

**MEMORANDUM**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Biologics Evaluation and Research**

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**Date:** May 27<sup>th</sup>, 2021

**From:** Andrew O'Carroll, DVM  
Pharmacology/Toxicology  
Division of Vaccines and Related Products Applications

**Through:** Dave Green, PhD  
Branch Chief, Pharmacology/Toxicology  
Division of Vaccines and Related Products Applications

**Subject:** BLA 125740 Toxicology Review

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**EXECUTIVE SUMMARY**

PF-06830414 was evaluated in a single-dose toxicity study and 2 local tolerance studies conducted to contribute to the nonclinical risk assessment for this product via the intramuscular (IM), (b) (4) routes of administration. 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. There was minimal nonclinical safety data included in this submission, but this was due to how this vaccine was developed nearly 40 years ago. While the data provided in this submission helps to provide a degree of reassurance should this vaccine be administered via the (b) (4) routes of administration, risk assessment for this product should be based on the decades worth of clinical data across multiple countries. This applies to risk assessment in women who are pregnant, lactating or of child-bearing potential as no developmental and reproductive toxicity studies have been conducted using PF-06830414 at this time.

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**INTRODUCTION**

**BLA:** 125740/0

**Sponsor:** Pfizer Ireland Pharmaceuticals

**Product:** Tick-Borne Encephalitis (TBE), PF-06830414

**Proposed use:** Indicated for active immunization to prevent tick-borne encephalitis (TBE) in individuals 1 year of age or older.

**Introduction:** Pfizer Ireland Pharmaceuticals has submitted an original biologics licensing application (BLA) for consideration of licensure in the US for their developed vaccine PF-06830414. This is an inactivated whole virus vaccine using the Neudörfl strain of the Tick-borne encephalitis virus adsorbed on aluminum hydroxide (Al(OH)<sub>3</sub>) adjuvant. This vaccine has two formulations: one

for individuals 16 years of age and older that contains 2.4 µg TBE virus and 0.35 mg Al(OH)<sub>3</sub> per 0.5 mL dose and another for individuals 1 to 15 years of age that contains 1.2 µg TBE virus and 0.17 mg Al(OH)<sub>3</sub> per 0.25 mL. Prior formulations of this vaccine contained the preservative thiomersal, but current formulations do not contain it. Therefore, this vaccine is available in single-dose vials containing either 0.5 mL or 0.25 mL. This vaccine is currently marketed in 28 countries for the 0.5 mL formulation and 27 countries for the 0.25 mL formulation and has over 40 years of clinical field experience. Current tradenames for this vaccine in other countries are TicoVac and FSME-IMMUN. The purpose for this BLA and seeking licensure in the United States is "...to enable those who live in or travel to high risk or endemic regions to be vaccinated against TBE." Pfizer acquired this vaccine from Baxter in 2015.

The intended clinical dosing regimen for PF-06830414 is for recipients to receive 3 doses of vaccine: an initial dose, a 2<sup>nd</sup> dose 1 to 3 months after the initial dose and a 3<sup>rd</sup> dose 5 to 12 months after the 2<sup>nd</sup> dose. A booster is recommended 3 years after the 3<sup>rd</sup> dose (b) (4)

(b) (4) For those over 60 years of age, boosters (b) (4)

The nonclinical toxicology program for this BLA submission includes one single-dose toxicity study and two local tolerance studies. Only study synopses without full sets of individual animal data are included because these studies were conducted in the 1980's prior to the introduction of the vaccine to Germany and Austria. None of these studies appear to be Good Laboratory Practice (GLP) compliant. There are no developmental and reproductive toxicity studies included in this submission with the provided rationale for omission being that:

- The TBE virus contained in the vaccine is unlikely to cross the placenta due to molecular size
- The antibodies produced by the vaccine virus are unlikely to cross-react with human tissues
- There are decades of post-marketing surveillance data to women of child-bearing potential and to pregnant or lactating women without identified safety signals

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## SINGLE-DOSE TOXICITY

### DETERMINATION OF TOXICITY IN MICE, GUINEA PIGS AND RABBITS AFTER SINGLE ADMINISTRATION OF FSME-IMMUN, TICK-BORNE ENCEPHALITIS VACCINE ADJUVANTED, IMMUNO

**Study number:** 154e

**Study completion date:** November 19<sup>th</sup>, 1987

**Study design:** In this single-dose toxicity study, 25 female mice, 10 female guinea pigs and 15 rabbits ("hybrids of either sex") were administered a single IM dose of FSME-IMMUN (lot nos. 37148612, 37018701 and 37098707). Mice received 0.5 mL (the human dose) and guinea pigs received 1.0 mL, both in the caudal thigh musculature whereas rabbits receive 0.5 mL/kg body weight intravenously (IV) via marginal ear veins. There were no control arms in this study. Clinical observations were recorded for either 14 or 21/22 days. Body weight measurements occurred on study days (SD) 0, 7, 14 and 21 in mice, SD 0, 3, 7, 14 and 21 in guinea pigs and SD 0, 5, 8, 12, 14, 19 and 22 in rabbits. Animals were euthanized on study days 14 or 21/22 via pentobarbital injection

(intraperitoneal (IP) in mice and guinea pigs and IV in rabbits) then subjected to gross necropsy examinations.

**Study results:** All animals survived until their scheduled terminations and there were no treatment-related clinical signs observed in any animals in this study. Clinical signs observed were considered incidental to the study and included self-limiting purulent conjunctivitis in one rabbit and self-limiting diarrhea in another. There was consistent and comparable weight gain observed in all of the mice, 11/15 guinea pigs and 13/15 rabbits. Among the guinea pigs, 4 experienced weight loss with 3 of these being transient and one persisting until termination. Among the rabbits, the weight loss in one animal was transient and the other persistent until termination. The conjunctivitis and diarrhea in rabbits were attributed to an incidental infectious disease which was the cause of weight loss in this animal, but no further details were provided.

During postmortem necropsy examinations, in any of the mice. Among the guinea pigs, one had a 1-2 mm gray-white node at the injection site and another had a “circumscribed purulent pneumonia.” Among the rabbits, one was found to have fibrinous peritonitis, and another was found to have both fibrinous peritonitis and rhinitis. None of these were considered related to treatment except for perhaps the small injection site nodule in the one guinea pig. The peritonitis in the two rabbits was attributed to incidental parasitism (coccidiosis).

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## LOCAL TOLERANCE

### INVESTIGATIONS ON LOCAL TOLERANCE AND LOCAL KINETICS AFTER SUBCUTANEOUS ADMINISTRATION OF FSME-IMMUNE TICK-BORNE ENCEPHALITIS VACCINE ADJUVANTED, IMMUNO, IN GUINEA PIGS

**Study number:** 153e

**Study completion date:** December 13<sup>th</sup>, 1989

**Study design:** In this repeat-dose local tolerance study, 2 groups of 14 male (b) (4) guinea pigs were administered either 2 subcutaneous (SC), 1 mL doses of FSME-IMMUN or isotonic saline control in their neck region. No clinical observations or any antemortem endpoints were recorded in this study. Instead, 2 animals per group were euthanized via IP administration of pentobarbital 1, 2, 4, 6, 8, 10 and 12 weeks after administration. Following termination, the only postmortem examination that occurred was histologic examination of injection sites. Microscopic examination findings were graded in severity from 1+ (minimum) to 5+ (maximum).

**Study results:** Histologic examination of injection sites found that administration with FSME-IMMUN resulted in a 3+ to 4+ granulomatous inflammatory response in the dermis consisting “...mainly of histiocytes (macrophages), multinucleated giant cells, mixed with lower number of polymorphonuclear leucocytes (PMN) and lymphocytes.” This was eventually reversible but took approximately 6 to 8 weeks to resolve. In addition, the injected material was observed as a pale eosinophilic mass for up to 4 weeks.

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## INVESTIGATIONS ON LOCAL TOLERANCE AFTER INTRADERMAL ADMINISTRATION OF FSME-IMMUN, TICK-BORNE ENCEPHALITIS VACCINE ADJUVANTED, IMMUNO, IN GUINEA PIGS

**Study number:** 163e

**Study completion date:** November 19<sup>th</sup>, 1987

**Study design:** In this single dose local tolerance study, 16 female (b) (4) guinea pigs were administered 100 µL each FSME-IMMUN (lot nos. 37148612, 37018701 and 37098707) and vehicle control (saline with Al(OH)<sub>3</sub> adjuvant) via intradermal injection. Animals were paired into 8 different groups: A1, A2, B1, B2, C1, C2, D1 and D2. Two symmetrical areas on the dorsum of each animal was shaved and depilated with 8 areas marked for injection to allow both test and control articles to be administered in a concentrated form as well as in dilutions of 1:3, 1:10 and 1:30. Injection sites from groups A1, B1, C1 and D1 were observed 6 hours later, then administered Evan's Blue dye IV to visualize enhanced vascular permeability from capillary leakage and re-examined 10-15 minutes later. The same process was used for groups A2, B2, C2 and D2 but injection sites were first observed 24 hours after administration of test and control articles. Evidence of gross inflammation, or lack thereof but positive Evan's Blue staining was marked as (+) with a 1 for mild reddening, 2 for mild infiltration and 3 for discoloration.

**Study results:** Administration of the test article appeared to be well tolerated by the study guinea pigs when administered intradermally within the bounds of this study's design. Reddening, discoloration and infiltration were observed in 2 animals receiving test article at the concentrated and 1:3 dilution injection sites as well as both animals receiving vehicle control. This implies that the adjuvant Al(OH)<sub>3</sub> is involved in the intradermal inflammatory response observed. However, the limitations of the study include a lack of severity grading plus no means of assessing reversibility.

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### CONCLUSIONS

This submission is acceptable with regards to nonclinical toxicology and there are no toxicologic issues identified which would preclude approval of the BLA in the intended human populations. Overall, minimal nonclinical safety data were submitted, but this is due to the age of this product. The initial evaluation and development of this product occurred nearly 40 years ago and the nonclinical standards for vaccine development were different at that time. This is why no GLP-compliant repeat-dose toxicity studies were submitted for this product. As a result, the included studies are limited in their ability to assess toxicity to PF-06830414 and there were no thorough histologic examinations of entire carcasses as is commonly done today. For example, while the weight loss observed in guinea pigs is possibly due to administration of PF-06830414, this was not further investigated via endpoints considered commonplace in toxicity studies for vaccines today: e.g. body temperature, food consumption, clinical pathology and histologic examinations. The granulomatous inflammatory response observed at injection sites following administration can be directly attributed to the intended immune response to vaccination and is not considered adverse.

However, this product has decades worth of clinical experience across numerous countries so the risk assessment for this product should be based on the available clinical data. Similarly, no developmental and reproductive toxicity studies have been conducted using PF-06830414 and risk assessment for pregnant women, lactating women and those of childbearing potential should be based on the available clinical data in those groups. The product insert included with this submission accurately states this lack of nonclinical data, but the sponsor's rationale for this lack of data is

insufficient. The sponsor-provided reference[1] does not make any mention of molecular size and there is evidence that molecular weight does not play a role in transport across the placenta. In fact, immunoglobulin G (IgG) fragments are more poorly transported across the placenta than intact IgG immunoglobulins[2]. Viral transcytosis across the placenta is, at a minimum, theoretically possible and is well understood with cytomegalovirus, for example[3]. At this time, the capacity for this Neudörfl strain to cross the placenta is not known, but there is evidence of vertical transmission of TBE in naturally infected, reservoir, small rodent hosts[4]. If there is concern about the risk in women who are pregnant, lactating or of childbearing potential based on the available clinical data, a developmental and reproductive toxicology study can be considered.

#### References:

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3. Liu X, Palaniyandi S, Zhu I, Tang J, Li W, Wu X, Ochsner SP, Pauza CD, Cohen JI, Zhu X. Human cytomegalovirus evades antibody-mediated immunity through endoplasmic reticulum-associated degradation of the FcRn receptor. *Nat Commun.* 2019 Jul 9;10(1):3020.
4. Bakhvalova VN, Potapova OF, Panov VV, Morozova OV. Vertical transmission of tick-borne encephalitis virus between generations of adapted reservoir small rodents. *Virus Res.* 2009 Mar;140(1-2):172-8.