determine whether FSME-IMMUN has a different safety or immunogenicity profile in the elderly. Study 690601 was an open-label safety and immunogenicity study in adults without an upper age limit, designed to investigate the use of the vaccine with the second dose given 14 days after the first dose. This study enrolled 73 subjects 60 years of age and older, including 31 subjects 65 years of age and older.

Reviewer's Comment: Study 690601 is discussed in Section 9.2.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

9.2.1 Adult Studies

9.2.1.1 Study IMAG-062: A Phase III Double-blind, Placebo-controlled Study on the Safety and Immunogenicity of FSME-IMMUN NEW Formulation

Study IMAG-062 was a study conducted by IMMUNO-AG (Marketing Authorization Holder prior to Baxter) in Hungary from May 1994 through February 1997 to compare old and new formulations of FSME-IMMUN. IMAG-062 was a prospective, randomized, placebo-controlled double-blind study.

Reviewer's Comments: In Study IMAG-062, the current formulation of FSME-IMMUN is referred to as FSME-IMMUN CC-Hg (i.e., without the addition of thimerosal as preservative).

The study was stratified into parts A, B and C:

- In Part A, 1191 healthy adults who were seronegative for TBEV antibodies at baseline were enrolled into four cohorts: one cohort received FSME-IMMUN produced with CC-derived virus seed with thiomersal (FSME-IMMUN CC+Hg), the second cohort received the same formulation without thiomersal (FSME-IMMUN CC-Hg), the third cohort received FSME-IMMUN produced with mouse brain-derived virus seed (FSME-IMMUN MC) and the fourth arm received placebo (1 mg aluminum hydroxide, 0.05 mg thimerosal, ≤0.6 mg human serum albumin (HSA) per 0.5mL dose). All cohorts received two doses of each investigational product given 28 to 35 days apart.

- In Part B, 776 subjects who had received vaccine in one of the vaccine cohorts in Part A (FSME-IMMUN CC with or without thiomersal and FSME-MC cohorts) received a third dose of the same vaccine from Part A 8 to 10 months after the second vaccination. Part B did not include a placebo arm. Prior to the third vaccination, antibody persistence was assessed by calculating the seroconversion rate.
- In Part C, 229 healthy, TBEV-antibody negative adults at baseline and prior to enrollment in Part C, who had received placebo in Part A of the study were randomized to one of the three study arms (FSME-IMMUN CC+Hg, FSME-IMMUN CC-Hg, FSME-IMMUN-MC). Subjects received two vaccinations with one of the three vaccines mentioned above 21 to 35 days apart and a third vaccination 8 to 10 months after the second vaccine. There was no placebo arm in Part C of the study.

Reviewer's Comments: At the time Study IMAG-062 was conducted, the TBE vaccine had been commercially available in Austria for 16 years. The licensed vaccine at the time was produced from formalin-inactivated TBEV produced through passage of the seed virus in mouse brain, adsorbed to aluminum hydroxide and preserved by the addition of thiomersal (Hg). The objective of this study was to demonstrate equivalence between a new TBE vaccine produced through passage of the virus seed in chick embryo cells available both with and without thiomersal (preservative) and the Austrian licensed vaccine produced with mouse brain-derived virus seed and to show that all three vaccines were more immunogenic than placebo. The FSME-IMMUN CC-Hg has the same formulation as the current TBE vaccine discussed in this application. Only the immunogenicity data from Part A is discussed in this review because it provides support for the immunological assays used in this application. The immunogenicity data of Parts B (prior and after the third dose) and C (three dose schedule) are not being considered to support FSME-IMMUN safety and immunogenicity because the vaccine formulations used in this study were produced in a former facility using a previously approved small-scale production with a different process. The need for a third dose of the vaccine is based on the totality of the data submitted to this BLA.

The primary immunogenicity endpoint for Part A of this study was seroconversion rate 28 to 35 days after the second vaccination. Seroconversion was defined as a two-fold geometric titer increase compared with baseline quantified by ELISA and/or NT. For the latter, the titers resulting in 100% inhibition of virus growth was determined. The ELISA tests were performed centrally at the Sponsor's immunological laboratory (Dr. Aicher). The neutralization tests were performed at the Sponsor's serological control laboratory at (b) (4) (Dr. Enzerberger) and used the NT method described by Adner. ELISA test results are expressed in VIEU/mL, neutralization test results in terms of dilutions between 1:5 and 1:1280.

The seroconversion rate after the second vaccination based on ELISA was calculated for FSME IMMUN CC-Hg (88.6%; 95% CI: 84.3%, 92.1%) and the placebo recipients (2.1%; 95% CI: 0.78%, 4.56%). The seroconversion rate by NT after the second vaccination and 95% CI for the FSME IMMUN CC-Hg recipients were 84.6% (95% CI: 79.9%, 88.7%) and 0% (95% CI: 0%, 1.05%) in the placebo group.

Prior to the first vaccination, the medians of the titers of the four study groups determined by NT were found to be <1:5. After the second vaccination no change in the

median was observed in the placebo group, while the median was 1:57 for the group who received the current formulation of the vaccine (Table 36).

Table 36. TBEV Antibody Titer Determined by Neutralization Test at Baseline and Post Dose 2

Study Group	N	Mean	Median	Min	Max	10% Quantile	90% Quantile	95% CI of Median	
Baseline FSME CC + Hg	281	<1:5	<1:5	<1:5	1:20	<1:5	<1:5	<1:5	<1:5
Baseline FSME CC – Hg	280	<1:5	<1:5	<1:5	1:17	<1:5	<1:5	<1:5	<1:5
Baseline FSME IMMUN	283	<1:5	<1:5	<1:5	1:20	<1:5	<1:5	<1:5	<1:5
Baseline Placebo	283	<1:5	<1:5	<1:5	1:20	<1:5	<1:5	<1:5	<1:5
Post Dose 2 FSME CC + Hg	281	1:86	1:48	<1:5	>1:1280	1:17	1:190	1:34	1:67
Post Dose 2 FSME CC – Hg	280	1:77	1:57	<1:5	1:905	1:14	1:160	1:40	1:67
Post Dose 2 FSME IMMUN	283	1:102	1:80	<1:5	>1:1280	1:20	1:226	1:67	1:80
Post Dose 2 Placebo	283	<1:5	<1:5	<1:5	1:20	1:5	1:5	1:5	1:5

Source: Original BLA, CSR for IMAG-064, page 123
The missing neutralization test result of the 2nd blood draw of subject (b) (6) (in study group FSME CC+Hg) was replaced by value determined at screening
Total N=1127 for both baseline and post dose 2 groups.

Subjects vaccinated with FSME-IMMUN CC-Hg had GMCs of 287 (95% CI: 254, 314) after the second dose compared with values of 25 (95% CI: 23, 27) reported in subjects from the placebo group.

Reviewer's Comments: We will limit our discussion of this study to the immunogenicity results among recipients of the vaccine formulation intended for US licensure (FSME-IMMUN CC-Hg) and placebo recipients from Part A. IMAG-062 was the only study with placebo-controlled immunogenicity data (through dose 2) submitted to this BLA, and it provides valuable controlled data for the immunogenicity assessment. However, protocols and immunogenicity datasets were not available for this study. Therefore, these data could only be used as supportive of the immunological assays used in the immunogenicity analyses. Subjects who received placebo for the first two doses were not seropositive by NT/ELISA, while subjects who received two FSME-IMMUN doses were seropositive by NT/ELISA.

In summary, immunogenicity analyses post dose 2 from IMAG-062 showed that FSME-IMMUN was immunogenic and induced significantly higher TBEV titers than placebo. Since the vaccine formulations in this study were produced in a former facility using a previously approved small-scale production with a different process, safety data for the

current formulation was reviewed only for SAEs. No serious adverse events were observed in this study.

9.2.1.2 Studies 201/202: Double-blind, Randomized, Multicenter Dose-Finding Study in Adults

Study 201 was a double-blind, randomized, dose-finding study that evaluated the safety and immunogenicity of three dosage levels of FSME-IMMUN administered to healthy subjects 16 to < 65-years of age. A total of 405 subjects were randomized in a 1:1:1 ratio to receive 1 of the 3 dosage levels of TBEV antigen (0.6 µg, 1.2 µg, or 2.4 µg). Each subject was to receive two vaccinations administered 21 to 35 days apart. Blood was drawn for determination of TBEV antibodies before vaccination and 21 to 35 days after the second vaccination. Study 202 was a follow-up study to Study 201 and was planned to enroll all subjects who had received the two vaccinations in t Study 201. The study evaluated the safety and immunogenicity of a third dose of FSME-IMMUN (at the same dosage level as received in Study 201) administered 6 months after the first vaccination. Blood was drawn for determination of TBEV antibodies before and 21 to 28 days after the third vaccination.

In both studies, subjects were monitored for the occurrence of solicited adverse reactions for four days following each dose using a diary card. In Study 201, subjects also recorded unsolicited adverse events occurring up to 21 to 35 days after dose 2. For subjects enrolled in Study 202, unsolicited adverse events occurring after the last blood draw in Study 201 and before vaccine administration in Study 202 were reported to the investigator and recorded in the eCRF. Subjects were followed for adverse events for 35 to 42 days after the third dose. The frequency of occurrence of local reactions after each of the three vaccinations showed no clear patterns of dose dependency and did not increase or decrease consistently from dose 1 through dose 3. In all study arms, the most frequent local reactions after each dose were injection site pain and tenderness and they were predominantly classified as mild. For the 2.4 µg dose of FSME-IMMUN, the reported rates of local adverse events were 32.6%, 21.2% and 36.4% after first, second and third dose. Systemic reactions during the Studies 201/202 were reported with similar frequency across dose groups, and most were of mild severity. The most common systemic reactions reported were headache and muscle pain. Adverse events reported to have occurred during the period between the end of Study 201 and the start of Study 202 were mostly mild and all classified as unrelated to vaccination except for one mild case of myalgia that according to the subject occurred "shortly" after the completion of Study 201 The subject was unable to recall when the event occurred in relation to vaccine administration since he was queried six months after completion of Study 201.

There were four SAEs reported in these two studies. All were considered unrelated to the study vaccine by the Principal Investigator:

- Subject (b) (6) , 61 years of age had ascending lymphangitis caused by an infected cat bite 25 days after dose 2 of vaccine (0.6 µg dose)
- Subject (b) (6) , 28 years of age had tonsillitis 27 days after dose 2 of vaccine (0.6 µg dose)
- Subject (b) (6) , 40 years of age had a hospitalization for neurological investigation (due to occipital pain and paresthesia) related to a previous traumatic injury 13 days after dose 2 of vaccine (1.2 µg dose)

- Subject (b) (6), 38 years of age was diagnosed with breast cancer and hospitalized for therapeutic surgery 19 days after receiving the third immunization (2.4 µg dose)

Reviewer's Comments: Based on the SAE listings and narratives provided, we agree with the Principal Investigator's assessment that the SAEs listed above were probably not related to the vaccine because there are alternative explanations for the occurrence of SAEs that argues against association of the adverse event with the use of the vaccine.

Two subjects were withdrawn from Study 201 after the first vaccination due to adverse events:

- Subject (b) (6), who received the 0.6 µg dose of FSME-IMMUN was withdrawn from the study due to hypersensitivity, considered possibly related to study vaccine.
- Subject (b) (6), who received the 2.4 µg dose of FSME-IMMUN was withdrawn from the study due to an aggravated allergic reaction considered probably related to study vaccine. No subjects were withdrawn from Study 202 due to adverse events.

A dose-dependent response was observed with the neutralization test results after the third vaccination, with seroconversion rates of 73.0%, 93.0%, and 94.9% for the 0.6 µg, 1.2 µg, and 2.4 µg study arms, respectively.

Reviewer's Comments: These safety and immunogenicity results supported selection of the 2.4 µg dose of FSME-IMMUN in adults for further clinical development.

9.2.2 Antibody Persistence and Studies that Evaluated Booster Immunizations

9.2.2.1 Study 223: Antibody Persistence and First Booster

Subjects in the immunogenicity subgroup of Study 213 were invited to take part in Study 223, an open-label, multicenter study. Per Study 223 protocol, seropersistence would be assessed at 2 years ±28 days and 3 years ±28 days after the third vaccination in Study 213 and all subjects would receive one booster vaccination with 0.5 mL FSME-IMMUN three years ±28 days after the third vaccination had been administered in Study 213.

Participants from Study 213 were eligible to enroll in Study 223 if:

- they had received the third dose of FSME-IMMUN 0.5 ml,
- they were determined to have an ELISA concentration >126 VIEU/mL and / or a NT titer ≥1:10 after the third vaccination in Study 213; and
- they agreed with the provisions of the study, did not meet the exclusion criteria outlined in the initial Study 208 (see Section 6.1.3), signed an informed consent and kept a subject diary.

Study 223 had a total of three visits:

- Visit 1: a blood sample was taken to assess the seropersistence of TBEV antibodies 2 years (±28 days) after the third vaccination with FSME-IMMUN 0.5 mL administered during Study 213.

- Visit 2: a blood sample was taken to assess the seropersistence of TBEV antibodies 3 years (±28 days) after the third vaccination with FSME-IMMUN 0.5 mL administered during Study 213. Administration of booster vaccination.
- Visit 3: a blood sample was taken 21 to 35 days after administration of the booster vaccination to assess immune response.

The Study endpoints were:

- Primary Endpoint: Point estimates and 95% CIs for the seropositivity rate measured by ELISA and/or NT at two and three years after the third vaccination and after the booster vaccination in this study.
    - The dependence of seropositivity of study subjects 2 and 3 years after the third vaccination on demographic factors (age, gender) was analyzed by logistic regression at the end of the study period.
- Secondary Endpoints: Point estimates and 95% CIs for:
    - Seropositivity rate measured by ELISA and NT two and three years after the third vaccination in Study 213 and after the booster vaccination in the present study
        - Seropositivity based on ELISA – Using ELISA values (determined using the Immunozym FSME-IgG assay), a subject was considered seropositive if the subject had an anti-TBEV antibody concentration >126 VIE U/mL.
        - Seropositivity based on NT - Using NT values a subject was considered seropositive if the subject had an NT titer ≥1:10.
    - Antibody concentration and titers two and three years after the third vaccination in Study 213 and after the booster vaccination in the present study measured by ELISA and NT respectively
    - Local and systemic reactions after the booster vaccination.

<u>Reviewer's Comments:</u> The difference between the primary and the secondary endpoints is that seropositivity in the primary endpoint is based on the ELISA and/or NT and in the secondary endpoint seropositivity is analyzed by each test individually.

A total of 346 subjects who had immunogenicity results at 2 years after the third TBE dose were included in the 2-year analysis (252 subjects who received all three vaccinations with FSME IMMUN and 94 subjects who received two immunizations with the active comparator and the third with FSME-IMMUN). A total of 328 subjects who received the booster dose 3 years after the third TBE dose and had immunogenicity results after the booster dose were included in the 3-year and booster-dose analysis (240 subjects in the FSME-IMMUN 0.5 mL group and 88 in the TBE vaccine comparator /FSME-IMMUN 0.5 group).

In concordance with the demographics from the immunogenicity population in Study 213 discussed in 6.1.10.1.1, there were slightly more female than male subjects in Study 223, and the largest proportion of subjects were aged 36-45 years in both study groups. Only 19/328 subjects (7.9%) who received the first booster dose were >55 years of age.

For the subjects who received the primary immunization series with FSME-IMMUN in Study 213, the seropositivity rates by NT one month, 2 years, and 3 years after the third dose were 100% (252/252; 95% CI: 98.5%, 100%), 96% (242/252; 95% CI: 92.8%, 98.1%) and 94.2% (226/240 95% CI: 90.4%, 96.8%), respectively.

The likelihood of remaining seropositive two and three years after the third vaccination based on demographics was analyzed by logistic regression. The model included study group, age, weight, height and gender as exploratory variables. The analysis revealed that only age had a significant influence on a subject's probability of remaining TBEV seropositive (assessed by ELISA and/or NT combined) two or three years after the third vaccination. With regard to odds, an increase in age by one year is associated with an approximately 0.9 times smaller likelihood of being seropositive.

Reviewer's Comments: The immunogenicity analysis per age stratum for the subjects who received three doses of FSME-IMMUN ("FSME-IMMUN only") was based on data from 211 subjects who were 18 to less than 50 years of age and 41 subjects ≥50 years of age. Subjects ≥50 years of age have a smaller likelihood of remaining seropositive 3 years after the third vaccination. However, the number of subjects older than 50 (n=41) and older than 60 (n=15) limits this exploratory analysis. Most seropositivity data include subjects who completed the primary series while still younger than 50 years of age.

Comparing the immunogenicity of the vaccine in older subjects (51-67 years of age, n=41) with younger subjects (18 to <50 years of age, n=211) the following was observed:

- Seropositivity rate based on NT was similar in both age groups one month after the third vaccination (100%). Three years after the third vaccination, fewer older subjects had seropositive NT levels than younger subjects (82.9%, 95% CI: 67.9%, 92.8% vs 96.5%, 95% CI: 92.9%, 98.6%, respectively).

- GMT based on NT were slightly lower for older vs younger subjects (122.4, 95% CI: 86.7, 172.9 vs 302.8, 95% CI: 268.7, 341.2, respectively) after the third vaccination and the same trend was observed three years after the third vaccination (25.8, 95% CI: 18.4, 36.2 and 54.5, 95% CI: 46.7, 63.5, respectively).

- GMC values in older subjects were approximately half the GMC values in younger subjects both at 1 month after the third vaccination and at 3 years after the third vaccination. After the booster vaccination, seropositivity rates as determined by ELISA and/or NT were 100% in both age groups, although GMC values were lower in older subjects than in younger subjects (refer to Table 37 and Table 38 copied below).

- Seropositivity rate based on ELISA was similar in the different age groups one month after the third vaccination but were lower in older subjects (85.4%) compared to younger subjects (97%) three years after the third vaccination.

Table 37. Geometric Mean Concentration (VIEU/mL) of IgG as Measured by ELISA at 1 Month and 3 Years After the Third Vaccination in Study 213 and 1 Month After the Booster Vaccination in Study 223, by Age Group, Subjects Who Received FSME-IMMUN Only in Study 213

	1 Month After Third Vaccination			3 Years After Third Vaccination			1 Month After Booster Vaccination		
Age Group	N	GMC	95% CI	N	GMC	95% CI	N	GMC	95% CI
18-50 years	211	2103.2	1849.8, 2391.4	199	442.5	387.0, 505.9	199	5296.7	4792.0, 5794.9
51-67 years	41	1031.0	759.4, 1399.7	41	220.8	156.5, 311.5	41	3435.6	2724.6, 4332.2

Source: Summary of Clinical Efficacy page 55.

Table 38. Geometric Mean Titers (GMT) of IgG as Measured by NT at 1 Month and 3 Years After the Third Vaccination in Study 213 and 1 Month After Booster Vaccination in Study 223 by Age Group: Subjects Who Received Three Doses of FSME-IMMUN in Study 213

	1 Month After Third Vaccination			3 Years After Third Vaccination			1 Month After Booster Vaccination		
Age Group	N	GMT	95% CI	N	GMT	95% CI	N	GMT	95% CI
18-50 years	211	302.8	268.7, 341.2	199	54.5	46.7, 63.5	199	458.9	424.2, 496.6
51-67 years	41	122.4	86.7, 172.9	41	25.8	18.4, 36.2	41	303	227.7, 403.1

Source: CSR for Study 223, adapted from Tables 14.2.2-15, 14 2.3-21 and 14.2.3-22 pages 104, 114

Reviewer's Comments: It should be noted that the lower values of the 95% CIs for the GMT and GMC were still above the cut-off levels for seropositivity regardless of age of the subject one month and three years after the third vaccination. Although NT seropositivity rates were high (>82.9%) up to three years after the primary series, the GMTs had waned especially in adults older than 50 years of age. The Applicant provided insufficient data to address the optimal time for a booster dose. However, considering the totality of the data provided, the Applicant's proposal for a booster dose 3 or more years after completion of the primary series is acceptable. Thus, the prescribing information will include language addressing a booster dose 3 years after the primary series if continued potential exposure to TBEV is anticipated.

Seropositivity rate (ELISA and/or NT; NT only and ELISA only) after the booster vaccination for the FSME-IMMUN only group was 240/240 (100%; 95% CI: 98.5%, 100%).

Reviewer's Comments: Following a fourth dose of FSME-IMMUN all subjects were seropositive. The post dose 4 GMCs and GMTs relative to pre-dose 4 antibody levels demonstrate an anamnestic response.

Safety

Subjects were to record information regarding fever, as well as the occurrence of queried local and systemic reactions in diaries, on the day of vaccination and for the following 3 days (a total of 4 days). Body temperature in Study 223 was measured only if the subject felt unwell or feverish. If fever occurred (temperature ≥38.0°C), the subject was required to continue measuring body temperature at least once daily in the evening and more often at the discretion of the subject until the temperature returned to normal.

All measured temperatures were to be documented in the diary. The highest temperature each day after vaccination was documented in the case report form. Fever was categorized by severity grade according to the Common Toxicity Criteria guidelines as follows: mild (38.0°C-39.0°C); moderate (39.1°C-40.0°C); and severe (>40°C) (National Cancer Institute 1999). Local and systemic reaction rates after the booster vaccination were provided in tabular format, and the probabilities of occurrence of adverse experiences and their 95% CIs have been calculated. The safety dataset included all subjects who had received the booster vaccination with FSME-IMMUN 0.5 mL and provided documentation on all AEs, at least immediately after vaccination. Solicited injection site reactions included swelling, induration, redness, injection site pain and tenderness. Systemic symptoms included headache, nausea, vomiting, muscle pain, joint pain, fatigue, malaise and swelling of the lymph-nodes.

Fever was not reported for any subjects (N=240) after the booster dose. Local reactions were reported for 22 (6.7%) subjects and were all mild. Tenderness was reported for 16 (4.9%) subjects and injection site pain was reported for 13 (4.0%) subjects; all of these local reactions were of mild intensity. Systemic reactions were reported for 2 (0.6%) subjects. Mild malaise was reported for 1(0.4%) subject, and mild muscle pain was reported for 1(0.4%) subject. In addition to the queried symptoms, mild headache, considered not related to study vaccine was reported for 1(0.4%) subject. There were no SAEs or deaths reported in this study.

Conclusion

In Study 223, the overall seropositivity rate of 95% suggests that a booster dose is not necessary within the three years after completion of the primary series. An exploratory data analysis suggest it may be possible to administer the first booster vaccination at a later date (>3 years) in subjects <50 years, given their high seropositivity rates and NTs at 3 years. The comparison of the NT data in subjects younger than 50 and ≥50, one month and three years after the primary series supports findings from other studies (Study 690601) which indicate that older subjects may have a lower immune response than those under the age of 50 years. However, after the booster dose (administered 3 years after completion of the primary series), seropositivity rates were 100% regardless of age and there was an increase in NT GMT showing a good anamnestic response.

Reviewer's Comments: The results of Study 223 shows seropositivity before the first booster at 3 years was high overall (95%) but with clear decline in GMT. A booster dose administered 3 years after the primary series generated an anamnestic response. This data supports administration of a booster dose three years after the primary series if ongoing exposure or re-exposure to TBEV is expected.

9.2.2.2 Study 690701/691101: Antibody Persistence for 10 Years and Booster Response

Studies 690701 and 691101 (also referred to as Study B9371010) were follow-up studies in healthy adults who had received their primary immunization series in Studies 208/213, first booster in Study 223, and were followed through 10 years post-first booster. In Study 690701, blood was drawn to assess the seropersistence of TBEV antibodies at 27, 34, 46 and 58 months after the first booster vaccination administered during Study 223. In Study 691101, blood was drawn at 82, 94, 106, and 118 months after the booster immunization in Study 223. The dependence of seropositivity of study subjects 27, 34, 46 and 58 months after the first booster vaccination on demographic factors (age, body mass index and gender) was analyzed by logistic regression at the

end of the study period. At each time point, subjects with NT titer ≤20 and / or ELISA value ≤126 VIEU/mL) were offered a second booster vaccination. For the subjects who received a booster in these studies, antibody responses were evaluated 21 to 35 days after the booster vaccination by means of ELISA and NT.

Reviewer's Comments: In Studies 213 and 223 the definition of seroconversion was based on NT titers ≥10. In Studies 690701 and 691101 a booster dose was administered to individuals with NT ≤20.

In Study 690701, slightly more female (51.4%) than male subjects (48.6%) were included in the immunogenicity and per protocol dataset (n=315), with the largest percentage (32.1%) aged 41-50. There were 55 (17.5%) subjects 51-60 and 15 subjects older than 60 years of age (4.8%). A trend of faster decline of antibody levels in the older age groups was noted in Studies 690701 and 691101. Seropositivity rates decreased to 98.0% (18-49 years), 94.1% (50-60 years), and 77.8% (>60 years) at Month 46 as measured by ELISA or NT. Seropositivity rates continuously decreased to 88.6% (18-49 years), 74.5% (50-60 years), and 37.5% (>60 years) at Month 118 as measured by ELISA or NT. However, the sample sizes in the older age groups are too small to draw conclusions regarding recommendation for booster intervals based on age. At the end of Study 691101 (NT at 10 years post-first booster), 84.9% of the subjects were still considered seropositive as measured by NT at 10 years post-first booster (end of Study 691101).

Only 32 of 315 subjects (10.16%) received (as defined by titers decreasing below predefined NT or ELISA thresholds) a second booster dose within 5 years after the first booster administered in Study 223. Seven subjects were vaccinated prior to 34 months after the first booster vaccination; 11 subjects were vaccinated at 34 months, 5 at 36 months, 2 at 48 months, and 7 at 60 months after the first booster vaccination. In follow-up Study 691101, 15 of 243 subjects (6.2%) received a second booster dose within 7 to 10 years after the first booster administered in Study 223 (two additional subjects met the second booster criteria but were working abroad and did not return for their booster visit).

For subjects who received a second booster (either in Study 690701 or 691101), GMTs of antibody levels measured by NT were below the protocol-defined criterion for a booster dose (NT ≤20) prior to booster administration. After administration of a second booster dose NT GMTs increased 12.1-13.5-fold over pre-booster levels.

Reviewer's Comments: From the datasets for Study 690701, of the 32 subjects who received the booster dose in Study 690701, 26 had received a primary immunization series with three doses of FSME-IMMUN and 6 had received two doses of the comparator TBE vaccine and one of FSME-IMMUN. We are unable to verify how many of the 15 subjects who received the second booster in Study 691101 had the primary series with FSME-IMMUN only. The immunogenicity data from Studies 690701 and 691101 are very limited and insufficient to draw conclusions regarding recommended intervals for (b) (4) *immunizations.*

Safety

Subjects were included in the safety analysis dataset if they received the booster vaccination. For Study 69071, subjects received a subject diary for documentation of

AEs for a total period of 4 days (including vaccination day, with queried systemic and injection site reactions as has been reported in Studies 208/213). Two of 32 subjects who received booster vaccinations in Study 690701 reported mild adverse reactions to the booster vaccination, fatigue and injection site pain in one subject, and malaise in the other. No other AEs were reported during the study. In contrast, only serious SAEs were to be reported for Study 691101. Seven SAEs were reported in Study 690701, and none were considered related to the investigational product. No SAEs were reported in Study 691101.

Reviewer's Comments: We have reviewed the SAE listing and agree with the Applicant's assessment of the SAEs reported in Study 690701 as not related because the diagnoses were consistent with diseases that are common for this age group and the biological plausibility of the events does not support a causal association for the event to be linked with the vaccine use. The available data did not raise concerns regarding the safety of (b) (4) *and did demonstrate an immune response to FSME-IMMUN; however, the number of subjects was limited which limits our ability to draw conclusions regarding safety and timing of* (b) (4) *.*

9.2.3 Studies Evaluating Alternative Dosing Schedules

9.2.3.1 Studies 225 and 69051

Study 225: Open-label Phase IV Clinical Study to Evaluate the Immunogenicity and Safety of a Rapid Immunization Schedule with FSME-IMMUN 0.5 mL in Healthy Adults Aged 16 - 65 Years
March 24, 2004 to May 19, 2004 (Belgium)

Study 690501: Open Label, Follow-up, Phase IV Clinical Study to Evaluate the Immunogenicity and Safety of a Third Vaccination with FSME-IMMUN 0.5 mL in Subjects Previously Vaccinated Using a Rapid Immunization Schedule
May 30, 2005-June 21, 2005 (Belgium)

Study 225 was an open-label, single center, phase IV study to evaluate the safety and immunogenicity of FSME-IMMUN 0.5 mL when the first and second doses were administered 12±2 days apart. Planned enrollment was a total of 60 healthy adults of either gender, aged ≥16 years and ≤65 years. Blood drawing for determination of TBEV antibody response was performed on Days 3+1, 7+1, 14+1, 21+1, and 42+1 after the second vaccination. The objective of this study was to establish the earliest time point at which vaccinees are expected to show seropositive TBEV antibody levels after vaccination with FSME-IMMUN 0.5 ml. A subject was classified as seropositive by ELISA if she/he had an ELISA value >126 VIE U/ml after vaccination and by NT if she/he had an NT value ≥1:10.

Reviewer's Comments: The following rationale was provided by the Applicant regarding the choice of the design of the clinical study: an open-label, non-controlled design was considered acceptable for this study at the time because of the data already available regarding the immunogenicity of the vaccine from Study 201 and 202 in adults reporting high seroconversion rates after a three-dose vaccination schedule with the first and second vaccine given 21 days apart. In these studies, a substantial proportion of the subjects (N=98) demonstrated an immune response as early as 6 weeks after the first vaccination (Ehrlich et al. 2003).

Study 690501 was an open-label, follow-up, phase IV study in subjects who already participated in Study 225 and had received two vaccinations during that study. Subjects who met the inclusion/exclusion criteria and consented to participate in this follow-up study would receive a third vaccination approximately 12 months after the second dose of vaccine was administered in Study 225. After vaccination, they were monitored for 21 days post-vaccination. However, due to the delayed start of this study, all subjects received the third vaccination 13 to 14 months after the second vaccine in Study 225, instead of 12 months as planned in the study protocol.

The eligibility criteria for Study 225 and 208 and 690701 and 690501 were similar (please refer to Section 6.1.3 for more information). One additional criterion that was not mentioned in the CSR for Study 208 is that subjects who met the inclusion criteria but had a febrile illness (body temperature ≥38.0°C, measured orally) at the scheduled time of vaccination, were not to be vaccinated until their body temperature returned to normal. If subjects had received antipyretics within 4 hours prior to the scheduled time of vaccination, the vaccination was to be performed at a later date.

FSME-IMMUN 0.5 mL was provided in pre-filled syringes each containing one dose, i.e., 2.4 µg ±15% of TBEV antigen. Lot numbers 370403HF and 371304KJ were the vaccine lots used in Studies 225 and 690501, respectively. The test product was administered intramuscularly into the deltoid muscle. In Study 225, the two vaccinations were to be administered in alternating arms (first left, second right or vice versa).

Both studies were conducted at SGS Biopharma Research Unit Stuivenberg, Lange Beedekensstraat, 267 B-2060 Antwerp, Belgium.

Sixty-two subjects were enrolled in Study 225, but two had a history of vaccination against yellow fever/Japanese encephalitis, therefore they were not vaccinated with the study product. Additionally, 4 subjects were seropositive for TBEV antibodies as determined by ELISA and NT. These subjects were not included in the analysis of immunogenicity (56 subjects) but were included in the safety analysis dataset (60 subjects). A total of 44 subjects received the third vaccination in Study 690501.

Reviewer's Comments: There were substantially more females than males (67.9% vs 32.1%) in the immunogenicity population, and only 16.1% in Study 225 and 9.8% in Study 690501 were older than 55 years of age.

Only subjects who had seronegative antibody concentrations and titers (as determined by ELISA and NT) at baseline were included in the assessment of immunogenicity. The antibody kinetics following two vaccinations with FSME-IMMUN 0.5 mL administered 12+2 days apart are demonstrated by the seropositivity rates at different time points during the study. When determined by ELISA, these rates were 21.4% at Day 3 and 28.6% at Day 7 and increased to 92.9% by Day 14. By Day 21, 96.4% of subjects were seropositive and on the last day of assessment (Day 42) the seropositivity rate was 98.2%. Only one subject did not achieve seropositivity via ELISA measurement throughout the study period. This subject was seropositive in the NT from Day 14 after the second vaccination. The GMC of TBEV antibody as determined by ELISA show a similar trend to the rates of seropositivity, reaching a peak of 593.2 VIEU/mL on Day 21.

Seropositivity rates determined by NT after the second vaccination were higher and showed a more rapid increase than those determined by ELISA. On Day 3 after the second vaccination, 89.3% of the subjects were seropositive, and the rate increased to 98.2% by Day 14. At Days 21 and 42 after the second vaccination with FSME-IMMUN 0.5 mL all subjects showed seropositive titers in the NT.

GMTs determined by NT increased more rapidly than ELISA concentrations and also reached their peak (142.2) on Day 21 after the second vaccination. A similar trend was observed in the analysis of fold increase in TBEV antibody response as determined by ELISA and NT after the second vaccination and in the classification of fold increase.

Immunogenicity data from Study 690501 just before the third vaccination was administered (12 months after dose 2) showed that titers had decreased to levels very close to or below the seropositivity cut-off for both tests. GMC values just before the third vaccination were slightly below the seropositive level (113 VIEU/mL; ELISA >126 VIEU/mL is considered positive) and GMT values were just above the seropositive level (13.4; NT ≥10 is considered positive). These results support the need for the third vaccination to achieve longer term protection.

ELISA and NT data demonstrate a response to the third vaccination: all subjects (regardless of age group) were found to be seropositive by Day 7 after the third vaccination (according to ELISA and NT analyzed separately and ELISA and/or NT together). Prior to administration of the third dose GMC and GMT were 113.1 VIEU/mL and 13.4, respectively. At 21 days after administration of the third dose of FSME-IMMUN the GMC and GMT were 2938.8 VIEU/mL and 360.2, respectively. GMC and GMT values were also significantly higher after the third vaccination than after the second vaccination in Study 225 (Day 21 after third vaccination in all subjects: GMC=2938.8 VIEU/mL; GMT=360.2. Day 21 after the second vaccination in all subjects: GMC=593.2 VIEU/mL; GMT =142.2).

Safety

For both studies, safety was assessed by a 30-minute observation period following vaccination and by documentation of AEs in the subject diary over a period of 4 days (including the day of vaccination). In case the subject felt unwell or feverish, body temperature was measured orally at least once daily until the temperature returned to normal and all measured temperatures were recorded in the diary. To optimize the comparability of documented body temperatures, the Sponsor provided each subject with a digital thermometer and the temperature was measured orally in all subjects. The subject was asked to monitor local reactions including swelling, induration, redness, injection site pain, and tenderness, as well as systemic symptoms such as headache, nausea, vomiting, muscle pain, joint pain, fatigue, malaise, and swelling of the lymph nodes which were specifically queried in the subject diary. All other local or systemic symptoms that occurred within 4 days from vaccination were also to be documented in the diary. All AEs that occurred during the study period were evaluated, graded for severity and relatedness to the study product, and recorded in the electronic case report forms by the investigator. Safety parameters were also assessed during follow-up visits Severity grading of fever and other vaccine-specific criteria was performed according to the Common Toxicity Criteria (National Cancer Institute 2003).

Only one fever reaction (38.8°C) was reported during the study (after the second vaccination); this case was categorized as being mild and related to the vaccination in the CSR. No subjects reported fever after the first or third vaccinations. Local reactions were reported for 23 subjects (38.3%, 95% CI: 26.1%, 51.8%) after the first vaccination, 28 subjects (46.7%, 95% CI: 33.7%, 60.0%) after the second vaccination, and 15 subjects (34.1%; 95% CI: 20.5%, 49.9%) after the third vaccination. All reports of local reactions after each of the vaccinations were of mild intensity. After the first vaccination, these reports included injection site pain in 14 subjects (23.3%) and tenderness in 13 subjects (21.7%). After the second vaccination, tenderness was reported for 20 subjects (33.3%), injection site pain was reported for 10 subjects (16.7%), induration was reported for 2 subjects (3.3%), and injection site haemorrhage was reported for 1 subject (1.7%). After the third vaccination, these reports of local reactions included injection site pain in 10 subjects (22.7%) and tenderness in 10 subjects (22.7%).

Systemic reactions were reported for nine subjects (15.0%) after the first vaccination, for eight subjects (13.3%) after the second vaccination, and for six subjects (13.6%) after the third vaccination. All reports were of mild or moderate intensity. After the first vaccination, the systemic reactions included muscle pain in three subjects (5.0%), fatigue in two subjects (3.3%), and headache, nausea, joint pain, and malaise in one subject each. After the second vaccination the systemic reactions reported were headache in three subjects (5.0%), muscle pain, joint pain, fatigue, and malaise in two subjects (3.3%) each, and fever and vomiting in one subject each. After the third vaccination these reports included headache in three subjects (6.8%), and muscle pain and swelling of lymph nodes in one subject each (2.3%).

After the first vaccination, adverse events other than the specifically queried symptoms were reported for few subjects, and no particular AE (i.e., Preferred Term) was reported for more than one subject each. After the second vaccination, the most frequently reported unsolicited adverse events were included in the PT Infections and Infestations (e.g., nasopharyngitis, five subjects; rhinitis, three subjects; sinusitis, two subjects). No other significant AEs were reported after the third vaccination. No SAEs, deaths or other significant AEs were reported for both studies.

9.2.3.2 Study 690601

Study 690601: Open Label Phase IIIB Clinical Study to Evaluate the Immunogenicity and Safety of FSME-IMMUN 0.5 mL with the First and Second Vaccination Being Administered According to a Rapid Immunization Schedule in Healthy Adults Aged 16 Years or Older
September 2006-May 2007 (Poland)

Study 690601 was an open-label, multicenter, phase 3B study. All subjects were to receive three vaccinations, with the first two vaccinations given 12±2 days apart and the third vaccination given 180±14 days (approximately 6 months) after the first dose. Duration of participation in the study was 6 to 7 months for each subject. Outcomes were evaluated in two age strata: Stratum A, subjects aged 16-49 years (N=170) and Stratum B, subjects aged ≥50 years (N=170). Blood was drawn at the following intervals: at baseline; before the second vaccination; at 7, 14, 21 and 90 days after the second vaccination; before the third vaccination; and at 7 and 21 days after the third vaccination.

Reviewer's Comments: At the time of Study 690601, the rapid immunization schedule had been used in Austria for 20 years and the effectiveness of vaccination against TBE had been established (Kunz 2002). The goal of this study was to characterize the kinetics of the immune response in subjects vaccinated according to the rapid immunization schedule in a larger population of healthy adults (n=348) stratified by age.

The study was conducted at four centers in Poland and enrolled subjects using the eligibility criteria similar to Studies 208. Please refer to Section 6.1.3 of this review. The age range for this study was 16 and older. The study was divided in two parts: Part A (from Day 0 up to 21 days after the second vaccination) and Part B (blood draw 3 months after second vaccination and up to 21 days after the third vaccination).

The study was comprised of five visits in Part A:

- Screening (up to 14 days prior to visit 1): review of inclusion and exclusion criteria, medical history, physical examination and pregnancy test (if applicable)
- Visit 1 and 2 (Days 0 and 12±2 days): review of the inclusion and exclusion criteria, physical examination, pregnancy test (if applicable), blood draw (5 ml) for determination of TBEV antibodies, vaccination, post-vaccination observation and distribution of subject diary
- Visit 3 (Day 19: Day 7±1 from visit 2): review/collect subject diary, physical examination, AE documentation and blood draw for determination of TBEV antibodies.
- Visit 4 and 5 (Days 26 and 33: Days 14 and 21±1 day from visit 2): AE documentation and blood draw for determination of TBEV antibodies

The study had four visits for Part B:

- Visit 6 (Day 102: Day 90±7 days from visit 2): AE documentation and blood draw
- Visit 7 (Day 180±14 days): physical examination, AE documentation, pregnancy test (if applicable), blood draw (5 mL for determination of TBEV antibodies), eligibility for vaccination, third vaccination, post-vaccination observation, distribute subject diary
- Visit 8 (Day 187: Day 7±1 day from visit 7): review and collect subject diary, physical examination, AE documentation and blood draw for determination of TBEV antibodies
- Visit 9 (Day 201: Day 21±1 day from visit 7): physical examination, AE documentation and blood draw for determination of TBEV antibodies

Primary Endpoint

Immunogenicity

- Seropositivity rate as determined by ELISA and NT at Days 7, 14 and 21 after the second vaccination, in Stratum A and Stratum B separately, and in the two age strata combined.

Reviewer's Comment: A subject was classified as seropositive based on ELISA if she/he had an ELISA value >126 VIE U/ml. For the neutralization test, a titer of ≥10 was considered seropositive.

Secondary Endpoint

Immunogenicity

- Seropositivity rate determined by ELISA and also by NT before and 90 days after the second vaccination, as well as before and 7 and 21 days after the third vaccination, in age Stratum A and Stratum B separately, and in the two strata combined;
- Antibody response measured by ELISA and also by NT at each time point that blood is drawn before and after the second and third vaccinations, in Stratum A and Stratum B separately, and in the two strata combined;
- Fold increase of antibody concentration measured by ELISA and also by NT at each time point that blood is drawn before and after the second and third vaccinations as compared to baseline, in Stratum A and Stratum B separately, and in the two strata combined

Safety

- Local and systemic AEs occurring after each vaccination
- AEs occurring between the end of part A (Day 21 after second vaccination) and the third vaccination

Disposition of Subjects (Parts A and B):

- Subjects enrolled (Subjects who signed the informed consent) N=348
    - Subjects who were excluded from the analysis of immune response after the 2nd vaccination (N=35). The most common reason for exclusion was a baseline positive value by ELISA or NT (N=21). Subjects who showed evidence of a previous infection with the TBEV (as demonstrated by ELISA >126 VIEU/mL and / or NT ≥1:10 at baseline) were included in the analysis of safety but excluded from the assessment of immunogenicity. One subject left the study due to adverse event (subject (b) (6) : mild injection site pain: moderate oral herpes).
- Subjects included in the analysis of immune response after the second vaccination N=313
    - Subjects who were excluded from the analysis of immune response after the third vaccination N=13. The most common reason was loss to follow-up. Three subjects were excluded due to the occurrence of an adverse event: subject (b) (6) (moderate urinary tract infection and severe benign prostatic hyperplasia); subject (b) (6) (severe myocardial infarction, severe hypercholesterolemia), (b) (6) (moderate choroiditis; moderate iridocyclitis)
- Subjects included in the analysis of immune response after the third vaccination (N=300).

A total of 115 protocol deviations were reported in the study.

Reviewer's Comments: Protocol deviations were minor and are not expected to impact safety and immunogenicity results.

The proportion of female to male subjects who were vaccinated and included in the analysis of immunogenicity in Parts A and B was approximately 2:1 (n=207, 66.1% female, n=106, 33.9% male). In the analysis of immunogenicity after the third vaccination in Part B, it was also approximately 2:1 (n=201, 67.0% female, n=99, 33.0% male).

There were fewer subjects in the youngest (16-19 years old: N=15 or 4.8%) and oldest (70-79 years old: N=10 or 3.2%) age groups. About half of the study population was aged 16-49 years, between 28.4%-28.7% were 50-59-year-olds, 19.2%-19.3% were 60-69-year-olds and 3.2%-3.3% were 70-79-year-olds, depending on the immunogenicity dataset used for analysis. A high proportion (between 49.8%-50.3%) of subjects were overweight, with a body mass index of >25 kg/m2.

Reviewer's Comments: High BMI may negatively impact the immune response elicited by the TBE vaccination (Garner-Spitzer et al. 2020).

The ELISA and NT assay methods used to quantify humoral response were the same as the ones used in Study 225 and the data is shown in Table 39 below. Seropositivity rates prior to the second vaccination were 51.6% and 27.0% in Stratum A (16-49 years of age) and B (≥50 years), respectively. 76.5% of subjects in Stratum A and 48.4% of subjects in Stratum B tested seropositive as early as at Day 7 after the second vaccination. Rates increased to 96.7% and 88.0% 21 days after the second dose but dropped to 70.6% and 60.5% 90 days after the second dose in Stratum A and B, respectively. Seropositivity rates after the third dose were close to 100% for both age strata.

Regarding NT results for the population older than 50, prior to the third dose, 61.6%, 69.5% and 60.0% of subjects ages 50-59, 60-69 and 70-79 years, were still seropositive. At Day 21 after the third dose, seropositivity rates as determined by ELISA were 97.6%, 96.6% and 80.0% and for NT were 98.8%, 98.3% and 100% in subjects ages 50-59 and 60-69 and 70-79 years old, respectively.

Table 39. Seropositivity Rate as Determined by NT Before and After the Second and Third Vaccination by Age Strata, Study 690601

Timepoint	SPR in NT 16-49 years n/N (%)	95% CI 16-49 years	SPR in NT ≥50 years n/N (%)	95% CI ≥50 years	SPR in NT Total n/N (%)	95% CI Total
Immediately before 2nd vaccination	79/153 (51.6%)	43.4, 59.8	43/159 (27.0%)	20.3, 34.7	122/312 (39.1%)	33.7, 44.8
7 days after 2nd vaccination	117/153 (76.5%)	68.9, 82.9	76/157 (48.4%)	40.4, 56.5	193/310 (62.3%)	56.6, 67.7
14 days after 2nd vaccination	145/153 (94.8%)	90.0, 97.7	127/157 (80.9%)	73.9, 86.7	272/310 (87.7%)	83.6, 91.2
21 days after 2nd vaccination	148/153 (96.7%)	92.5, 98.9	139/158 (88.0%)	81.9, 92.6	287/311 (92.3%)	88.7, 95.0
90 days after 2nd vaccination	108/153 (70.6%)	62.7, 77.7	95/157 (60.5%)	52.4, 68.2	203/310 (65.5%)	59.9, 70.8
Immediately before 3rd vaccination	117/148 (79.1%)	71.6, 85.3	100/155 (64.5%)	56.4, 72.0	217/303 (71.6%)	66.2, 76.6
7 days after 3rd vaccination	141/145 (97.2%)	93.1, 99.2	129/153 (84.3%)	77.6, 89.7	270/298 (90.6%)	86.7, 93.7
21 days after 3rd vaccination	144/144 (100%)	97.5, 100.0	151/153 (98.7%)	95.4, 99.8	295/297 (99.3%)	97.6, 99.9

Source: Original BLA, Page 105 of the CSR
SPR = Seropositivity Rate
95% CI = confidence interval of Seropositivity Rate in NT

A marked increase in antibody response by NT (GMT) from immediately before the second dose (Stratum A: 11.1; Stratum B: 8.3) to Day 7 after the second dose (Stratum A: 22.1 [95% C.I. 18.6; 26.2]; Stratum B: 12.5; [95% C.I. 10.5; 14.9]) and subsequently to Day 14 (Stratum A: 42.6 [95% C.I. 36.2; 50.3; Stratum B: 23.9; [95% C.I. 20.2; 28.3]) was seen in both age strata. GMTs at 21 days after dose 2 (53.2 [95% C.I. 45.3; 62.4] in Stratum A and 29.6 [95% C.I. 25.3; 34.7] in Stratum B) represent the highest antibody titers after the second vaccination. However, by Day 90 after dose 2, GMTs had decreased to 13.6 (95% C.I. 12.0; 15.5) in Stratum A and 11.3 (95% C.I. 10.1; 12.6) in Stratum B and remained at similar levels until the third vaccination. At Day 7 after the third vaccination, GMTs were found to have risen to 63.3 (95% C.I. 54.1; 73.9) and 29.1 (95% C.I. 24.5; 34.5) in Stratum A and B, respectively, which either approached or exceeded those attained 21 days after the second vaccination. Again, the highest GMTs in NT were determined at 21 days after the third vaccination of 207.5 (95% C.I. 174.4%; 246.9%) in Stratum A and 104.4 (95% C.I. 86.1%; 126.6%) in Stratum B. Please refer to Table 42 below.

Table 40. Kinetics Of the Geometric Mean Antibody Response Measured by NT, Study 690601

Timepoint	N 16-49 years	GMT 16-49 years	95% CI 16-49 years	N ≥50 years	GMT ≥50 years	95% CI ≥50 years	N Total	GMT Total	95% CI Total
Baseline	154	5.0	5.0, 5.1	159	5.1	5.0, 5.1	313	5.0	5.0, 5.1
Immediately before 2nd vaccination	153	11.1	9.7, 12.5	159	8.3	7.1, 9.7	312	9.5	8.6, 10.6
7 days after 2nd vaccination	153	22.1	18.6, 26.2	157	12.5	10.5, 14.9	310	16.6	14.6, 18.8
14 days after 2nd vaccination	153	42.6	36.2, 50.3	157	23.9	20.3, 28.3	310	31.8	28.2, 35.9
21 days after 2nd vaccination	153	53.2	45.3, 62.4	158	29.6	25.3, 34.7	311	39.5	35.1, 44.4
90 days after 2nd vaccination	153	13.6	12.0, 15.5	157	11.3	10.1, 12.6	310	12.4	11.4, 13.5
Immediately before 3rd vaccination	148	14.4	12.7, 16.2	155	10.9	9.8, 12.1	303	12.5	11.5, 13.5
7 days after 3rd vaccination	145	63.3	54.1, 73.9	153	29.1	24.5, 34.5	298	42.4	37.5, 48.0
21 days after 3rd vaccination	144	207.5	174.4, 246.9	153	104.4	86.1, 126.6	297	145.6	127.2, 166.8

Source: Original BLA, Page 108 of the CSR for Study 690601
GMT = geometric mean titer
95% CI = confidence interval of GMT

<u>Reviewer's Comments</u>: Although more than 80% of the subjects seroconverted after the second dose, the GMTs had decreased from 53.2 (21 days after the second dose) to 13.6 (prior to the third dose) in Stratum A (16 to <50 years of age) and from 29.6 (21 days after the second dose) to 11.3 (prior to the third dose in Stratum B (≥50 years of age), respectively. Administration of a third dose of FSME-IMMUN led to an approximate seven-fold increase in GMT titers (GMT 207.5 and 104.4 in Stratum A and B, respectively).

GMC results showed the same trend as the GMT, and a comparison between the two age groups again reveals that GMCs and GMTs were markedly lower in Stratum B than in Stratum A throughout.

The methods used for the safety monitoring were similar to what was applied in Study 225. Across both age groups, a total of eight cases of fever were reported: five of these were mild (≥38.0-39ºC) and three were moderate (>39-40ºC). No subject reported more than one episode of fever.

In age strata A and B, local reactions were reported for 17.6% and 13.5% of subjects after vaccination 1, for 19.2% and 17.3% of subjects after vaccination 2, and for 19.6% and 12.8% of subjects after the third vaccination, respectively. All reactions were mild or moderate, except for one severe reaction (injection site pain) reported after the third vaccination in Stratum B (Table 41). The most frequently reported local reactions after any of the three vaccinations were injection site pain (11.2% to 15.8% Stratum A, 7.1% to 8.9% Stratum B) and injection site tenderness (8.2% to 12.0% Stratum A, 5.5% to 11.9% Stratum B). Other local reactions reported included hematoma, swelling, and redness, each of which were reported for no more than two subjects (1.2%) in either age stratum after any of the three vaccinations.

Table 41. Number (%) of Subjects Reporting Any Local Reaction by Severity After Each Vaccination, Study 690601

Age Stratum	No Reaction n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total
First vaccination 16-49 years	140 (82.4%)	26 (15.3%)	4 (2.4%)	0 (0.0%)	170 (100%)
First vaccination ≥50 years	147 (86.5%)	19 (11.2%)	4 (2.4%)	0 (0.0%)	170 (100%)
First vaccination Total	287 (84.4%)	45 (13.2%)	8 (2.4%)	0 (0.0%)	340 (100%)
Second vaccination 16-49 years	135 (80.8%)	27 (16.2%)	5 (3.0%)	0 (0.0%)	167 (100%)
Second vaccination ≥50 years	139 (82.7%)	26 (15.5%)	3 (1.8%)	0 (0.0%)	168 (100%)
Second vaccination Total	274 (81.8%)	53 (15.8%)	8 (2.4%)	0 (0.0%)	335 (100%)
Third vaccination 16-49 years	127 (80.4%)	27 (17.1%)	4 (2.5%)	0 (0.0%)	158 (100%)
Third vaccination ≥50 years	143 (87.2%)	19 (11.6%)	1 (0.6%)	1 (0.6%)	164 (100%)
Third vaccination Total	270 (83.9%)	46 (14.3%)	5 (1.6%)	1 (0.3%)	322 (100%)

Source: Original BLA, page 48 of the Summary of Clinical Safety
n = number of subjects reporting local reactions

In age strata A and B systemic reactions were reported for 10.0% and 9.4% of subjects after vaccination 1, for 12.0% and 6.5% of subjects after vaccination 2, and for 5.1% and 3.7% of subjects after the third vaccination, respectively. Most systemic reactions were mild or moderate (Table 42), with 3 subjects (1.8%) in the 16-49 years age stratum reporting severe systemic reactions after the second vaccination (symptoms including fatigue, malaise, arthralgia, myalgia, and headache) and 1 subject (0.3%) in the ≥50 years age stratum reporting a severe systemic reaction (myalgia) after the third vaccination.

Table 42. Number (%) of Subjects Reporting Any Systemic Reactions by Severity After Each Vaccination, Study 690601

Age Stratum	No Reaction n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total
First vaccination 16-49 years	153 (90.0%)	12 (7.1%)	5 (2.9%)	0 (0.0%)	170 (100%)
First vaccination ≥50 years	154 (90.6%)	14 (8.2%)	2 (1.2%)	0 (0.0%)	170 (100%)
First vaccination Total	307 (90.3%)	26 (7.6%)	7 (2.1%)	0 (0.0%)	340 (100%)
Second vaccination 16-49 years	147(88.0%)	11 (6.6%)	6 (3.6%)	3 (1.8%)	167 (100%)
Second vaccination ≥50 years	157 (93.5%)	10 (6.0%)	1 (0.6%)	0 (0.0%)	168 (100%)
Second vaccination Total	304 (90.7%)	21 (6.3%)	7 (2.1%)	3 (0.9%)	335 (100%)
Third vaccination 16-49 years	150 (94.9%)	5 (3.2%)	3 (1.9%)	0 (0.0%)	158 (100%)
Third vaccination ≥50 years	158 (96.3%)	4 (2.4%)	1 (0.6%)	1 (0.6%)	164 (100%)
Third vaccination Total	308 (95.7%)	9 (2.8%)	4 (1.2%)	1 (0.3%)	322 (100%)

Source: Original BLA, page 49, Summary of Clinical Safety
n = number of subjects reporting systemic reactions

In addition to the specifically queried symptoms, other non-serious systemic adverse events reported during the study were mostly mild or moderate, with few reports of severe AEs, and most AEs were considered not related to study vaccine by the investigator. The most frequently reported types of systemic AEs were Infections and Infestations (largely respiratory tract infections); other types of AEs were reported for only 1 or 2 subjects each. No deaths occurred during this study.

Twelve SAEs were reported for a total of eight subjects: three subjects in the 16-49 years age stratum A, and five subjects in the ≥50 years age stratum B. None of the SAEs were considered related to study vaccine.

During the active portion of the study: (Parts A and B)

- Subject (b) (6), female, 46 years of age developed torsion of sigmoid and severe ileus, 2 days after the second vaccination.
- Subject (b) (6), female, 38 years of age had surgery for moderate varicose veins 19 days after the third vaccination.
- Subject (b) (6), male, 57 years of age had surgery for mild nasal polyps 20 days after the third vaccination

During the period from the last visit after the second vaccination (end of Part A, visit 5) and the first visit prior to the third vaccination (beginning of Part B, visit 6) the following SAEs were reported:

- Subject (b) (6) (female, 35 years of age) – planned arthroscopy for moderate exostosis and ligament disorder, 91 days after second vaccination.
- Subject (b) (6) (male, 58 years of age) – mild hypoacusis and tinnitus, 156 days after the second vaccination.
- Subject (b) (6) (male, 57 years of age) – mild hemorrhoids and irritable bowel syndrome, 113 days after second vaccination.

- Subject (b) (6) (male, 57 years of age), – moderate brain contusion and facial bones fracture, 78 days after the second vaccination.
- Subject (b) (6) (male, 57 years of age) – severe myocardial infarction and hypercholesterolemia, 109 days after second vaccination.

Reviewer's Comments: We have reviewed the SAE narratives and agree with the Applicant's assessment of these SAEs as not related. For the SAEs that happened in the active portion of the study, the biological plausibility of the events does not support a causal association. SAEs that occurred in the interval between Parts A and B occurred more than 30 days after vaccine administration.

One female (Subject (b) (6)) had a positive urine pregnancy test just prior to the third vaccination (visit 7 taking place 180±14 days after the first vaccination). She had been unaware of a pregnancy up until that point in time. She did not receive the third vaccination, and the CSR states that the subject was "discontinued from the study." The outcome of pregnancy is not known.

Five subjects were withdrawn from Study 690601 due to adverse events:

- Subject (b) (6) , a 46-year-old female, was withdrawn from the study after receiving the first vaccination due to adverse events of mild injection site pain and moderate oral herpes.
- Subject (b) (6) , a 46-year-old female, was withdrawn from the study after receiving the second vaccination due to the SAEs of severe colonic obstruction and ileus.
- Subject (b) (6) , a 54-year-old male, was withdrawn from the study after receiving the second vaccination due to the AEs of moderate urinary tract infection and severe benign prostatic hyperplasia.
- Subject (b) (6) a 57-year-old male, was withdrawn from the study after receiving the second vaccination due to the SAEs of severe myocardial infarction and severe hypercholesterolemia.
- Subject (b) (6) , a 44-year-old male, was withdrawn from the study after receiving the second vaccination due to the AEs of moderate choroiditis and moderate iridocyclitis.

Overall, two vaccinations given on Days 0 and 14 induced seropositivity in all but 20 of 340 vaccinated subjects who were found to be seronegative both in the ELISA and NT at Day 21 after the second vaccination. This suggests that subjects, especially those 16-49 years of age (in Stratum A) may achieve seropositivity after two vaccinations. However, the humoral immunity wanes over time, and GMTs and seropositivity rates were decreased before the third dose especially in subjects older than 50 years of age. At 21 days after the third vaccination, 100.0% (95% C.I. 97.5%; 100.0%) and 98.7% (95% C.I. 95.4%; 99.8%) of subjects attaining seropositivity in Stratum A and B, respectively. Following three vaccinations, only 1 subject was found to be a non-responder both in the ELISA and the NT. The highest seropositivity rates after the second vaccination were observed in both age strata at Day 21, with seropositivity rates determined by NT being higher and increasing more rapidly than the corresponding rates determined by ELISA. On Day 21 after the third vaccination, all subjects in Stratum A (100.0%) and 98.7% of Stratum B subjects showed seropositive titers in the NT.

Reviewer's Comments: The proportion of subjects with seropositive titers as determined by NT at Day 14 after the second vaccination shows that the majority of subjects have neutralizing antibodies about one month into the vaccination schedule but the neutralization titers decrease over time. Antibody titers had increased by Day 7 after the third vaccination and continued to increase through Day 21 post dose 3. The rapid induction of antibody titers in both age strata subsequent to the third vaccination indicates effective priming by the first two vaccinations, but the increase after the third dose reinforces the need to complete the primary series based on three doses of the vaccine.

9.2.4 Pediatric Studies

9.2.4.1 Study 197: Postmarketing Surveillance Observational Safety Study in Children 6 Months to <13 Years of Age

A total of 1922 children aged 6 months to 12 years were vaccinated with half the adult dose of FSME-IMMUN vaccine (i.e., the same as the pediatric dose used in the other pediatric studies in this application, TBEV antigen 1.2 µg) at 110 medical centers throughout Austria, during the period between January 8, 2001 and August 23, 2001. Fever was the only adverse event that was actively reported. No evaluations of immunogenicity or efficacy were included in the study. A total of 1899 children were included in the analysis of fever. Temperature, measured for a total of 4 days after vaccination (including the day of vaccination), was the only safety parameter evaluated during the study.

Fever (>38ºC) was reported for 386/1899 subjects (20.3%, 95% CI: 18.5%, 22.2%). Most reports of fever were mild (>38ºC to <39.0ºC), reported for 15.8% of subjects; moderate fever (>39ºC to <40.0ºC) was reported for 4.3%, and severe fever (>40.0ºC) was reported for 5 subjects (0.3%). Fever rates were as follows: 6months to <1 year, 15.0%; 4-6 years, 15.4%; 7-9 years, 9.1%; 10-12 years, 13.9%. The highest frequency of fever was observed among subjects 1-3 years of age (23.7%), and all five of the severe reports of fever were in this age group. Three of these cases recorded fever in the evening of the vaccination day.

Reviewer's Comments: The proportions of mild, moderate and severe fever do not add to 20.3% (total rates of fever) due to rounding.

One of the severe fever cases in a 12-month-old boy was associated with febrile convulsion and was therefore classified as a SAE. The boy experienced a febrile convulsion 2 days after vaccination. Rhinopharyngitis, gastroenteritis, and otitis media were diagnosed and may have contributed to the magnitude of the fever (>40ºC) and the occurrence of the febrile convulsion. This SAE was considered possibly related to the vaccination. No other SAE was reported in this study.

Reviewer's Comments: Research on another TBE vaccine demonstrated that reducing the amount of antigen (i.e., administering the half adult dose for the first injection) for the vaccination of children decreased the reactogenicity in terms of fever reactions and general side effects, such as headache, nausea, vomiting and joint pain, while preserving an adequate immune response (Girgsdies and Rosenkranz 1996). This prompted Study 197 for the assessment of fever rates for a half-dose of FSME-IMMUN. This study supported that a dose of 1.2 µg of TBEV antigen (in this study administered

as half the adult dose of FSME-IMMUN vaccine) was not unacceptably pyrogenic for the first vaccination in children aged 1-12 years.

9.2.4.2 Studies 198/215: Pilot Safety and Immunogenicity Studies in Children 1 to <13 Years of Age

Study 198 was an open-label, multicenter pilot study that examined the safety and immunogenicity of 2 vaccinations (administered 14 to 32 days apart) with FSME-IMMUN 0.25 mL (1.2 µg TBEV antigen, prefilled syringe) in children aged 1 to <13 years of age (N=101). The study evaluated the tolerability, assessed by body temperature measurements and monitoring of adverse events, after the first and second vaccinations. The immunogenicity objective of the study was to examine the seroconversion rates after the second vaccination. Blood draws for determination of anti-TBEV antibodies were performed before the first vaccination and 28 to 35 days after the second vaccination.

Study 215 was a follow-up study to Study 198 in which subjects who had received two vaccinations with FSME-IMMUN 0.25 mL during Study 198 were administered a third vaccination 9 to 10 months after the second vaccination in Study 198. A total of 99 subjects were vaccinated in the study and evaluated for safety. Seroconversion rates were evaluated 21 to 35 days after the third vaccination.

The primary endpoint of seroconversion (after the second and third vaccinations) was measured by ELISA and/or NT (performed according to (b) (4) A seroconversion rate of 99% (100/101) (95%CI: 94.6%,100%) was observed after the second vaccination and the rate increased to 100% (98/98) (95% CI: 96.3%, 100%) after the third immunization. The majority (98%) of the subjects had antibody titer increases of >4-fold as determined by NT over the course of the two studies.

Safety

Each subject received a subject diary immediately after each vaccination and temperatures were to be recorded in the evening of vaccination day, the following morning, and in the evening each day for 7 days after vaccination. The parents of all subjects were also contacted via a phone call either on the first or second day after vaccination and were asked about any AEs. The subject diaries and the telephone contact notes were defined as “Source Data.” The percentage of subjects experiencing fever was higher after dose 1 (29.7%) than after dose 2 (8.9%) or dose 3 (12.3%). Among children 1-3 years of age, 29.7% experienced fever after the first vaccination. All reports of fever were mild or moderate and there were no reports of severe fever (>40ºC). In most cases, fever duration was one day.

The solicited adverse events were injection site pain, tenderness, fever, headache, nausea, vomiting, muscle pain, appetite loss, sleeping disorder and swelling of local lymph nodes. The occurrence of erythema, induration, or swelling with the diameter <25 cm^2 were not defined as an AE according to the protocol. Descriptions of reactions <25 cm^2 were recorded, nonetheless. The largest erythema recorded was 2 cm^2; other cases were described as “minimal” or “punctual.” Local reactions were reported for 10.9% of subjects after dose 1, 5.0% after dose 2, and for 11.1% after dose 3. All reports of local reactions were mild, except for reports of moderate reactions in 3 subjects (3.0%) after dose 1. The most frequently reported type of local reaction was injection site pain (5.0%

to 10.9%, across doses), followed by erythema and induration (all cases <25 cm^2), which were reported for 5.0% to 12.9% after the first 2 doses.

Systemic reactions were reported for 34.7% of subjects after dose 1, 11.9% after dose 2, and 5.1% after dose 3. All reports of systemic reactions were mild or moderate in severity. After fever, the most frequently reported types of systemic reactions were appetite loss (5.9% after dose 1, 1.0% after dose 3) and sleeping disorder (5.0% after dose 1, 3.0% after dose 2).

There were seven SAEs, all considered unrelated to the investigational product. The SAE cases of febrile convulsion are described below:

- Subject (b) (6) , male, 1 year of age, had a febrile convulsion (40.7º C) beginning 16 days after the second vaccination. He was treated with diazepam 5 mg ((b) (6) , paracetamol and ibuprofen (dates of administration not known). He developed exanthem subitum 4 days later. The subject was hospitalized for 4 days (b) (6)), and it is reported to have recovered without sequelae. Total duration of the SAE event: 5 days. Relevant medical history was that the subject had been hospitalized previously for his first febrile convulsion ((b) (6)
- Subject (b) (6) , male, 2 years of age, experienced a convulsion with a 10-minute duration, 66 days after the second vaccination. A blood test demonstrated leukocytosis, which was attributed to an unspecified viral infection. He was hospitalized for 3 days and recovered without sequelae.

Reviewer's Comments: The safety findings regarding fever post-vaccination in this study are comparable with the findings from Study 209 (described in Section 6.3). For the two SAEs of febrile seizures described above, the fever happened in the context of other viral infections and in the second case, it occurred 66 days post-vaccination. We agree with the Principal Investigator's assessment of these SAEs as not related.

In addition to the two unrelated SAEs of febrile convulsion described above, there were five additional SAEs that were also reported as unrelated:

1. Stomatitis aphthous (canker sore) was reported for a 2-year-old female (Subject (b) (6) beginning 27 days after the second vaccination and lasting for 10 days.
2. Inguinal hernia was reported for a 1-year-old male (Subject (b) (6)) beginning on the day of the second vaccination and lasting 27 days.
3. Subject (b) (6) (male, aged 12 years) was diagnosed with contusion of the thorax, sternum, capitulum and pelvis after falling from a tree 278 days after the second vaccination. The subject was treated with paracetamol and recovered without sequelae. The SAE lasted 3 days.
4. Subject (b) (6) (male, aged 1 year) suffered from aspiration pneumonia and gastroenteritis after falling into a pond 288 days after the second vaccination. Infection with *Pseudomonas aeruginosa* was determined by stool test one week after the onset of the infection. The SAE lasted 19 days. The subject was treated with antibiotics and recovered from the SAE without sequelae.
5. Subject (b) (6) (female, aged 1 year) was diagnosed with chronic seromucinous otitis media and enlarged adenoids 89 days after the second vaccination. The subject, who had a history of recurrent otitis media, was hospitalized for

adenotomy and paracentesis. The SAE lasted 4 days and the subject recovered fully with no sequelae.

Reviewer's Comments: Even though the protocol allowed the administration of the second dose 14 to 32 days after the first, only a small number of individuals received the second dose 14 days after the first (five subjects total). Further, the field effectiveness data (discussed in the Real World Evidence BLA Memorandum) does not provide enough data to support use of this schedule for children because only a small subset (about 5% of the Austrian population based on 2004 data) received the second dose within 8 to 16 days after the first dose and the age of these individuals is unknown.

9.2.4.3 Studies 199/206: Double-blind, Randomized, Multicenter, Dose-Finding Studies in Children 1 to <6 Years of Age

Study 199 was a double-blind, randomized, dose-finding study that assessed the safety and immunogenicity of 2 vaccinations of FSME-IMMUN 0.25 mL in subjects aged 1 to <6 years of age. A total of 39 study centers participated in this phase 2 study, 639 subjects were randomly assigned in a 1:1:1 ratio to receive 0.3 µg, 0.6 µg, or 1.2 µg antigen (each contained in 0.25 mL). The 2 vaccinations were administered 21 to 35 days apart. Blood was drawn 21 to 35 days after second vaccination for measuring TBEV antibodies.

Reviewer's Comments: In order to provide data to help address the range of different target vaccination ages and to ensure that one pediatric dose was suitable for both children and adolescents, in terms of both safety and immunogenicity, after Studies 197 and 198/215, Baxter conducted dose-finding and safety studies in children and adolescents up to the age of 15 years.

Study 206 was a follow-up study to Study 199 in which subjects who had received 2 vaccinations in Study 199 were administered a third vaccination (at the same antigen dose as in the previous study: 0.3 µg, 0.6 µg, or 1.2 µg) 6 months ±14 days after the first vaccination. A total of 625 subjects received a third vaccination and were evaluated for safety. Blood was drawn for determination of immune response 21 to 28 days after the third vaccination. The optimal dose was to be the highest dose of FSME-IMMUN that induced a sufficient immune response after the second vaccination (based on protocol-defined criteria) and was non-inferior to the lowest eligible dose with respect to fever rate after the first vaccination.

The primary endpoint of Study 199 was fever rate after the first vaccination and secondary endpoints included seroconversion rate after the second vaccination, fever rate after the second vaccination, and local and systemic adverse events, other than fever, up to the blood draw after the second vaccination. The eligibility criteria were similar to the criteria used in the pivotal study discussed in Section 6.

The seroconversion rates after the second vaccination as determined by NT performed according to (b) (4) showed seroconversion rates of 67.1%, 79.9% and 90.5% and GMTs of 10.4, 12.8 and 17.4 for the 0.3 µg, 0.6 µg, or 1.2 µg dose groups, respectively. The seroconversion rates after the third immunization were 84.2%, 95.6% and 99.5% with GMTs of 28.8, 41.8 and 71.6 for the 0.3 µg, 0.6 µg, or 1.2 µg dose groups, respectively.

Safety

Fever occurrence was reported regardless of relationship with the vaccine for the first 4 days and classified as mild, moderate or severe per CTC (similar to Study 209 discussed in Section 6). Fever after the first vaccination was not dose dependent. Most fever cases that occurred after the first vaccination were mild in all three dose level groups, with no reports of severe fever. Among children who received the 1.2 µg vaccine dose, 15.9% had fever after the first dose, all classified as mild. The occurrence of fever after the first vaccination was shown to be age-dependent, with the highest fever rate occurring among children aged 1-2 years and lower rates observed among older children.

Similar to the observations from Study 209, fever occurred more frequently in children 1-2 years of age. The number of subjects with fever after dose 1 by age and dose level is summarized in Table 43 below:

Table 43. Number (%) of Subjects With Fever (≥38°C) After Dose 1 by Age and Dose Level Group, Study 199

Age	0.3µg n/N	0.3µg %	0.6µg n/N	0.6µg %	1.2µg n/N	1.2µg %	Total n/N	Total %
1 year	17/47	36.2	16/39	41.0	10/43	23.3	43/129	33.3
2 years	9/40	22.5	8/41	19.5	6/36	16.7	23/117	19.7
3 years	7/42	16.7	8/57	14.0	4/50	8.0	19/149	12.8
4 years	5/39	12.8	1/36	2.8	9/35	25.7	15/110	13.6
5 years	3/39	7.7	1/36	2.8	3/37	8.1	7/112	6.3

Source: Original BLA, page 53 Summary of Clinical Safety

The occurrence of fever after the second vaccination was very similar to what was observed after the first vaccination with respect to fever rates, intensity, and distribution by age. One case of severe fever (0.5%) was reported in the 0.3 µg dose level group. Fever rates after the third vaccination were lower than after the first vaccination (10.3%, 12.2%, and 11.0% in the 0.3 µg, 0.6 µg, and 1.2 µg dose level groups, respectively). Severe fever was reported for 3 subjects (1.5%) in the 0.6 µg group after dose 3. In all 3 cases, the fever was associated with infections.

A total of 25/208 (12%) of the children who received the 1.2 µg dose experienced local reactions (10.6% mild and 1.4% moderate). Rates and intensities of local reactions after dose 2 and dose 3 were similar to those after dose 1. The most frequently reported types of local reactions were injection site pain (4.4% to 9.8% of subjects across groups and across doses) and erythema (2.8% to 7.7%), followed by induration (1.9% to 4.8%) and swelling (0.9% to 3.8%). There was no evidence of a dose response, and the frequencies of reports for these types of reactions were similar after dose 1, dose 2, and dose 3. As for local reactions, there was no indication of a dose response with respect to either the frequency or intensity of systemic reactions. After dose 1, systemic reactions were reported for 12.0% to 16.7% of subjects across dose level groups; most reports were mild or moderate, and no severe systemic reactions were reported. Results for dose 2 and dose 3 were similar to those after dose 1, with no trends for increasing or decreasing frequency or intensity from dose 1 through dose 3. The most frequently reported systemic events were restlessness (1.5% to 6.1% of subjects across groups and across doses), sleep disorder (0.9% to 3.8%), and loss of appetite (0.5% to 4.7%).

Table 44 below reports the % of subjects with fever, local and systemic reactions (except for fever) after the first, second and third vaccination in individuals who received the 1.2 µg dose.

Table 44. Number (%) of Subjects Reporting Fever, Local Reactions and Systemic Reactions by Severity After Each Vaccination for 1.2 µg dose, Studies 199/206

Reaction Type	Any Reaction n/N	% of Subjects (95% CI)	No Reaction n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Dose 1 FSME-IMMUN Fever	32/201	15.9% (11.2, 21.7)	169 (84.1%)	32 (15.9%)	0 (0%)	0 (0%)
Dose 1 FSME-IMMUN Local Reactions	25/208	12% (7.9, 17.2)	183 (88%)	22 (10.6%%)	3 (1.4%)	0 (0%)
Dose 1 FSME-IMMUN Systemic Reactions	16/208	7.7% (4.5, 12.2)	192 (92.3%)	14 (6.7%)	2 (1%)	0 (0%)
Dose 2 FSME-IMMUN Fever	27/202	13.4% (9, 18.9)	175 (86.6%)	23 (11.4%)	4 (2%)	0 (0.5%)
Dose 2 FSME-IMMUN Local Reactions	23/206	11.2% (7.2, 16.3)	183 (88.8%)	19 (9.2%)	4 (1.9%)	0 (0%)
Dose 2 FSME-IMMUN Systemic Reactions	15/206	7.3% (4.1, 11.7)	191 (92.7%)	14 (6.8%)	1 (0.5%)	0 (0%)
Dose 3 FSME-IMMUN Fever	22/200	11% (7, 16.2)	178 (89%)	18 (9%)	4 (2%)	0 (0%)
Dose 3 FSME-IMMUN Local Reactions	20/204	9.8% (6.1, 14.7)	184 (90.2%)	18 (8.8%%)	2 (1%)	0 (0%)
Dose 3 FSME-IMMUN Systemic Reactions	12/204	5.9% (3.1, 10)	192 (94.1%)	11 (5.4%)	1 (0.5%)	0 (0%)

Source: Original BLA, CSR for Study 199 pages 73-80 and CSR for Study 206 pages 89-92
** The queried local and systemic reactions in this study included injection site reactions (swelling, induration, erythema, haemorrhage, pain, tenderness), headache, nausea, vomiting, myalgia, loss of appetite, sleeping disorder, restlessness, lymphadenopathy.

A total of 27 SAEs occurred in 25 subjects in Studies 199/206. Two SAEs occurred during Study 199 (Concussion and otitis media with effusion), both of which were judged to be unrelated to vaccination by the investigator. In the follow-up period between the last visit of Study 199 and the first visit of Study 206, 20 SAEs (in 18 subjects and one death occurred. The death was caused by aspiration of a grape in a one-year-old girl. Five SAEs occurred after the third vaccination. All SAEs were classified as unrelated, nine subjects had received the 0.3 µg dose, 11 subjects had received the 0.6 µg dose, and five subjects had received the 1.2 µg dose of FSME-IMMUN.

Reviewer's Comments: Pfizer provided SAE listings and narratives for Studies 199/206. The most frequent SAEs were infections and surgical procedures. Based on the information provided we agree with the investigator's assessment of the SAEs as not related. The five SAEs in the 1.2 µg dose of FSME-IMMUN were: (1) Adenoidectomy, (2) Pseudocroup, (3) Exanthem 57 days after the second dose, (3) Foreign body aspiration; (4) Gastroenteritis and (5) Eustachian tube dysfunction.

There were three SAEs of febrile convulsion in this study:

- *Subject* (b) (6) *: 3 years old, female, febrile convulsion, pyelonephritis, 12 days after dose 3 (0.6ug). The subject recovered without sequelae after 14 days. She was treated with antibiotics for the bacterial infection.*

- *Subject* (b) (6) *3 years old, female, febrile convulsion, 39 days after the second dose (0.6 µg). First convulsion, she recovered without sequelae and she was not hospitalized.*
- *Subject* (b) (6) *1 year old, male, febrile convulsion 77 days after dose 2, 0.3 µg dose (it was his third febrile convulsion).*

We also agree with the Principal Investigator's assessment of these SAEs as not related. The febrile convulsion that occurred at 12 days post vaccination was associated with a bacterial infection. The other two events occurred 39 and77 days post vaccination.

9.2.4.4 Studies 205/207: Double-blind, Randomized, Multicenter Dose-Finding Studies in Children 6 to <16 Years of Age

Studies 205 and 207 were dose-finding studies in subjects 6 to <16 years of age. These studies used the same design and methods as the dose-finding study in children 1 to <6 years of age discussed above (199/206).

After the second vaccination, the seroconversion rate by NT (performed according to (b) (4) was highest in the 1.2 µg dose group (84%, 173/206), with rates of 70.6% and 49.2%% observed in the 0.6 µg and 0.3 µg dose groups, respectively. The seroconversion increased to 91.6% (185/202) after the third immunization in the 1.2 µg dose group, with rates of 81.5% and 72.3% observed in the 0.6 µg and 0.3 µg dose groups, respectively.

Safety

The proportions of subjects with fever (oral temperature ≥38ºC) reported after the first vaccination were similar across the 3 dose level groups, ranging from 3.3% to 4.5% (3.4% for the 1.2 µg dose group); most occurrences were mild, and there were no reports of severe fever (>40ºC). No age-dependency with respect to fever rate was apparent after dose 1. Fever rates observed after dose 2 (range 0.5% to 3.9% across dose level groups) and dose 3 (1.9% to 5.5%) were similar to those after dose 1, and there were no reports of severe fever (>40ºC).

After the first vaccination, rates of local reactions showed no dose-dependency and ranged from 17.5% to 24.9% across the dose level groups; most reports were mild, or moderate, with only 1 severe reaction reported. In the 1.2 µg group, local reaction rates after dose 2 (15.1%) and dose 3 (14.4%) were similar to those after dose 1. In all dose level groups, the local reactions were mostly mild, with no severe reactions after dose 2 and a total of 3 severe reactions after dose 3. Injection site pain was the most frequently reported local reaction, with reporting rates somewhat higher after dose 1 (13.2% to 19.0% across the dose level groups) than after dose 2 and dose 3 (ranging from 9.0% to 13.7%). Other types of local reactions were reported at similar rates across dose level groups and from dose 1 through dose 3: Tenderness, induration, swelling, and erythema were reported for between 1.4% and 7.5% of subjects after any dose.

Systemic reactions were reported at similar frequency across the dose level groups, ranging from 10.2% to 12.2% after dose 1; these reactions were mostly mild, with a small percentage of subjects reporting moderate systemic reactions (0.5% for the 1.2 µg dose group). One severe case was reported in the 1.2 µg dose level group – one 6-year-old girl was reported to have experienced severe vomiting and malaise one day post-

vaccination, followed by nausea and fatigue 2 days after vaccination; these symptoms were considered possibly related to vaccination by the investigator. After dose 2 and dose 3, systemic reaction rates ranged from 3.4% to 9.1% across the 3 dose level groups, with no severe reactions reported. The most frequently reported types of systemic reactions were headache and fatigue; across dose level groups and from dose 1 through dose 3, the frequencies of these reactions ranged from 2.0% to 7.2% for headache and from 0.9% to 5.0% for fatigue.

There was one SAE reported in Study 205:

- Subject (b) (6) (aged 10 years, female, 0.6 µg group) was treated for a serious ear infection 17 days after receiving the first vaccination. The subject was diagnosed as having acute otitis media and was hospitalized for 8 days. She received intravenous antibiotic treatment while in the hospital and recovered without sequelae.

Three SAEs were reported in Study 207:

- Subject (b) (6) (aged 8 years, female, 0.6 µg group) was hospitalized for 6 days for Abdominal pain upper, Headache, Pyrexia, Flatulence, and Tonsillitis 10 days after the third vaccination. The subject was treated with Acetylcystein, Xylometazolin, and Infectocillin, and recovered without sequelae.
- Subject (b) (6) (aged 12 years, male, 0.6 µg group), was hospitalized for 7 days for appendicitis 42 days after the third vaccination. Appendectomy was performed and the subject received perioperative treatment with Cefotiam and Metronidazol and recovered without sequelae.
- Subject (b) (6) (aged 15 years, male, 0.6 µg group), was hospitalized for 5 days for appendicitis 2 days after the third vaccination. Appendectomy was performed and the subject recovered fully with no sequelae

Five SAEs in four subjects occurred in the interval between the end of Study 205 and the beginning of Study 207:

- Subject (b) (6) (aged 10 years, female, 1.2 µg group), was hospitalized for 3 days with an eye injury 36 days after the second vaccination. The subject experienced a second SAE of proctitis 80 days after the second dose.
- Subject (b) (6) (aged 6 years, male, 0.3 µg group) was hospitalized for 3 days for a strabotomy 153 days after the second vaccination.
- Subject (b) (6) (aged 8 years, male, 1.2 µg group), was hospitalized for 9 days for cholecystectomy 120 days after the second vaccination.
- Subject (b) (6) (aged 15 years, female, 1.2 µg group), was hospitalized for 3 days for gastritis 112 days after the second vaccination.

No SAEs were considered related to the study product by the Principal Investigator.

<u>Reviewer's Comments:</u> Based on the information provided regarding the SAEs in these studies, the clinical reviewer agrees with the Applicant's assessment of these adverse events as not related.

Conclusion: The 1.2 µg antigen dose was identified as the optimal dose for pediatric use based on the data from the four studies summarized above (199/206 and 205/207), inducing high seroconversion rates following the three-dose primary vaccination series. The vaccine was well-tolerated with no safety signals identified. The seroconversion

rates after the third vaccination in adolescents aged 12-15 years of age who received the 1.2 µg antigen dose in Study 207 were comparable with the seroconversion of the population 16-35 years of age who received the 2.4µg antigen dose in adult Study 202 and Study 213, both groups attained similarly high seroprotective rates.

9.2.4.5 Study 700401: Follow-up Study to Study 209, Antibody Persistence and Booster Response

Study 700401 was a follow-up study in healthy children and adolescents aged 3-18 years who had previously participated in Study 209 at the age of 1 to <16 years. The objectives of Study 700401 were to assess seropersistence of TBEV antibodies 24 and 34 months after the third vaccination of FSME-IMMUN 0.25 mL administered during Study 209. Subjects who showed highly positive TBEV antibody concentrations as determined by enzyme-linked immunosorbent assay (ELISA) (>1000 VIEU/mL) and positive NT titers (≥10) at Month 34 after the third vaccination did not receive a booster vaccination at this time point. The remaining subjects were offered a booster vaccination at Month 36±28 days after the third vaccination. Subjects who did not receive the booster at Month 36 were further evaluated for TBEV antibody persistence at 46 or 58 months after the third vaccination, and, depending on their TBEV antibody levels, were offered a booster vaccination at either Month 48 or Month 60 after the third vaccination in Study 209. For the booster vaccination, subjects received either FSME-IMMUN 0.25 mL or FSME-IMMUN 0.5 mL according to their age (subjects ≥16 years of age received the adult dose). Immune responses to the booster vaccinations were determined 21 to 35 days after each booster vaccination.

<u>Reviewer's Comments:</u> The CSR for this study explains that the selection of >1000 VIEU/mL for ELISA as the cut-off value for seropositivity was based on a very conservative approach in order not to put the subjects at risk of an infection with TBEV. Children with titers below this level were offered a booster vaccination at three years after conclusion of the primary series. Three years after completion of the primary vaccination series in Study 209, approximately 50% of children and adolescents had TBEV IgG antibody concentrations >1000 VIEU/mL as determined by ELISA and therefore did not receive a 3-year booster vaccination. Their TBEV antibody persistence was further followed up; consequently, the planned booster at 3 years was prolonged via protocol amendment to 4 and 5 years. Before the 5-year booster, several subjects demonstrated TBEV antibody concentrations slightly under the cut-off level of 1000 VIEU/mL. However, their TBEV antibody titers assessed by NT (Adner et al. 2001) ranged from 40 to 160 showing that the TBEV antibody levels were still high up to five years after the primary vaccination in a large proportion of children and adolescents. The antibody titers based on NT are shown on Table 45 and Table 46 below.

Table 45. Seropositivity Rate Measured by NT, After the Third Vaccination Received During Study 209, Intent-to-Treat Dataset, Study 700401

	1 Month*		24 Months		34 Months		46 Months[a]		58 Months[a]	
Age	**n/N (%)**	**95% CI**	**n/N (%)**	**95% CI**	**n/N (%)**	**95% CI**	**n/N (%)**	**95% CI**	**n/N (%)**	**95% CI**
1-2 YOA	75/75 (100.0)	92.2, 100.0	75/75 (100.0)	92.2, 100.0	73/73 (100.0)	95.1, 100.0	69/73 (94.5)	86.6, 98.5	63/73 (86.3)	76.2, 93.2
3-6 YOA	69/70 (98.6)	92.3, 100.0	69/70 (98.6)	92.3, 100.0	67/68 (98.5)	92.1, 100.0	66/68 (97.1)	89.8, 99.6	65/68 (95.6)	87.6, 99.1
7-15 YOA	212/213 (99.5)	97.4, 100.0	208/213 (97.7)	94.6, 99.2	206/212 (97.2)	93.9, 99.0	194/211 (91.9)	87.4, 95.2	172/210 (81.9)	76.0, 86.9
12-15 YOA	78/79 (98.7)	93.1, 100.0	78/79 (98.7)	93.1, 100.0	76/78 (97.4)	91.0, 99.7	68/77 (88.3)	79.0, 94.5	57/76 (75.0)	63.7, 84.2

Source: Original BLA, CSR for Study 700401 pages 176 and 178, NT according to Adner et al., 2001
*Timing after 3rd vaccination in Study 209
[a] For subjects who received a booster and for drop outs this analysis is based on the extrapolated result
YOA = years of age

Table 46. Geometric Mean Antibody Response After the Third Vaccination Received During Study 209, Intent-to-Treat Dataset, Study 700401

	1 Month			24 Months			34 Months			46 Months[a]			58 Months[a]		
Age	**N**	**GM**	**95% CI**	**N**	**GM**	**95% CI**	**N**	**GM**	**95% CI**	**N**	**GM**	**95% CI**	**N**	**GM**	**95% CI**
1-2 YOA	75	567.6	526.6, 611.8	75	153.5	124.9, 188.7	73	166.3	134.9, 204.9	73	74.1	58.1, 94.5	73	57.1	41.2, 79.1
3-6 YOA	70	461.5	386.4, 549.8	70	204.0	165.1, 252.1	68	188.4	150.2, 236.3	68	95.1	76.5, 118.2	68	81.9	62.5, 107.3
7-15 YOA	213	303.1	267.5, 343.3	213	110.8	95.3, 128.7	212	97.1	83.2, 113.3	211	50.6	43.0, 59.6	210	36.4	29.5, 44.9
12-15 YOA	79	227.8	182.0, 285.1	79	94.0	73.2, 120.7	78	74.6	57.1, 97.5	77	42.5	32.8, 56.9	76	29.3	20.3, 42.1

Source: Original BLA, CSR for Study 700401 pages 176 and 178
[a] For subjects who received a booster and for drop outs this analysis is based on the extrapolated result.
Geometric Mean Antibody Measured by NT according to Adner et al.; GM = geometric mean, YOA: years of age

Reviewer's Comments: The Intent-to-treat dataset for analysis of seropersistence included subjects who fulfilled all inclusion and exclusion criteria and had available ELISA and/or NT results at 24, 34, 46 and/or 58 months after the third vaccination in Study 209. The data in Table 45 and Table 46 above demonstrate that a three-dose series of FSME-IMMUN is immunogenic in children and adolescents 1to <16 years of age and provides evidence of persistence of TBEV antibodies in the majority of subjects through 58 months after the third dose of the primary series.

A total of 358 subjects from Study 209 were enrolled in the study. All younger subjects (N=156) received the FSME-IMMUN 0.25 mL as the booster, but a total of 49 subjects (who were 12 to <16 years of age in Study 209) received FSME-IMMUN 0.5 mL as a booster. The timing of the booster dose administration was as follows:

- After 3 years (Month 36), a total of 175 subjects received the booster vaccination; 138 children were boosted with the 0.25 mL and 37 adolescents with the 0.5 mL FSME-IMMUN vaccine dose.
    - GMTs determined by NT rose for the 1-2 years age group from 69.3 before the booster to 564.9 after the booster; for the 3-6 years age group from 91.2 to 349.1; for the 7-15 years age group who received the 0.25 mL booster dose from 58.9 to 330.3; and for the 7-15 years age group who received the 0.5 mL booster dose from 40.6 to 332.8. A booster after 3 years led to an increase in TBEV antibody concentrations as determined by ELISA up to GMCs of 8686.5, 5867.5, 3805.0, and 2737.6 VIEU/mL, for the four ascending age groups, respectively. For these subjects, the GMFI in NT were 8.2, 3.8, 5.7 and the GMs of fold increase in TBEV IgG concentrations determined by ELISA were 13.5, 8.2, 7.7f, and 8.2, for the four ascending age groups, respectively.
- After 4 years (Month 48), altogether 29 subjects received the booster, with 18 receiving the dose (0.25 mL) for children and 11 the dose (0.5 mL) for adults.
    - GMTs determined by NT rose for the 1-2 years age group from 56.7 before the booster to 570.2 after the booster; for the 3-6 years age group from 71.3 to 522.7; for the 7-15 years age group who received the 0.25 mL booster dose from 50.2 to 553.9; and for the 7-15 years age group who received the 0.5 mL booster dose from 50.0 to 489.6. A booster after 4 years increased TBEV antibody concentrations determined by ELISA up to GMCs of 7636.3, 5373.8, 8400.8 and 5483.4 VIEU/mL, for the respective ascending age groups. For these subjects, the GMs of fold increase for NT were 10.1, 7.3, 11.0, and 9.8; GMs of fold increase for ELISA were 9.1, 7.1, 12.6, and 7.0 for the four ascending age groups.
- After 5 years (Month 60), 1 subject received 0.5 mL FSME-IMMUN booster vaccination.
    - At 5 years after the primary vaccination series in Study 209, one 14-year-old (in Study 209) female subject (b) (6) received the booster vaccination at Month 60. Her NT before the booster was 7.0, and it was 80 after booster (21 to 35 days after the 60 months booster).

Temperature and local and systemic events were monitored and recorded for 4 days after the booster vaccination. Diaries were returned 21 to 35 days after the booster vaccination and blood was drawn for analysis of the booster response. Safety assessments in this study included fever, overall local reactions and overall systemic events reported after the booster vaccination received. AE term, such as each local

reaction term or each systemic event term were not included in the dataset. For assessment of fever (≥38.0°C), subjects and/or their parents / legal guardians were instructed to measure body temperature in the evening of the vaccination day, the following morning and in the evening for 3 days after the booster (altogether 4 days).

No fever episode was reported for any booster vaccination. The majority of subjects (82.3%, 82.8%, and 100%) reported no local reactions after any booster vaccination after 3, 4, or 5 years, respectively. All local reactions were of mild or moderate intensity, except for 1 subject (male, 10 years old in Study 209) who had swelling and induration of the injection site both rated as severe on the day of receiving 0.25 mL of FSME-IMMUN after 3 years. Both local reactions were resolved after 1 and 3 days, respectively. Data on local reactions were missing from 1 subject (0.25 mL) after the 3-year booster. Of the queried symptoms of local reactions, injection site pain (the preferred term for both injection site pain and injection site tenderness) was the most frequently reported symptom in the two FSME-IMMUN dose groups. After the 3-year booster, injection site pain was reported by 19 (13.8%) and 6 (16.2%) subjects and tenderness by 14 (10.1%) and 1 (2.7%) subjects after the FSME-IMMUN 0.25 mL or 0.5 mL dose, respectively. The 4-year booster vaccination resulted in injection site pain in 4 (22.2%) and 1 (9.1%) subjects and in injection site tenderness in 2 (11.1%) and 0 (0%) subjects after the FSME-IMMUN 0.25 mL or 0.5 mL dose, respectively. Among the other queried symptoms of local reactions, swelling and induration were reported by 3 (2.2%) subjects each and redness (erythema) by 1 (0.7%) subject after the 0.25 mL booster dose at 3 years. Most of the subjects (94.9%, 89.7%, and 100%) had no systemic reactions after any booster vaccination, at 3-years, 4-years, and 5-years, respectively. All systemic reactions were of mild to moderate intensity.

No related SAE was reported in this study. Two SAEs were reported in two subjects; the investigator considered both SAEs to be unrelated to the investigational product:

- For Subject (b) (6), the SAE 'headache and pain' was reported. The subject came to the hospital for an ambulatory visit for a right thoracic contusion and distortion of the cervical spine following an unspecified accident on April 11, 2006, the day before her booster vaccination. The subject received the booster vaccination and later the day, she was hospitalized due to headache and right-side pain.
- Subject (b) (6) had an accidental fall, 24 days after the booster vaccination.

The results of this follow-up study demonstrated that a three-dose primary vaccination regimen with FSME-IMMUN 0.25 mL given to children and adolescents aged 1 to <16 years was immunogenic and resulted in a long-term seropersistence of TBEV antibodies in the majority of subjects as measured by NT and ELISA that exceeded the proposed 3-year interval. A booster after 3, 4, or 5 years with FSME-IMMUN 0.25 mL or 0.5 mL (based on subject age) induced a substantial immune response, irrespective of age of the subject or booster interval. The reactogenicity of the first booster dose was limited to mild reactions.

9.2.4.6 Study 700802 (Pfizer Study B9371021): Follow-up to Study 700401, Antibody Persistence and Booster Response

Study 700802 (Pfizer Study B9371021) was a follow-up study in subjects who had received all 3 vaccinations in Study 209 and a first booster dose in Study 700401. The

study was designed to assess seropersistence of TBEV antibodies through 10 years after the first booster, and to evaluate the response to a second booster vaccination given in the study. Blood samples were taken at approximately 1 month and on a yearly basis from 3 to 10 years after the first booster vaccination administered in Study 700401. Subjects with NT titer ≤20 and/or ELISA value ≤126 VIEU/mL were invited to receive the second booster vaccination at either 40, 48, 60, 72, 84, 96, 108, or 120 months after the first booster. Immune responses were evaluated 21 to 35 days after the booster vaccination. Subjects who did not receive the booster vaccination continued in the study to have seropersistence evaluated up to the final time point. In the context of this study, safety measurements (local reactions, systemic events, and adverse events) were assessed after administration of the second booster vaccination. Seropositivity was defined as ELISA (IMMUNOZYM FSME IgG) titers >126 VIE U/mL or NT (Adner et al., 2001) titers ≥10.

Approximately 1 month after the first booster in Study 700401, 100% of subjects evaluable for this follow-up study were seropositive by NT and 98.8% were seropositive by ELISA. Seropositivity of TBEV antibodies remained at or above 96.6% for all age groups through 5 years as measured by NT and at or above 92.9% for all age groups as measured by ELISA. By 10 years, seropositivity rates were 86.2% (1-2 years), 92.0% (3-6 years), 93.4% (7-11 years), 91.1% (7-15 years), and 87.5% (12-15 years). Seropositivity rates as measured by ELISA were comparable to those of NT. GMTs declined over time from 380.7 approximately one month after the first booster in this study to 53.9 by 10 years after the first booster, all pediatric ages combined. A logistic regression showed no demographic factor influenced the chances of remaining seropositive after the first booster.

Twenty-six (26) of 179 subjects (14.5%) received a second booster vaccination in this study due to NT titers ≤20 or ELISA <126 VIEU/mL. Among the 26 subjects who received the booster, 10 subjects (5.8%) were 1 to <16 years of age and 16 subjects (9.3%) were ≥16 years at the time of the boost and received FSME-IMMUN 0.5 mL. Subjects who received the second booster, even after a prolonged interval, showed a pronounced increase in antibody levels demonstrating a robust booster response.

One subject reported an AE of injection site tenderness following second booster vaccination with duration of one day. No deaths occurred and no vaccine related SAEs were reported in this study.

<u>Reviewer's Comments:</u> Seropositivity rates by NT at 5 to 10 years after the first booster dose ranged from 92% to 82%, but GMTs decreased over time. Vaccine breakthrough cases have not been reported in this study. Only a small percentage of children and teenagers received a second booster in the context of this clinical study based on immunological criteria. Therefore, the data presented above, does not provide enough information to draw conclusions regarding the safety and the need for (b) (4) *in children.*

9.2.4.7 Study 700801: Single-Blind, Randomized, Phase IIIB Study in Children 1-11 Years to Investigate the Immunogenicity, Safety and Interchangeability of FSME-IMMUN and Encepur

Study 700801 was a single-blind, randomized study that assessed the immunogenicity, safety, and interchangeability of two different TBE vaccines in children aged 1 to <12 years. Children were stratified by age as follows:1-2 years of age, 3-6 years and 7-11 years. Subjects were to receive 3 vaccinations according to the following vaccination schedule: the first and second vaccinations were administered 28 (±3) days apart, with the third vaccination given 360 (±14) days after the first. Subjects were randomized 1:1 to receive either FSME-IMMUN 0.25 mL or the pediatric formulation of a non-US-licensed TBE vaccine (Encepur Children). A total of 302 subjects were vaccinated and evaluated for safety (150 received FSME-IMMUN and 152 received the comparator for the two initial vaccinations). Blood samples were drawn for ELISA (IMMUNOZYM ELISA) and NT analysis (performed according to Adner et al.) 28 (±3) days after the second vaccination (i.e., Day 56); 180 (±14) days after the first vaccination (Day 180), and 28 (±3) days after the third vaccination (Day 388).

The primary immunogenicity endpoint of this study was the seropositivity rate as determined by NT 28 days after the second vaccination (Day 56). At this time point, 100% of subjects who received two vaccinations with FSME-IMMUN 0.25 mL were seropositive as determined by NT, regardless of age. Seropositivity rates after the third vaccination was also included as a secondary endpoint.

Reviewer's Comments: As measured, both by NT and by ELISA, seropositivity rates 28 days after the third TBE vaccination with FSME-IMMUN 0.25 mL (Day 388) were 100% in all age strata.

Table 47. Number (%) of Subjects With Seropositive Titer (≥1:10) as Determined by NT at Different Timepoints After Vaccination, by Age Group, Study 700801, Modified Intent-To-Treat Dataset

Age	Day 0 n/N (%) 95% CI	Day 56 n/N (%) 95% CI	Day 180 n/N (%) 95% CI	Day 388 n/N (%) 95% CI
1-2 YOA	0/49 (0%) 0, 7.3%	49/49 (100%) 92.7, 100%	47/49 (95.9%) 86, 99.5%	48/48 (100%) 92.6, 100%
3-6 YOA	0/41 (0%) 0, 8.6%	41/41 (100%) 91.4, 100%	40/41 (97.6%) 87.1, 99.9%	41/41 (100%) 91.4, 100%
7-11 YOA	0/39 (0%) 0, 9%	39/39 (100%) 91, 100%	36/39 (92.3%) 79.1, 98.4%	39/39 (100%) 91, 100%
Total	0/129 (0%) 0, 2.8%	129/129 (100%) 97.2, 100%	123/129 (95.3%) 90.2, 98.3%	128/128 (100%) 97.2, 100%

Source: pages 110 and 112 of the Summary of Clinical Efficacy
Day 56: after first vaccine (28 days after second vaccine)
Day 180 after first vaccine
Day 388, 28 days after third vaccine)

Table 48. Geometric Mean Antibody Response Measured by NT at Different Timepoints After Vaccination, by Age Group, Study 700801, Modified Intent-To-Treat Dataset

Age	Day 0 GMT 95% CI	Day 56 GMT 95% CI	Day 180 GMT 95% CI	Day 388 GMT 95% CI
1-2 YOA	5.1 5, 5.2	247.2 186.4, 327.9	50.9 39.5, 65.6	593.3 547.8, 642.5
3-6 YOA	5.0 5, 5.1	267.9 202.1, 355.2	34.7 27.5, 43.8	552 497, 613.1
7-11 YOA	5.0 5.0, 5.1	197.2 139.7, 278.5	33.5 26.3, 42.6	464.8 381.3, 566.6
Total	5.0 5.0, 5.1	236.8 199.6, 281.0	39.7 34.4, 45.8	538.2 499.2, 580.2

Source: pages 110 and 112 of the Summary of Clinical Efficacy
Day 56: after first vaccine (28 days after second vaccine)
Day 180 after first vaccine
Day 388, 28 days after third vaccine)

Safety

Safety was assessed by body temperature, local reactions, and systemic symptoms recorded for 6 days after each vaccination. Certain symptoms of local (injection site swelling, induration, erythema, pain, tenderness, ecchymosis and hematoma) and systemic reactions (headache, nausea, vomiting, muscle pain, joint pain, swelling of the lymph nodes, loss of appetite, change in sleeping behavior, restlessness in children aged 1-2 years, malaise and fatigue in subjects aged 3-11 years, and fever with onset later than Day 6 after vaccination) were specifically queried in the subject diary. Other adverse events were monitored throughout the study. Fever rates were comparable between the FSME-IMMUN and the comparator group. After the first vaccination, fever rates were higher among subjects 1-2 years of age (18.0% in both vaccine groups) than in the older two age groups (2.0% to 5.9%). Most reports of fever were mild, with moderate fever reported for only four subjects, with no reports of severe fever. After dose 2, among subjects 1-2 years of age, fever rates were lower than they had been after the first vaccination (4.0% after FSME-IMMUN and 6.0% after the vaccine comparator); in the other two age groups, fever rates after dose 2 were similar to those observed for dose 1. After dose 3, when all subjects received FSME-IMMUN, fever was reported for 3.0% of subjects 1-2 years of age, 4.0% of subjects 3-6 years of age, and for no subjects 7-11 years of age. All reports of fever after dose 2 and dose 3 were mild or moderate, and no severe fevers were reported.

A summary of the frequencies of fever, local and systemic reactions in the different age strata within 7 days after the first vaccination is shown in Table 49 below for the FSME-IMMUN group. These rates were similar to what was observed in the comparator group.

Table 49.Number (%) of Subjects With Fever, Local and Systemic Adverse Reactions After the First Vaccination With FSME-IMMUN, by Age Group, Study 700801

Age Reaction Type	Any Reaction n/N (%)	Mild n (%)	Moderate n (%)	Severe n (%)
1-2 YOA				
Fever*	9/50 (18)	9 (18)	0 (0)	0 (0)
3-6 YOA				
Fever*	2/51 (3.9)	1 (2)	1 (2)	0 (0)

Age Reaction Type	Any Reaction n/N (%)	Mild n (%)	Moderate n (%)	Severe n (%)
7-11 YOA Fever*	1/49 (2)	1 (2)	1 (2)	0 (0)
1-2 YOA Local reactions	3/50 (6)	3 (6)	1 (2)	0 (0)
3-6 YOA Local reactions	5/51 (9.8)	4 (7.8)	0 (0)	0 (0)
7-11 YOA Local reactions	11/49 (22.4)	11 (22.4)	0 (0)	0 (0)
1-2 YOA Systemic reactions	5/50 (10)	5 (10)	0 (0)	0 (0)
3-6 YOA Systemic reactions	3/51 (5.9)	3 (5.9)	0 (0)	0 (0)
7-11 YOA Systemic reactions	6/49 (12.2)	5 (10.2)	1 (2)	0 (0)

Source: Original BLA, CSR for Study 700801 pages 118-121 and Tables 36, 37 and 38 Summary of Clinical Safety, pages 63-65

* Fever was rated according to CTC, Version 3.0, December 12, 2003 as follows: mild (38-39ºC); moderate (39.1-40ºC) and severe (greater than 40ºC)

YOA = years of Age.

For the FSME-IMMUN group, an SAE was reported for one subject during the active portion of Study 700801 (laryngitis in a 2-year-old female, 23 days after the first vaccination) and six between 28 days after the second vaccination and before the third vaccination (the SAEs diagnoses were hypospadias, ingestion of a foreign metal particle which stopped in stomach, adenoid hypertrophy, otitis media chronic, concussion and acquired phimosis). There were 10 SAEs experienced by subjects who received the TBE vaccine comparator as their two initial vaccinations. No SAEs were reported after the third vaccination.

None of the SAEs reported during the study were considered related to study vaccine.

Reviewer's Comments: Based on the description of the SAEs, we agree that they were probably not related to the use of the investigational product.

Real World Evidence

FSME-IMMUN has been in use for decades in Europe. Due to various dosing regimens and country-specific vaccination schedules, it is not possible to determine with certainty the number of individuals who have received FSME-IMMUN vaccine, so estimated worldwide unit distribution has been considered as an indicator of patient exposure. The cumulative worldwide unit distribution for FSME-IMMUN vaccine from launch through January 31, 2020 is estimated to be (b) (4) doses, of which approximately 30% is for the pediatric formulation of FSME-IMMUN.

Reviewer's Comments: Although there is no information regarding race for the clinical studies, there is postmarketing experience with the use of the vaccine in Europe across multiple ethnic groups with no identification of any safety signal or difference in vaccine effectiveness among people from different races.

Vaccination coverage in most endemic countries is too low to allow firm conclusions concerning its impact on TBE morbidity. Recommendations for TBE vaccination vary in

endemic countries. However, Austria has a national vaccination program that recommends vaccination for all individuals and evidence for the impact of mass vaccination has been documented in Austria (Heinz et al. 2007; Heinz et al. 2013; European Medicines Agency 2018; Kunze and Haditsch 2019). In the past two to three decades, the decrease in TBE incidence in Austria is correlated with vaccination rates. According to published data from 2000 to 2011 in Austria (population of about 8 million), an estimate of 4,000 cases of TBE were prevented by vaccination (Heinz et al. 2013).

Reviewer's Comments: Published data on TBE vaccine effectiveness were available from three sources: Kunz 2003, Heinz et. al., 2007 and Heinz et al, 2013. Because the current vaccine formulation has been used since 2001, the most relevant of those studies are Heinz et. al., 2007, and Heinz et. al., 2013.

In Austria, FSME-IMMUN has been in use since 1976, and another non-US-licensed TBE vaccine was introduced in 1999. Baxter was the only distributor of a TBE vaccine until the year of 2000.The field effectiveness studies that support FSME-IMMUN vaccine effectiveness do not differentiate between the two vaccines used in Austria after 2000. However, the publications have reported and Pfizer's market shares have confirmed that approximately 90% of the TBE vaccinations administered in Austria during the study period were FSME-IMMUN. The field effectiveness studies demonstrated high vaccine effectiveness among regularly vaccinated individuals (above 90%) despite potential source of bias.

Reviewer's Comments: The field effectiveness data reported was based on reporting in Austria and the Czech Republic of laboratory-confirmed, hospitalized, TBE cases with neurological symptoms, analyzed by age and TBE vaccination status for the period of 2000 to 2011). There are no data to show the impact of vaccination on TBE regardless of severity or whether vaccination can attenuate disease severity. Field efficacy studies demonstrated vaccine effectiveness for individuals vaccinated according to the licensed schedule (Heinz et al. 2007; Heinz et al. 2015; Kunze and Haditsch 2019). For a detailed discussion of the field effectiveness studies submitted by the Applicant please refer to the Real World Evidence BLA Memorandum.

10. Conclusions

No randomized, clinical disease efficacy endpoints have been performed to demonstrate the efficacy of FSME-IMMUN. Such trials would be infeasible in non-endemic areas; given FSME-IMMUN's public health record with demonstration of vaccine effectiveness based on field studies, execution of randomized placebo-controlled trials would now be considered unethical in TBEV-endemic areas. In 2011, the WHO published a position paper on TBE vaccination. The WHO recommends vaccination of all age groups in areas of high pre-vaccination disease incidence, defined as an incidence of 5 or more cases per 100,000 population per year. In lower incidence areas, the WHO recommends that TBE vaccination should be confined to populations with a particular risk of exposure. The observational studies of FSME-IMMUN over the past 30 years since the vaccine was first introduced, have estimated consistently high levels of effectiveness, generally greater than 95%, after three doses. Use of TBE vaccines in Austria, where FSME-IMMUN has been the predominantly used vaccine, has been associated with control of TBE.

The ability to rely on NT levels as a marker of seropositivity to determine dosing schedule is derived from an understanding of the TBEV antigens along with an understanding of the importance of the E glycoprotein as a dominant protective antigen. Antibody to the E glycoprotein has been clearly correlated with neutralization of the virus in subjects naïve to other potentially cross-reactive flaviviruses. In clinical trials, reliably high seropositivity levels are seen based both on the E glycoprotein ELISA and virus neutralization. The immunogenicity data together with the effectiveness estimates from field effectiveness studies submitted to the BLA demonstrate the effectiveness of FSME-IMMUN.

The clinical safety database along with postmarketing experience in Europe is supportive for use of FSME-IMMUN in both the adult and the pediatric population. No safety signals were identified with the use of the vaccine. As discussed in our review, there are safety and immunogenicity data from clinical studies submitted in this application to support (b) (4) if continued exposure to TBEV is anticipated. However, data are insufficient to provide (b) (4) and as noted by WHO, there are significant knowledge gaps that exist regarding (b) (4) .

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

Table 50. Risk-Benefit Considerations of Vaccination With FSME-IMMUN in Individuals ≥1 Year of Age

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Although TBE is asymptomatic in most cases, it can also cause a symptomatic biphasic disease that may progress with neurologic complications and cause death. • The case fatality rate from infection with TBEV-EU is between 1% to 2%; however, mortality rates of up to 35% have been reported for people infected with the Far Eastern subtype. • TBE is associated with a high burden of disease and may have disabling long-term central nervous sequelae including neuropsychiatric and cognitive complaints characteristic of the postencephalitic syndrome.	• TBE can be life threatening and may result in long-term neurologic sequelae
Unmet Medical Need	• No US-licensed vaccine to prevent TBE or antiviral treatment. Clinical treatment of the disease is mainly supportive. • People working or travelling outdoors in warm weather in TBEV-endemic areas are at highest risk for TBE. This group includes many thousands of active US military personnel and their families.	• There is a need for a US-licensed vaccine that can be used in people at risk of contracting TBEV before they travel to TBEV-endemic areas and engage in outdoor warm weather activities that put them at risk of tick-transmitted diseases.
Clinical Benefit	• The immunogenicity and effectiveness of FSME-IMMUN has been demonstrated in both clinical studies and observational field studies. • Seroconversion rates after the third vaccination as determined by ELISA were similar in Study 202 (100%), Study 213 (98.8%), Study 650501 (100%) and slightly lower in Study 690601 (97.6%) in a total of 883 subjects treated in these studies. • The presence of neutralizing antibodies to the TBEV (e.g., an NT titer of ≥10) is commonly considered to be a marker of protection (WHO 2011b). • Seroconversion rates in subjects 16-65 years of age after the third vaccination as determined by NT was 99.3% in Study 213, 100% in Study 690501 and 99.3% in Study 690601 in a total of 755 subjects treated in these studies. • Seroconversion rates after the third vaccination as determined by NT in children and adolescents (1 to <16 years of age) was close to 100%. • Follow-up studies show high levels of antibody titers against TBEV after the primary series for at least 3 years after the primary series and an anamnestic response to the booster dose. • FSME-IMMUN has been in use in Europe for decades and no safety signal has been identified. TBE vaccine effectiveness for preventing hospitalized TBE was estimated to be above 95% following the recommended vaccine schedule in field effectiveness studies conducted in Austria. Market shares analysis for the years that vaccine effectiveness was quantified shows that FSME-IMMUN was the main vaccine used in Austria during this period.	• Seropositivity (defined as NT titers ≥1:10 and ELISA >126 VIE U/ml) close to 100% was noted in individuals one month after they received the third dose. • After the primary series approximately 90% of subjects had NT levels ≥10 for 3 years. • The first booster dose, three years after the primary series, led to an anamnestic response. However, it is not clear when (b) (4) . • The clinical benefit of FSME-IMMUN was demonstrated with high vaccine effectiveness and safety based on the use of the vaccine during decades in Austria.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The primary risks of vaccination with FSME-IMMUN are mild injection site pain and tenderness. • Fever rates in pediatric studies were highest among subjects 1-2 years of age after the first vaccination (approximately 35%) but most cases were mild in severity. • The risk profile of the FSME-IMMUN booster dose is favorable compared to primary immunization. However, there are limited data to guide the need for and timing of (b) (4) . • The safety and effectiveness of FSME-IMMUN have not been established in individuals living in TBEV non-endemic areas who travel to TBEV-endemic areas. • There are limited data on effectiveness of the vaccine among persons older than 60 years of age. • As the immunogenicity results from clinical studies enrolled TBEV-seronegative subjects, there are insufficient data in seropositive subjects to inform the safety and immunogenicity of the vaccine in this population. • Data regarding the use of FSME-IMMUN in flavivirus seropositive individuals were not included in the licensure application. • Data regarding the safety and reactogenicity of the vaccine when co-administered with other vaccines were not included in the licensure application. • There are insufficient data on the use of the vaccine in immunocompromised subjects, pregnant or lactating women. • Information regarding race and ethnicity was not collected in the clinical studies submitted to this BLA. All submitted studies in the clinical developmental program were completed in 5 countries in Europe (Austria, Belgium, Czech Republic, Germany, and Poland), so there is a high probability that the majority of subjects were White. However, there is postmarketing experience with the use of the vaccine in Europe across multiple ethnic groups with no identification of any safety signal or difference in vaccine effectiveness among people from different races. • Data regarding the use of the vaccine in patients suffering from autoimmune disease or who use chronic treatment that could be expected to influence immunological functions are missing. These subjects were excluded from clinical trial participation. • FSME-IMMUN contains 0.5 mg of albumin, a derivative of human blood. Based on effective donor screening, and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmissions of viral diseases or CJD have ever been identified for human albumin. • Hypersensitivity may occur to the vaccine active substance, excipients or other production residues. • Vaccination with FSME-IMMUN may not protect all individuals, it is recommended to continue personal protection measures against tick bites after vaccination.	• The totality of the data indicates that the risks of vaccination with FSME-IMMUN are minor, including risks associated with (b) (4)
Risk Management	• Biological products may induce hypersensitivity reactions. FSME-IMMUN is contraindicated in individuals with severe allergic reaction (e.g., anaphylaxis) to any component of FSME-IMMUN or who had severe allergic reaction after a previous dose of FSME-IMMUN. • The proposed pharmacovigilance plan includes systematic collection and regular review of adverse events (AE) reports using standard operating procedures for pharmacovigilance.	• Planned routine pharmacovigilance following licensure of FSME-IMMUN is adequate to manage expected risks.

11.2 Risk-Benefit Summary and Assessment

Overall, the benefit-risk assessment of FSME-IMMUN is favorable. Although much of the data submitted in support of the safety and effectiveness of FSME-IMMUN could not be independently verified, these data, together with the existing postmarketing safety data from the use of the vaccine for more than two decades in Europe and the field effectiveness data over 10 years of use in Austria, demonstrate that the benefits of FSME-IMMUN vaccination outweigh the risks.

11.3 Discussion of Regulatory Options

The Applicant has requested and the data support traditional approval for FSME-IMMUN for individuals ≥1 year of age.

11.4 Recommendations on Regulatory Actions

The clinical reviewer recommends approval of FSME-IMMUN for the prevention of TBE in individuals ≥1 year of age at risk of exposure to TBEV.

11.5 Labeling Review and Recommendations

The review team negotiated revisions to the Package Insert with the Applicant that are briefly described here:

- The Applicant (b) (4) in the Package Insert: in (b) (4) However, there is not enough vaccine effectiveness data to support a (b) (4) . Therefore, the dosing schedule for the adult population is presented in the PI as a three-dose regimen with the second dose being administered from 14 days to 3 months after the first dose and the third dose 5 to 12 months after the first vaccination and reference to (b) (4)
- The dosing schedule for individuals 1 through 15 years of age in the package insert now consists of three doses similar to the dose schedule in adult population but the recommended interval between the first and second dose is 1 to 3 months. (b) (4)
- The first booster dose may be considered at least three years after the conclusion of the primary series if continued exposure to TBEV is anticipated. However, the information regarding the use of (b) (4)
- Section 6 was revised to incorporate safety data from the representative Studies 208/213 and 209.
- Reference to published literature in the package insert was limited to the references for Section 14.2 Real World Evidence discussion.

- Immunogenicity data were revised to remove any immunogenicity data post dose 2 and use post dose 3 from one pediatric and two adult studies instead of pooled immunogenicity data.
- The section regarding (b) (4)

11.6 Recommendations on Postmarketing Actions

Pfizer proposes routine postmarketing surveillance. Please refer to the Office of Biostatistics and Epidemiology review for details regarding postmarketing activities and pharmacovigilance.