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Report Title: Final Report: A Phase 3, Single-Arm, Open-Label Study to Evaluate the Immunogenicity, Safety, and Tolerability of a Tick-Borne Encephalitis Vaccine in Healthy Japanese Participants 1 Year of Age and Older

Study Number: B9371039

Regulatory Agency or Public Disclosure Identifier Number: NCT04648241/jRCT2031200302

Study Phase: Phase 3

Name of Study Intervention: PF-06830414

Name of Sponsor/Company: Pfizer Inc.

CSR Version and Report Date: 1.0/ 20 January 2023

Number of Study Center(s) and Investigator(s): This study was conducted at 6 sites in Japan.

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications:

None

Study Period:

This report covers the full study period from 18 January 2021 (first participant first visit) through 21 February 2022 (last participant last visit).

This study was neither discontinued nor interrupted.

Rationale:

Tick-borne encephalitis (TBE) vaccine 0.5 and 0.25 mL are inactivated vaccines that are approved for prevention of TBE in multiple European and other countries and are in development in Japan for the prevention of TBE.

The purpose of the study was to evaluate the immunogenicity, safety, and tolerability of TBE vaccine in healthy Japanese participants 1 year of age and older. Many clinical studies in adults and children have been conducted in the European Union, which have confirmed the safety and immunogenicity of this vaccine in both adults and pediatric non-Japanese

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populations. The field effectiveness of this vaccine has also been demonstrated in endemic countries where the vaccine has been approved.

The first TBE case in Japan was reported in Hokkaido in 1993. As of the end of February 2019, 4 additional cases have been reported in Hokkaido. Underdiagnosis is a possibility as there are no commercially available diagnostic enzyme-linked immunosorbent assay (ELISA) kits for TBE currently available in Japan and patients with central nervous system (CNS) symptoms in Japan are not routinely tested for TBE infection. Epizootiological surveys report that the virus is circulating in nature in Japan.

As described above, there have recently been cases of TBE reported in Japan. In addition, there is a medical need for immunization based on the World Health Organization (WHO) recommendation that travelers visiting various endemic areas be immunized if their visits will include extensive outdoor activities. However, there is no TBE vaccine currently approved in Japan. To address this situation, the Japanese Society of Travel and Health has submitted to the Ministry of Health, Labour and Welfare (MHLW) a recommendation that a development request for TBE vaccine be submitted in Japan, and the MHLW issued this development request to Pfizer Japan Inc on 19 September 2019.

Objectives, Endpoints, and Statistical Methods:

Table S1. Study Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary Immunogenicity		
• To evaluate the immunogenicity of TBE vaccine 0.5 mL by NT. • To evaluate the immunogenicity of TBE vaccine 0.25 mL by NT.	• In healthy Japanese adult participants 16 years of age and older who received 3-dose TBE vaccine 0.5 mL in compliance with the key protocol criteria (evaluable participants): The proportion who are seropositive (achieving NT titer ≥1:10) 4 weeks after the third dose. • In healthy Japanese pediatric participants ≥1 to <16 years of age who received 3-dose TBE vaccine 0.25 mL in compliance with the key protocol criteria (evaluable participants): The proportion who are seropositive (achieving NT titer ≥1:10) 4 weeks after the third dose.	TBEV-neutralizing antibody titers.
Primary Safety		
• To evaluate the safety profile of TBE vaccine 0.5 mL.	In healthy Japanese participants from each age group receiving at least 1 dose of investigational product: • The percentage of participants reporting local reactions within 7 days after each vaccination.	• Prespecified local reactions (redness, swelling, and pain at the injection site). • Prespecified systemic events (fever, decreased

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Table S1. Study Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
• To evaluate the safety profile of TBE vaccine 0.25 mL.	• The percentage of participants reporting systemic events within 7 days after each vaccination. • The percentage of participants reporting AEs within 1 month after each dose. • The percentage of participants reporting SAEs during the study period.	appetite, drowsiness, and irritability for participants 1 to ≤2 years of age; fever, fatigue, headache, vomiting, diarrhea, muscle pain, and joint pain for participants >2 years of age). • AEs within 1 month after vaccination. • SAEs throughout the study.
Secondary Immunogenicity		
• To describe the immunogenicity of TBE vaccine 0.5 mL by NT. • To describe the immunogenicity of TBE vaccine 0.25 mL by NT.	In healthy Japanese adult participants 16 years of age and older who received 3-dose TBE vaccine 0.5 mL in compliance with the key protocol criteria (evaluable participants): • The proportion who are seropositive (achieving NT titer ≥1:10) 4 weeks after the second dose. • NT GMTs 4 weeks after the second and 4 weeks after the third dose. • NT GMFRs 4 weeks after the second and 4 weeks after the third dose as compared to baseline. • NT GMFR 4 weeks after the third dose as compared to 4 weeks after the second dose. In healthy Japanese pediatric participants 1 through 15 years of age who received 3-dose TBE vaccine 0.25 mL in compliance with the key protocol criteria (evaluable participants): • The proportion who are seropositive (achieving NT titer ≥1:10) 4 weeks after the second dose. • NT GMTs 4 weeks after the second and 4 weeks after the third dose.	TBEV-neutralizing antibody titers.

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Table S1. Study Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
	• NT GMFRs 4 weeks after the second and 4 weeks after the third dose as compared to baseline. • NT GMFR 4 weeks after the third dose as compared to 4 weeks after the second dose.	
[redacted]		

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Table S1. Study Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
[redacted]		

Abbreviations: AE = adverse event; [redacted] GMFR = geometric mean fold rise; GMT = geometric mean titer; [redacted]; NT = neutralization test; SAE = serious adverse event; TBE = tick-borne encephalitis; TBEV = tick-borne encephalitis virus.
Source: Appendix 16.1.1, Protocol Section 3

Methodology:

This Phase 3, multicenter, single-arm, open-label study was conducted at investigator sites in Japan. This study was part of the Phase 3 clinical development plan to support use of TBE vaccine 0.5 and 0.25 mL in healthy Japanese adults (≥16 years of age) and the pediatric population (≥1 and <16 years of age). The purpose of this study was to provide key safety and immunogenicity data in Japanese participants.

Estimations for the immunogenicity and safety objects, estimands, and endpoints for this study are presented in Table S1.

The primary immunogenicity objective of the study was to assess the immunogenicity of the investigational product by neutralization test (NT) in samples collected from Japanese healthy adults and children when administered as a 3-dose schedule. The null hypothesis tested concerns the seropositivity rate for the primary endpoint in each age group. The immune response induced by TBE vaccine was evaluated in each age group, testing the hypotheses H_0: seropositivity rate ≤90% vs H_1 seropositivity rate >90%. These hypotheses were tested separately for each age group and no adjustment of multiplicity was considered. For each age group, if the lower bound of the 95% confidence interval (CI) on the NT seropositivity rate among the evaluable population was >90%, the objective was achieved.

The primary safety objective was evaluated for each vaccine group by descriptive summary statistics for reactogenicity events (local reactions and systemic events collected through an electronic diary [e-diary]), adverse events (AEs), and serious adverse events (SAEs).

The secondary [redacted] endpoints were analyzed by descriptive summary statistics.

Number of Participants (planned and analyzed):

Approximately 100 adult (≥16 years of age at the time of consent) and 65 pediatric participants (≥1 to <16 years of age at the time of consent) were planned and exactly 100 adult and 65 pediatric participants were enrolled in the study.

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Of the 100 adult participants and 65 pediatric participants enrolled in the study, 99 (99%) adult participants and 65 (100%) pediatric participants completed the study. One adult participant completed the blood draw after Dose 2 but was lost to follow-up prior to the blood draw before Dose 3.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Key eligibility criteria for participants in this study are briefly summarized below.

- Inclusion criteria: male or female, healthy Japanese participants ≥16 years of age for Group 1 (adults) or ≥1 to <16 years of age for Group 2 (pediatric) at time of consent (Visit 1).

- Exclusion criteria: medical or psychiatric conditions that may have increased the risk of study participation or, in the investigator's judgment, made the participant inappropriate for the study (including immunocompromised individuals with known or suspected immunodeficiency); known prior history of flavivirus infection, receipt of certain prior/concomitant therapies, which included immunosuppressive therapy and prior TBE vaccine.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

TBE vaccine was supplied as a suspension for injection in a pre-filled syringe. Participants received 1 dose of TBE vaccine at each vaccination visit (Visits 1, 2, and 4) in accordance with the protocol schedule of activities.

In participants ≥16 years of age, TBE vaccine 2.4 µg/0.5 mL was administered intramuscularly by injecting into the deltoid muscle of the right or left arm. In participants <16 years of age, TBE vaccine 1.2 µg/0.25 mL was administered intramuscularly by injecting into the deltoid muscle of the right or left arm. For children ≤18 months of age, TBE vaccine 1.2 µg/0.25 mL was administered intramuscularly by injecting into the anterolateral thigh muscle of the leg.

Investigational product lot numbers are provided in Table S2.

Table S2. Investigational Product Lot Numbers – Final

Investigational Product	Manufacturer	Vendor Lot Number (Manufacturer)	Lot Number[a] (Pfizer)
TBE vaccine (FSME-IMMUN)	Pfizer	CY4872	20-004443
0.25 mL		DT7329	21-AE-00088
0.5 mL		CW4626	20-004444
		DP2890	21-AE-00169

Abbreviation: TBE = tick-borne encephalitis.
a. Lot number assigned to the investigational product by Pfizer Global Clinical Supply.
Protocol B9371039 Investigational Product Lot Numbers Table – Final, Final, Version 1.0, 21Apr2022.

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Duration of Study Intervention:

Study duration was approximately between 7 to 15 months for each participant.

Summary of Results:

Demographic and Other Baseline Characteristics:

Demographic characteristics in the adult group were broadly similar with a balanced number of male and female participants. Pediatric participants were predominantly male (70.8%). All participants were non-Hispanic/non-Latino (100%) and Asian (100%). Adult participants age ranged from 16 through 75 years (mean age 44.3 years) while the pediatric population age ranged from 1 through 15 years (mean age 6.9 years).

Demographic characteristics of the immunogenicity population were similar to the safety population.

Exposure:

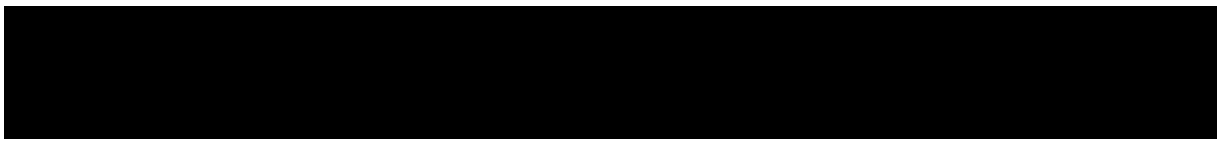
Of the 100 adult participants, 99 received 3 doses and 1 participant received 2 doses of TBE vaccine. All 65 pediatric participants received all 3 doses of TBE vaccine.

Immunogenicity Results:

The primary immunogenicity objective was achieved for both adult and pediatric participants 4 weeks after Dose 3 of TBE vaccine with 98.0% (95% CI: 92.9, 99.8) of adult participants and 100.0% (95% CI: 94.5, 100.0) of pediatric participants achieving tick-borne encephalitis virus (TBEV) neutralization seropositivity. Both age groups met the protocol-defined criteria of the lower bound of the 95% CI on the NT seropositivity rate being >90% for the evaluable immunogenicity population.

The reverse cumulative distribution curves (RCDCs) of TBEV neutralization titers increased 4 weeks after Dose 2 then decreased before Dose 3 and increased again 4 weeks after Dose 3. TBEV NT geometric mean titers (GMTs) followed the same pattern as the TBEV neutralization titers with all participants starting BLQ before Dose 1, increasing 4 weeks after Dose 2, decreasing before Dose 3, and reaching maximum values 4 weeks after Dose 3.

TBEV NT geometric mean fold rise (GMFRs) were higher for pediatric participants (93.2 [95% CI: 75.2, 115.6]) than adult participants (32.0 [95% CI: 26.0, 39.4]). The age groups were similar after Dose 2 but a greater increased response was observed for pediatric participants after Dose 3. Both adult and pediatric participants had higher TBEV NT GMFRs from 4 weeks after Dose 2 to 4 weeks after Dose 3.



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[redacted]

Safety Results:

Reactogenicity (local reactions and systemic events) were typically mild to moderate and short-lived. AEs were mild to moderate with only 1 reported severe AE (colitis ischaemic [adult]) and no reported life-threatening AEs. None of the AEs were considered related to the Investigational product by the investigator.

In the adult population, 2.0% to 6.1% of participants reported any AE within 1 month of each dose. AEs were most frequently reported in the system organ class (SOC) of infections and infestations (range of 1.0% to 4.0%).

In the pediatric population, 10.8% to 29.2% of participants reported any AE within 1 month of each dose. AEs within 1 month of each dose were most frequently reported in the SOC of infections and infestations (range of 7.7% to 18.5%). AEs reported after any dose and before the 1-month blood draw after any dose were most frequently reported in the SOC of infections and infestations and were more frequently reported in the younger age groups (50.0% for 1-2 years of age and 53.6% for 3 6 years of age) than the older age group (6.9% for 7-15 years of age).

No immediate AEs were reported. No AEs leading to discontinuation were reported and no deaths were reported.

SAEs were reported for 2 adult participants (abdominal pain and colitis ischaemic) and 1 pediatric participant (diarrhea)..

Overall, the safety results showed no new safety issues and were consistent with the known safety and tolerability profile of TBE vaccine.

Conclusions:

The 3-dose series of TBE vaccine was observed to elicit a robust immune response by TBEV neutralization in Japanese adult and pediatric participants. There was a ≥98% TBEV neutralization seropositivity rate demonstrated in both adult and pediatric populations 4 weeks after Dose 3.

The safety and tolerability of TBE vaccine in Japanese adult and pediatric participants was acceptable and consistent with the known profile of TBE vaccine.