Summary Basis for Regulatory Action

Date:	August 13, 2021
From:	Goutam Sen, PhD, Review Committee Chair, OVRR/DVRPA
BLA/NDA STN:	125740/0
Applicant:	Pfizer Ireland Pharmaceuticals (Pfizer Inc. as authorized representative)
Submission Receipt Date:	December 15, 2020
Action Due Date:	August 15, 2021
Proper Name:	Tick-Borne Encephalitis Vaccine
Proprietary Name:	TICOVAC
Indication:	TICOVAC is indicated for active immunization to prevent tick-borne encephalitis in individuals 1 year of age and older.

Recommended Action: The Review Committee recommends approval of the BLA for this product.

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Director, Office of Vaccines Research and Review

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Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (OVRR/DVP) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Tony Wang, PhD; 7/27/2021 Jie He; 7/02/2021 Debra Vause; 7/02/2021 Marie Anderson, PhD; 7/02/2021 Hsiaoling Wang, PhD; 7/02/2021 Simleen Kaur, MS; 7/02/2021 Anil Chowdhury, PhD, MBA; 7/02/2021
Clinical • Clinical (OVRR/DVRPA) • Postmarketing safety epidemiological review (OBE/DE) • Real World Evidence (OBE/ABRA)	Ihid Carneiro Leao, MD, PhD; 07/23/2021 Kerry Welsh, MD, PhD; 6/14/2021 Yun Lu, PhD; 7/12/2021
Statistical • Clinical data (OBE/DB) • Non-clinical data	Ruoxuan Xiang, PhD; 7/23/2021
Non-clinical/Pharmacology/Toxicology • Toxicology (OVRR/DVRPA) • Developmental toxicology (Product Office) • Animal pharmacology	LCDR Andrew O'Carroll, DVM; 6/10/2021
Labeling • Promotional (OCBQ/APLB) • Container/Carton (OVRR/DVRPA) • Package insert (OVRR/DVRPA)	Oluchi Elekwachi, PharmD, MPH; 07/02/2021 Daphne Stewart; 08/02/2021 Joseph Kulinski, PhD; 08/09/2021
Other Review categories not captured above: • Consult (OVRR) • Devices (CDRH/OPEQ/OHTIII/DHTIIIC) • Regulatory project manager (DVRPA/OVRR)	Hector Izurieta, MD, MPH, PhD Sreya Tarafdar, PhD; 07/09/2021 Shawn Shermer Josephine Resnick, PhD Joseph Kulinski, PhD Konstantin Virnik, PhD
Advisory Committee Summary	None

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1. Introduction

On December 15, 2020, Pfizer Ireland Pharmaceuticals, a subsidiary of Pfizer Inc., submitted a biologics license application (BLA) for licensure of an inactivated, whole virus, tick-borne encephalitis vaccine, TICOVAC. The proposed proper name of the vaccine is Tick-Borne Encephalitis Vaccine (whole virus inactivated) and the proposed proprietary name is TICOVAC. The proposed indication is for active immunization to prevent tick-borne encephalitis (TBE) in individuals 1 year of age and older.

TICOVAC is produced from (b) (4) of TBE virus (TBEV) infected chick embryo fibroblast cell cultures. The (b) (4) are inactivated with formaldehyde and virus antigen is purified using a sucrose gradient. TICOVAC (0.5 mL, adult dose) is a sterile suspension containing 2.4 µg of TBEV antigen adsorbed to aluminum hydroxide (0.35 mg $Al(OH)_3$), an adjuvant, and diluted in a phosphate buffer containing human serum albumin (HSA, 0.5 mg). The pediatric formulation for children 1 to <16 years of age (TICOVAC 0.25 mL) is the same as the adult formulation, but the pediatric dose is one half (0.25 mL) of the adult dose and thus, contains half the amount of antigen, adjuvant and other components of the adult dose. The vaccine contains no preservative.

2. Background

TBEV is a flavivirus, transmitted to humans by *Ixodes* tick species and is a significant cause of viral infections of the human central nervous system. TBE can result in permanent and severe neurological sequelae, coma, and even death in both children and adults. As there are no specific treatments available, preventive measures such as the control of tick populations, protection against tick bites (including protective clothing and repellents) or vaccination against TBEV are especially important in areas where TBEV infection is endemic.

TBE occurs mainly in areas corresponding to the distribution of the ixodid tick reservoir, including many parts of central Europe, countries that made up the former Soviet Union, and Asia. TBEV subtypes are closely related genetically and antigenically. There are three subtypes: the European, also called Western subtype (TBEV- Eu) which is prevalent in Continental Europe and the United Kingdom, and the Far Eastern (TBEV-Fe) and Siberian (TBEV- Sib) subtypes which are distributed throughout eastern Europe and Asia, including China and Japan[1]. The clinical outcome may in part depend on the infecting TBEV subtype. The Western European subtype is associated with milder disease, with mortality rates of 0.5% - 2% and severe neurologic sequelae in up to 10% of patients.

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. 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. Infected individuals older than approximately 40 years of age increasingly develop the encephalitic form of the disease. Older patients, especially those older than 60 years of age have higher risk of paralysis and death due to TBE. Paralysis occurs in 30% of patients who enter the acute phase of the illness.

There are currently no US licensed vaccines against TBE. US citizens, such as members of the US military deployed to endemic regions and travelers to those regions who engage in warm weather outdoor activities, are at risk for TBE. In recognition of the expected health benefit that this vaccine would bring to US military personnel and their families, the US Army Medical Research and Material Command has requested that Pfizer consider licensing TICOVAC in the US. 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. FSME-IMMUN has been used across the European Union for more than 40 years. Pfizer acquired FSME-IMMUN from Baxter in 1996 and the marketing authorizations were transferred from Baxter to Pfizer in 2015.

Pfizer is seeking licensure of FSME-IMMUN in the US under the trade name TICOVAC. Two presentations, TICOVAC 0.5 mL (adult dose, for individuals 16 years of age and older) and TICOVAC 0.25 mL (pediatric dose, for ages 1-15 years of age) are proposed. The indication is for active immunization to prevent TBE in individuals 1 year of age and older.

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 threshold of protection has not been defined for TBE vaccines[2] 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 adequately characterized and thus, found to be acceptable to measure immune responses induced. Of note, placebo-controlled immunogenicity data using these assays were submitted in which vaccine recipients demonstrated vaccine-induced immune responses as measured by NT, while placebo recipients had no measurable immune response. In addition, overall field effectiveness of TBE vaccines including FSME-IMMUN used in Austria for all age groups was above 90% for all vaccinated individuals (See Real World Evidence BLA Memorandum). Thus, data from these post-authorization field effectiveness studies provide supportive evidence of the effectiveness of TICOVAC.

This submission includes 11 clinical studies conducted in pediatric subjects from 1 year to <16 years of age, and 10 clinical studies conducted in adults (i.e., persons ≥16 years of age). All studies were conducted from 2001 to 2015 in five European countries. The primary immunogenicity endpoint was either the seroconversion rate or the seropositivity rate after vaccination with FSME-IMMUN. In both the pediatric and adult studies, the safety endpoints were the occurrence of fever, systemic reactions (excluding fever), and local reactions observed after each vaccination, as well as adverse events (AEs) reported throughout the studies. Data from clinical studies of FSME-IMMUN 0.5 mL and FSME-IMMUN 0.25 mL demonstrate that FSME-IMMUN is safe and immunogenic in subjects 16 to 65 years of age and 1 to <16 years of age, respectively. The immunogenicity data as a measure of vaccine effectiveness together with supportive vaccine effectiveness estimates from field studies submitted to the BLA provide "substantial evidence" of effectiveness of TICOVAC (also referred to as FSME-IMMUN) as required under section 351 of the PHS Act.

Regulatory History

Clinical trials evaluating the safety and effectiveness of TICOVAC were not conducted under US IND. In response to Pfizer's request for FDA advice on the adequacy of the available data to support a licensure application, the FDA advised Pfizer to submit a Drug Master File (DMF) (b) (4)

Table 1. **Regulatory Milestones, TICOVAC**

Regulatory Events / Milestones	**Date**
Type-C meeting (CRMTS# 11651)	March 5, 2019
Type V Master File (DMF (b) (4) submission	April 12, 2019
Pre-BLA meeting (Facility)	June 5, 2020
BLA 125740/0 submission	December 15, 2020
BLA filed	February 5, 2021
Priority Review granted	February 5, 2021
Mid-Cycle communication	April 5, 2021
Late-Cycle meeting communication	June 3, 2021
Action Due Date	August 15, 2021

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

The information provided in the BLA for TBE Vaccine (FSME-IMMUN) demonstrates that the manufacturing process is well-controlled with appropriate validations and in-process control testing. Moreover, adequate quality control testing has been conducted and stability data have been accrued with the drug substance and drug product.

Drug Substance (b) (4)

Manufacture

The manufacturing process of FSME-IMMUN DS (b) (4) consists of the following stages: (b) (4)

Control of Materials

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Drug Product Overview

FSME-IMMUN drug product (DP) is a sterile, off-white, homogenous, opalescent suspension for intramuscular injection. FSME-IMMUN DP is prepared from TBEV propagated in CEF cells. The harvested virus suspension is inactivated by treatment with formaldehyde, purified by sucrose gradient centrifugation and adsorbed onto $Al(OH)_3$. Each 0.5 mL adult dose is formulated to contain 2.4 µg TBEV, 0.5 mg human serum albumin (HSA), 0.35 mg $Al(OH)_3$, 3.45 mg of sodium chloride, 0.22 mg of dibasic sodium phosphate, and 0.045 mg of monobasic potassium phosphate. From the manufacturing process, each 0.5 mL also contains formaldehyde (≤5 µg), protamine sulfate (≤0.5 µg), chick protein (b) (4) and trace amounts of CEF host cell DNA, 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. The vaccine contains no preservative (e.g., thiomersal).

FSME-IMMUN DP is filled in sterile, single-use, 1 mL syringe barrels (b) (4) borosilicate glass) with a polystyrene plunger rod, a rubber plunger stopper (latex-free bromobutyl chlorobutyl) and a tip cap (latex-free isoprene bromobutyl rubber).

Manufacture

The manufacturing of DP involves adjuvanting the DS (formaldehyde-inactivated, sucrose gradient purified TBE-virus antigen) with $Al(OH)_3$ in a solution of phosphate buffered saline and HSA. (b) (4) The filled syringes are inspected and stored at 5 ± 3°C until secondary packaging, release, and shipping. The Manufacturing Process consists of the following steps:

(b) (4) Filling → Visual inspection → Labeling and packaging.

The control strategy includes process controls, in-process tests, process validation and release specifications, as well as analytical methods.

Control of Materials

Raw materials: HSA (b) (4) FSME-IMMUN DP. Other than HSA, no other excipients are of human or animal origin. HSA is not licensed in the US; however, it is derived from plasma sourced from the US according to the current plasma sourcing guidelines. CBER informed the applicant that use of non-US licensed HSA in DP of the TBE vaccine is acceptable as plasma was sourced from US donors and it was appropriately tested for HIV, HAV, HBV, HCV, and Parvovirus B19 (B19V).

Adventitious Agents Safety Evaluation for the DP: The applicant provided a risk assessment with respect to the potential presence of adventitious viruses and prions in HSA. In addition to donor selection and plasma donation testing, the overall Reduction Factor during the HSA manufacturing process is greater than (b) (4) for human viral pathogens (HIV, HAV, HBV, HCV, and B19V) and (b) (4) for Prion clearance during the HSA manufacturing process. Based on this risk assessment, the risk of introducing BSE/TSE contamination into the FSME-IMMUN DP during manufacture can be deemed negligible.

Specifications and Methods: The proposed tests, specifications and methods for the release of the DP are presented in Table 3.

Table 3: FSME-IMMUN Final Drug Product Release and Stability Specifications

Quality Attribute	Analytical Procedure	Acceptance Criteria (Release)	Acceptance Criteria (Stability)
Identity	(b) (4)	Identity Confirmed	Not Performed
(b) (4)	(b) (4)		
Sterility	(b) (4)	Sterile	Sterile
Extractable Volume for FSME-IMMUN 0.5 mL	(b) (4)	0.50 (b) (4)	Not Performed
Extractable Volume for FSME-IMMUN 0.25 mL	(b) (4)	0.25 (b) (4)	Not Performed
Visual Inspection (appearance)	(b) (4)	Complies[a]	Complies[a]
Endotoxin	(b) (4)		
(b) (4)			

a. Complies: no extraneous matters, after shaking the vaccine is an off-white, homogenous, opalescent suspension

(b) (4)

c. Release testing is done on Final (b) (4) Vaccine

Extractables and Leachables: No risk identified.

Stability of the DP and Proposed Shelf-life: The applicant provided a completed stability study by (b) (4) facility of (b) (4) lots of FSME-IMMUN 0.5 mL (b) (4) and (b) (4) lots of FSME-IMMUN 0.25 mL (b) (4) Tip Cap) at 5°C ± 3°C over a period of (b) (4) months with testing at 0, 3, 6, 9, 12, 18, 24, 30 (b) (4)-month time-points using tests and acceptance criteria shown in Table 2. Additional stability data from Pfizer (b) (4) facility is available. Up to (b) (4) months data is provided for (b) (4) and 30 months data is provided for the other (b) (4) process validation lots (b) (4) CBER concluded that the stability data provided support the proposed 30-month shelf-life for the 0.5 mL and 0.25 mL pre-filled syringe presentations of TICOVAC when stored at 5 ± 3 °C.

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the TICOVAC drug substance and drug product were found to be adequate for their intended use.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of TICOVAC are

listed in the Table 4 below. The activities performed, and inspectional histories are noted in the table, and are further described in the paragraphs that follow.

Table 4: Manufacturing Facilities for TICOVAC (Tick-Borne Encephalitis Vaccine)

Name/address	FEI number	DUNS number	Inspection/ Waiver	Results/ Justification
Pfizer (b) (4) *Drug Substance* Manufacturing, release and stability testing *Drug Product* Release and stability testing	(b) (4)		Inspection (Records Review)	Manufacturing site record review under Section 704(a)(4) in lieu of a pre-license inspection (b) (4)
Pfizer (b) (4) *Drug Product* Manufacturing (formulation, filling, primary and secondary packaging and labeling) and release testing	(b) (4)		Waiver	CDER (b) (4) NAI
(b) (4) *Drug Product* Release testing	(b) (4)		Waiver	ORA (b) (4) NAI
(b) (4) *Drug Product* Release testing	(b) (4)		Waiver	ORA (b) (4) VAI

Abbreviations: CDER, Center for Drug Evaluation and Research; ORA, Office of Regulatory Affairs

Due to the COVID-19 public health emergency, CBER used its authority under Section 704(a)(4) of the FD&C Act and requested manufacturing records from Pfizer (b) (4) The records review was conducted in lieu of performing an on-site inspection. All documents were reviewed and were acceptable. In addition, inspections conducted by the (b) (4) were reviewed and the corrective actions were deemed acceptable.

CDER conducted a pre-approval inspection of Pfizer (b) (4) for fill finish of small volume parenteral drugs. At the end of the inspection no Form 483 was issued. The inspection was classified as No Action Indicated (NAI).

ORA conducted a surveillance inspection of (b) (4) . At the end of the inspection no Form 483 was issued. The inspection was classified as NAI.

CDER conducted a surveillance inspection of (b) (4) The inspection was classified as Voluntary Action Indicated (VAI). All inspectional 483 observations were resolved.

e. Container/Closure System

The drug product is filled into 1 mL (b) (4) borosilicate glass syringe barrels (b) (4) with (b) (4) latex-free styrene-butadiene-bromobutyl siliconized rubber plunger stopper (b) (4) ; Polystyrene plunger rod (b) (4) , and (b) (4) latex-free bromobutyl and synthetic polyisoprene siliconized rubber tip cap (b) (4) Pfizer (b) (4) conducted the container closure integrity testing at the (b) (4) , employing the (b) (4) test methods; all acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product does not significantly alter the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

TICOVAC was evaluated in a single-dose toxicity study and 2 local tolerance studies using the intramuscular, (b) (4) routes of administration. These studies contributed to the nonclinical risk assessment for this product. No clinically significant toxicological findings were found which would preclude the use of this vaccine in its intended human populations at the doses of either 0.5 mL or 0.25 mL. Minimal nonclinical safety data was included in this submission due to the fact that this vaccine was developed nearly 40 years ago and presumably, such studies were not routinely required at that time. The limited nonclinical data provided in this submission provides a degree of assurance of safety in cases where this vaccine is administered via the non-licensed (b) (4) routes of administration. Of note, a favorable benefit/risk ratio of this product is supported by decades of use of this vaccine across multiple countries with an overall acceptable clinical safety profile. No developmental toxicology studies were conducted, and available data on the use of the vaccine in pregnant and lactating women are insufficient to inform vaccine-associated risks in pregnant and lactating women.

5. Clinical Pharmacology

Following administration, TICOVAC induces TBEV neutralizing antibodies to the envelope glycoprotein, a protein expressed on the virion surface, which are believed to confer protection. However, a protective antibody titer has not been defined.

6. Clinical/Statistical

a. Clinical Program

Pfizer has submitted 21 non-IND clinical studies in support of the safety and immunogenicity of FSME-IMMUN in pediatric and adult populations. FSME-IMMUN immunogenicity was assessed by measuring vaccine-induced neutralization antibody titers.

Pfizer is seeking US licensure of a three-dose regimen of TICOVAC. The dose for individuals 1 to < 16 years of age is 0.25 mL and that for individuals 16 years and older is 0.5 mL. In individuals 1 through < 16 years of age, the second dose should be administered 1 to 3 months following the first dose. In individuals 16 years of age and older, the second dose should be administered 14 days to 3 months following the first dose. This is supported by data from clinical trials in which adults received the second dose 12 - 35 days after the first dose. The clinical trials did not evaluate second dose administered up to 3 months after the first dose, but the 3 months dosing interval between the first two doses was used for decades in Europe, i.e., the second dose was administered within 14 days to 3 months after the first dose. The third dose should be given 5 to 12 months after the second vaccination in both the pediatric and adult populations. A booster dose may be given to children and adults 3 years after the third dose if ongoing exposure or re-exposure to TBEV is expected. The vaccine should be given by intramuscular injection into the upper arm (deltoid muscle).

Studies in Children and Adolescents (1 to <16 Years of Age)

Ten clinical studies evaluating the immunogenicity of FSME-IMMUNE in children and adolescents 1 to <16 years of age have been completed. In addition, one post-marketing surveillance study (Study 197) was conducted in children ages 6 months to 12 years of age.

1. Study 198: Pilot Safety and Immunogenicity of 2 vaccinations with FSME-IMMUN 0.25 mL (1.2 µg TBE antigen) in children 1 to <13 Years of Age (N=101).
2. Study 215: Subjects (N=99) in Study 198 received a third vaccination 9 to 10 months after the second vaccination. Seroconversion rates were evaluated 21 to 35 days after the third vaccination.
3. Study 199: Dose-Finding, safety and immunogenicity study in children 1 to <6 Years of Age (N= 639) of 2 vaccinations with FSME-IMMUN 0.25 mL (0.3 µg, 0.6 µg and 1.2 µg TBE antigen).
4. Study 206: Subjects who had received 2 vaccinations in Study 199 were (N= 625) administered a third vaccination (at the same antigen dose as in the Study 199, 6 months $\pm$14 days after the first vaccination). Seroconversion rates were evaluated 21 to 28 days after the third vaccination.

5. Study 205: Dose-finding study (N= 639) assessing the safety and immunogenicity of 2 vaccinations of FSME-IMMUN 0.25 mL (0.3 µg, 0.6 µg and 1.2 µg TBE antigen) in subjects 6 to <16 years of age.
6. Study 207: Subjects who had received 2 vaccinations in Study 205 were (N= 618) administered a third vaccination (at the same antigen dose as in the Study 199) 6 months ±14 days after the first vaccination. Seroconversion rates were evaluated 21 to 28 days after the third vaccination.
7. Study 209: Evaluated the safety and immunogenicity of five consecutive lots of FSME-IMMUN 0.25 mL in healthy children aged 1 to <16 years who received 3 consecutive vaccinations of FSME-IMMUN.
8. Study 700401: Follow-up study to Study 209, to assess the seropersistence of TBE antibodies 24 and 34 months after the third vaccination of FSME-IMMUN 0.25 mL administered inStudy 209, in healthy children and adolescents aged 3 to 18 years who had previously participated in Study 209 at the age of 1 to 15 years. Subjects who showed highly positive anti-TBE at Month 34 after the third vaccination did not receive a booster vaccination. The remaining subjects were offered a booster vaccination at Month 36 after the third vaccination, and a blood draw was performed 21 to 35 days thereafter to assess the booster response.
9. Study 700802(Pfizer Study B9371021): 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 TBE antibodies through 10 years after the first booster, and to evaluate the response to a second booster vaccination given in the study.
10. Study 700801: Assessed the immunogenicity, safety, and interchangeability of two different TBE vaccines (FSME-IMMUN and ENCEPUR) in children aged 1 to <12 years. Hereafter ENCEPUR will be described as: a non-US licensed TBE vaccine comparator. Subjects received either FSME-IMMUN or the non-US licensed comparator for the first and second vaccinations; the third vaccination was FSME-IMMUN for all subjects.
11. Study 197: Postmarketing observational safety study that enrolled 1922 children 6 months to 12 years of age to assess the rate of fever after the first vaccination with half the volume of FSME-IMMUN adult dose (1.2 µg TBEV antigen). Efficacy or immunogenicity was not evaluated in this study.

Studies in adults (≥16 years of Age)

Ten clinical studies evaluating the safety and immunogenicity of FSME-IMMUNE in subjects ages ≥16 years of age have been completed.

1. Study 201: Dose finding study to evaluate the safety and immunogenicity of 2 vaccinations with FSME-IMMUN (0.6 µg, 1.2 µg and 2.4 µg TBE antigen) administered to healthy subjects 16 to <65 years of age (N= 405).
2. Study 202: The study evaluated the safety and immunogenicity of a third dose of FSME-IMMUN (at the same dosage level as received in Study 201), which was administered 6 months after the first vaccination (N= 372).
3. Study 208: Evaluated the safety and consistency of five consecutive lots of FSME-IMMUN 0.5 mL (2.4 µg TBE antigen) compared with that of a non-US licensed TBE vaccine comparator (1.5 µg TBE antigen) in healthy subjects 16 to <65 years who received 2 vaccinations administered 21 to 35 days apart (N= 3966).

4. Study 213: Follow-up study of subjects who had received 2 vaccinations in Study 208. All subjects (regardless of which vaccine they received in Study 208) received one vaccination with FSME-IMMUN 6 months after the first vaccination in Study 208.
5. Study 223: Open-label follow-up study to Study 213, to assess TBE antibody persistence 2 and 3 years (± 28 days) after the third TBE vaccination with FSME-IMMUN administered in Study 213, and to assess the TBE antibody response to a booster vaccination of FSME-IMMUN administered at 3 years (± 28 days) after the third TBE vaccination (N=347).
6. Study 690701: Follow-up study in healthy adults who had received their primary immunization series in Studies 208/213, first booster in Study 223, and were followed through 5 years post-first booster. This study was planned to provide information on TBE antibody persistence.
7. Study 691101 (Pfizer Study B9371010): Follow-up study in healthy adults who had received first booster in Studies 223, 690701, and were followed through 10 years post-first booster. This study was planned to provide information on TBE antibody persistence.
8. Study 225: Evaluated the safety and immunogenicity of 2 vaccinations with FSME-IMMUN administered using a rapid immunization schedule (Day 0, Day 12±2) in healthy adults 16 to <66 years of age (N=60).
9. Study 690501: Evaluated the safety and immunogenicity of a third vaccination (given approximately 12 months after the second vaccination) with FSME-IMMUN in subjects who had received both vaccinations in Study 225.
10. Study 690601: Evaluated the immunogenicity and safety of FSME-IMMUN administered according to a rapid immunization schedule in healthy adults aged >16 years of age. All subjects received three vaccinations, with the first 2 vaccinations given 12 ± 2 days apart and the third vaccination given approximately 6 months after the first dose (N=170).

Analyses of Seroconversion and Seropositivity:

In most clinical studies of FSME-IMMUN, the primary immunogenicity endpoint was either the seroconversion rate (i.e., the proportion of subjects considered to have seroconverted) or the seropositivity rate (i.e., the proportion of subjects considered seropositive) after the vaccination.

Seroconversion rates were evaluated in Studies 201/202, and Study 213 in adults, and in 7 of the 12 immunogenicity studies conducted in pediatric subjects (all pediatric studies except Studies 700401, 700802, 700501, and 700801).

- *Seroconversion based on Immunozym ELISA* – Using ELISA values (determined using (b) (4) Immunozym FSME-IgG assay), a subject was considered to have seroconverted if the subject had ELISA values of <63 VIE U/mL (Vienna units per milliliter) at study entry and >126 VIE U/mL after the vaccination of interest. Seroconversion in subjects with screening ELISA values between 63 and 126 VIE U/ml was defined as a more than 2-fold rise in antibody titers.
- *Seroconversion based on* neutralization test (*NT)* - Using NT values (determined using the procedures of (b) (4) , or the procedures of Adner et al[4]), 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 the vaccination of interest.

Seropositivity rates based on results of the Immunozym ELISA or neutralization tests were evaluated in 8 adult studies (Studies 223, 690701, 691101, 225, 690501, 690601, B9371038 and WI208682) and in 5 pediatric studies (Studies 700401, 700802, 700501, and 700801).

- *Seropositivity based on Immunozym ELISA* – Using ELISA values (determined using the Immunozym FSME-IgG assay), a subject was considered seropositive if the subject had an anti-TBE antibody concentration >126 VIE U/mL.
- *Seropositivity based on NT* - Using NT values (determined using the procedures of (b) (4), or the procedures of Adner et al[4]), a subject was considered seropositive if the subject had an NT titer ≥1:10.

Clinical Serology Assays: Measurement and Analysis of the Immune Response to FSME-IMMUN

In most of the clinical studies, the primary immunogenicity endpoint (or a principal secondary endpoint) used a combination of both 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). Although neither the Immunozym FSME-IMMUN IgG ELISA nor the NT assay have been validated according to current standards, they have been in use for more than 40 years to reliably measure vaccine effectiveness in both adult and pediatric populations in Europe (Post-marketing experience) and FDA deemed these assays to be acceptable to measure vaccine-induced immune responses.

The ELISA assay used by (b) (4) (Immunozym FSME-IgG) for the determination of TBE virus-specific IgG antibodies was a three-layer ELISA quantitated in VIE U/mL using a standard human anti-TBE antiserum. Concentrations of >126 VIE U/mL are considered positive, values between 63 and 126 VIE U/mL are considered borderline, and values below 63 VIE U/mL are considered negative.

Functional antibodies, i.e., NT were assessed using assays by (b) (4) and Adner et al[4] in various clinical studies. The (b) (4) assay was used in adult Studies 201/202 and 213, as well as in pediatric studies 198/215, 199/206, and 205/207. The immune response determined by NT assay was lower than that determined by ELISA. Serum samples tested with the (b) (4) assay in adult Study 213 and pediatric Study 209 were subsequently reanalyzed using the Adner assay. It was found that NT titers measured using the Adner assay correlated well with the ELISA results, and thus, the Adner assay became the method of choice for determining neutralizing antibodies in recipients of FSME-IMMUN. The definition of seropositivity using the Adner assay is the same as that for the (b) (4) assay: i.e., titers <1:10 are considered negative, and titers ≥1:10 are considered positive[3,4].

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 690701/691101 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.

Real-World Vaccine Effectiveness: The applicant provided real-world vaccine effectiveness results from Austria for the years 2000-2011. During 2000 to 2011, two TBE vaccines were available in Austria. The market coverage in Austria for FSME-IMMUN was 95%, 90%, and 80% in 2000, 2006, and 2011, respectively. The real-world evidence demonstrated vaccine effectiveness (VE) among individuals who received at least 3 doses of TBE vaccine following the recommended vaccination schedule (2 vaccinations approximately 4 weeks apart followed by a third vaccination 5-12 months after the second dose, and a booster vaccination ≥3 years after the third dose) despite potential sources of biases.

Among the 883 TBE cases in Austria between 2000 and 2011, 45 patients did not have an accurate vaccination history and therefore two estimates of VE were calculated. For the best-case estimate of VE, these 45 patients were omitted from the calculation. For the worst-case estimate, these 45 patients were assumed to have been vaccinated according to the recommended schedule in Austria. Vaccine effectiveness for preventing hospitalized TBE was estimated to be 96.3% (95% CI: 95.5, 97.0) and 98.7% (95% CI: 98.2, 99.0) under the worst-case and best-case scenarios, respectively.

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[5-8]. 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[6].

The immunogenicity data together with the vaccine effectiveness estimates from field studies submitted to the BLA (see 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)

b. Pediatrics

Under the Pediatric Research Equity Act (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. The assessment of the safety and effectiveness of TICOVAC for the prevention of TBE in the pediatric population 1 - <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 in the pediatric population younger than 1 year of age, because necessary studies would be impossible or 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.

c. Other Special Populations: None

d. CDRH consult review:

TICOVAC is distributed in a pre-filled syringe (PFS) presentation. The PFS containing TICOVAC is considered as a combination product, and the Center for Devices and Radiological Health (CDRH) was consulted on the acceptability of the PFS. An information request was communicated to Pfizer with regards to essential performance requirements (dose accuracy/extractable volume, (b) (4) for the device constituent. Pfizer's responses have been reviewed by CDRH reviewers and found acceptable and adequate.

7. Safety and Pharmacovigilance

The sponsor's safety specifications and proposed pharmacovigilance actions are acceptable. Important identified risks in the pharmacovigilance plan include hypersensitivity reactions (e.g., anaphylaxis) and serious neurological reactions. Important potential risks include inadequate protection in persons >60 years of age, patients with impaired immune systems, precipitation and aggravation of autoimmune disorders in adults and children, and administration of adult dosage in children. Areas of important missing information include a lack of safety information in pregnant or lactating women and use in patients suffering from a disease or undergoing a form of treatment that could be expected to influence immunological functions. The applicant proposed routine pharmacovigilance and labeling to address these risks and missing information. There were no significant safety concerns from the clinical trials. Review of post-marketing data identified very few reports of most topics of interest such as allergic and immune system disorders, herpes zoster infections, nervous system disorders such as Guillain-Barré Syndrome, and reports of exposure in pregnancy or lactation. However, no significant safety concerns were identified from the review of post-market data. The

reviewed safety data does not substantiate a need for a Risk Evaluation and Mitigation Strategy, nor does it suggest a safety concern that needs to be further evaluated in a study in the CBER Sentinel Program, or a post-marketing requirement safety study.

Safety Results

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 0.5 mL 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).

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, but the clinical trial data were insufficient to characterize safety and effectiveness of additional booster doses.

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 1 to <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 (1 to <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%),
- 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 0.25 mL pediatric dose of TICOVAC. No safety signals were identified with the use of the vaccine in clinical studies.

Deaths were reported for 3 subjects who participated in clinical studies of FSME-IMMUN. None of the deaths were considered related to study vaccine.

Demographic Information:

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

In the pediatric clinical studies, 4096 children received at least one dose of any vaccine dosage (3240 received at least one vaccination with the dosage selected for marketing as well as an additional 856 children who received other dosages), of which 2118 subjects (51.7%) were male and 1978 (48.3%) were female. In Study 197 (a post-marketing surveillance study in children), among the 1899 subjects included in the evaluation of safety, 53.0% of subjects were male and 46.6% were female (0.4% not reported). Age distribution was as follows: 6 months - <1 year, 467 subjects (24.6%); 1-3 years, 1198 (63.1%); 4-6 years, 143 (7.5%); 7-9 years, 55 (2.9%); 10-12 years, 36 (1.9%).

In the adult clinical studies, 4697 adults received at least one dose of any vaccine dosage (4427 subjects received at least one dose of the final formulation and an additional 270 subjects received other dose levels), of which 2252 subjects (48%) were

male and 2445 subjects (52%) were female. In Studies 201, 225, and 690601, there was a preponderance of females (62.7% to 68.3%).

8. Labeling

The proposed proprietary name, TICOVAC, was reviewed and found acceptable by the Advertising and Promotional Labeling Branch (APLB) on January 21, 2021 and their recommendation was accepted by OVRR. CBER communicated the acceptability of the proprietary name to the applicant on February 16, 2021.

APLB reviewed the proposed Prescribing Information (PI) and package and container labeling on June 20, 2021 and found them to be acceptable from a promotional and comprehension perspective.

The review team negotiated revisions to the PI. All labeling issues regarding the PI and the carton and container labels were resolved following communications with the Applicant.

9. Advisory Committee Meeting

This submission was not discussed at a Vaccines and Related Biological Products Advisory Committee meeting because FDA review of information submitted in the BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

On February 5, 2021, FDA granted priority review designation for the BLA.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Based on the review of the clinical, nonclinical, and product-related data submitted in this original BLA submission, the Review Committee recommends approval of TICOVAC for the labeled indication and usage.

b. Benefit/Risk Assessment

Considering the data submitted to support the safety and effectiveness of TICOVAC that have been presented and discussed in this document, the Review Committee is in agreement that the risk/benefit analysis of TICOVAC is favorable and supports approval for use in individuals 1 year of age and older for the prevention of TBE.

c. Recommendation for Post-marketing Activities: None

12. References

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