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

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

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 1	10 Nov 2020	• Added fever to prespecified systemic events in primary safety endpoints for participants 1 to ≤2 years of age. • Prophylactic antipyretic/pain medication was removed from prohibited concomitant vaccines and treatments during the study in Section 6.5.2 and added to permitted concomitant vaccines and treatments during the study in Section 6.5.3, with clarification that use is not recommended on the day of vaccination. • Clarified that pandemic vaccines may be given at any time; however, an interval of >14 days prior to or 14 days after investigational product administration is preferred. • In Section 7.2, added 3 reasons for participant discontinuation/withdrawal from the study.
Original protocol	22 Jul 2020	N/A

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title

A Phase 3, Single-Arm, Open-Label Study to Evaluate the Immunogenicity, Safety, and Tolerability of a TBE Vaccine in Healthy Japanese Participants 1 Year of Age and Older.

Rationale

The Japanese Society of Travel and Health has submitted to the MHLW a recommendation to submit a development request for TBE vaccine in Japan, CCI [redacted]

The purpose of this study is to provide key safety and immunogenicity data in Japanese participants. Participants ≥16 years of age will receive the TBE vaccine 0.5 mL and participants ≥1 to <16 years of age will receive the TBE vaccine 0.25 mL.

Objectives, Estimands, and Endpoints

Primary Immunogenicity Objectives	Estimands	Primary Immunogenicity Endpoints
• 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 Objectives	**Estimands**	**Primary Safety Endpoints**
• To evaluate the safety profile of TBE vaccine 0.5 mL. • To evaluate the safety profile of TBE vaccine 0.25 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 appetite, drowsiness, and irritability for participants 1 to ≤2 years of age; fever, fatigue, headache,

	• 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.	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 Objectives	**Estimands**	**Secondary Immunogenicity Endpoints**
• 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. • NT GMFRs 4 weeks after the second and 4 weeks after the third dose as compared to baseline.	TBEV-neutralizing antibody titers.

	• NT GMFR 4 weeks after the third dose as compared to 4 weeks after the second dose.	
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Overall Design

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

Number of Participants

Approximately 100 adults (≥16 years of age at the time of consent) and 65 children (≥1 to <16 years of age at the time of consent) will be enrolled to receive study intervention such that approximately 150 evaluable participants complete the study.

Note: "Enrolled" means that a participant, or his or her legally authorized representative, has agreed to participate in a clinical study following completion of the informed consent process and is deemed eligible to participate. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For this study, the investigational product is TBE vaccine 0.5 mL and 0.25 mL.

Inactivated TBE Vaccine

TBE Vaccine 0.5 mL

TBE vaccine 0.5 mL contains formaldehyde-inactivated TBEV. The vaccine is formulated to contain 2 to 2.75 µg of inactivated TBEV (target: 2.4 µg) in 0.5 mL.

The dose will be administered intramuscularly into the deltoid muscle of the right or left upper arm (preferably in the nondominant arm) at Visits 1, 2, and 4 by an appropriately qualified site staff member or designee.

TBE Vaccine 0.25 mL

TBE vaccine 0.25 mL contains formaldehyde-inactivated TBEV. The vaccine is formulated to contain 1 to 1.38 µg of inactivated TBEV (target: 1.2 µg) in 0.25 mL.

The dose will be administered intramuscularly into the deltoid muscle of the right or left upper arm (preferably in the nondominant arm) at Visits 1, 2, and 4 by an appropriately qualified site staff member or designee. However, in children up to 18 months of age or

dependent on a child's development and nutrition status, TBE vaccine should be administered intramuscularly by injecting 0.25 mL into the anterolateral thigh muscle (refer to Section 6.1.1).

Vaccinations to Be Given at Visits 1, 2, and 4

Formulation/Schedule	Number of Participants (As Enrolled)
TBE vaccine 0.5 mL / Visits 1, 2, and 4	100
TBE vaccine 0.25 mL / Visits 1, 2, and 4	65

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[redacted]

Statistical Methods

The primary hypothesis to be tested is that the seropositivity rate based on the TBEV neutralization antibody level 4 weeks after the third dose is more than 90% in each age population. The primary endpoint will be tested by the exact method, which corresponds to evaluating 95% CI based on the Clopper-Pearson method comparing its lower limit to 90%. Assuming the expected seropositivity rate among 90 evaluable adults to be 99.4% and among 60 evaluable children to be 99.6%, the statistical power to reject each null hypothesis (equivalently to demonstrate that the lower limit of the 95% CI of the estimate will exceed 90%) is computed to be >99% and 97.3%, respectively. Considering 10% dropout, 100 adult participants and 65 pediatric participants are intended to be enrolled.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the Study Assessments and Procedures section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Number	**1**	**2**	**3**	**4**	**5**
Visit ID	**1st Vaccination**	**2nd Vaccination**	**Blood Draw**	**3rd Vaccination**	**Blood Draw**
Visit Window	**Day 1**	**21-35 Days After 1st Vaccination**	**21-35 Days After 2nd Vaccination**	**150-365 Days After 2nd Vaccination**	**21 -35 Days After 3rd Vaccination**
Informed consent/assent	X				
Provide participant contact card	X				
Demographics	X				
Medical history	X				
Concomitant vaccination and/or medication[a]	X	X	X	X	X
Physical examination[b]	X	X		X	
Prevaccination axillary temperature	X	X		X	
Urine pregnancy test (females of childbearing potential)[c]	X	X		X	
Discuss contraceptive use[c]	X	X		X	
Inclusion and exclusion criteria[c]	X				
Temporary vaccination delay criteria[b]	X	X		X	
Confirm continuing eligibility[c]		X	X	X	X
Immunogenicity blood sampling (TBEV NT CCI)[c]	X		X	X	X
CCI [redacted]	[redacted]				
Investigational product administration	X	X		X	

Visit Number	1	2	3	4	5
Visit ID	**1st Vaccination**	**2nd Vaccination**	**Blood Draw**	**3rd Vaccination**	**Blood Draw**
Visit Window	**Day 1**	**21-35 Days After 1st Vaccination**	**21-35 Days After 2nd Vaccination**	**150-365 Days After 2nd Vaccination**	**21 -35 Days After 3rd Vaccination**
30-Minute postvaccination observation and assessment of acute reactions	X	X		X	
Dispense e-diary, digital thermometer, and caliper	X				
Participants to record local reactions and systemic events in e-diary[d]	Days 1 to 7	From 2nd vaccination to 6 days after		From 3rd vaccination to 6 days after	
Review e-diary data	X--------	X--------		X--------	
Collect e-diary					X
AE/SAE assessment[e]	X	X	X	X	X

Abbreviations: [redacted] HI = hemagglutination inhibition; [redacted] NT = neutralization test; TBEV = tick-borne encephalitis virus.

a. Record only concomitant medications used to treat SAEs; the use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of vaccination. Administration of JEV vaccine is prohibited during a participant's participation in this study.
b. Prior to vaccination at Visit 1, a complete physical examination should be performed. Prior to vaccination at Visits 2 and 4, a physical examination should be performed if the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant. See Section 8.2.3.
c. Prior to vaccination, if at a vaccination visit.
d. The participant's legally acceptable representative/parents/legal guardian is to record local reactions and systemic events for participants 1 through 15 years of age. The participant's legally acceptable representative/patient/legal guardian should monitor the participant's compliance of data entry for participants 16 through 19 years of age.
e. The active collection period of AEs and SAEs for each participant begins from the time the participant/parent(s)/legal guardian/legally authorized representative provides informed consent through and including Visit 3, and from Visit 4 to Visit 5. Between Visit 3 and Visit 4, only SAEs will be reported. The detailed information is shown in Section 8.3.1.

2. INTRODUCTION

TBE vaccine 0.5 mL and 0.25 mL are inactivated vaccines that are approved for prevention of TBE in European and other countries [redacted]

2.1. Study Rationale

The purpose of the study is 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 overseas, which have confirmed the safety and immunogenicity of this vaccine in both adults and pediatric non-Japanese populations. The field effectiveness of this vaccine has also been demonstrated in endemic countries where the vaccine has been approved.

2.2. Background

2.2.1. Tick-Borne Encephalitis

TBE is a disease caused by infection with the TBEV, which belongs to the genus *Flavivirus* in the family *Flaviviridae*, and can be categorized into Far Eastern, Siberian, and European subtypes. The Siberian subtype is distributed mostly in Siberia, the Baltic states, and others; the Far Eastern subtype is distributed in China, Far Eastern Russia, Siberia, and Japan. The European subtype is distributed throughout Europe and South Korea. Recently the Baikalian subtype (Republic of Buryatia, Irkutsk, and Chita) and some other putatively new subtypes have been described.[1,2,3] TBEV infection is asymptomatic in most cases. In patients developing symptoms after infection, the incubation period is most commonly 7 to 14 days. Symptomatic infection due to the European subtype is characterized by a 2-phase illness. First symptoms include virus reproduction in the regional lymph nodes, as well as viremia and pyrexia, and then, after about a 1-week asymptomatic period, patients develop meningitis, encephalitis, myelitis, and combinations thereof. One year after the acute phase of viral infection, chronic impairment of the central nervous system occurs in approximately 30% of patients, and severe functional impairment requiring assistance for day-to-day activities occurs in 8.5% of patients.[4] The mortality among infected patients is said to be 1% to 2%, and it is up to 20% among patients infected with the Siberian subtype virus. The incubation period in patients infected with the Far Eastern subtype virus is 7 to 14 days. Disease due to infection with this subtype often does not have 2 phases as the disease caused by the European subtype does in many cases. After the incubation period, headache, pyrexia, nausea, and vomiting occur, and at the peak of disease, mental confusion, lethargy, convulsion, paralysis, and other symptoms of encephalitis may occur. The mortality can be ≥20%, and 30% to 40% of survivors continue to have neurological sequelae.[5]

There is no specific therapy for TBE. The WHO recommends vaccination as an effective means of prophylaxis for residents and people traveling to endemic areas.[6]

2.2.2. TBE Vaccine

These are vaccines that consist of a glass prefilled syringe with a 0.5-mL solution (brand name overseas: FSME-IMMUN/TicoVac) containing 2.4 µg of TBEV inactivated with formaldehyde, or a 0.25-mL solution (brand name overseas: FSME-IMMUN Junior/TicoVac Junior) containing 1.2 µg of TBEV inactivated with formaldehyde. These vaccines also contain human serum albumin as a stabilizer and aluminum hydroxide as an adjuvant.

These vaccines, 0.5 mL and 0.25 mL (hereafter referred to as "investigational product" or "study intervention"), were first commercially available in Austria in 1976 and have since been marketed in the UK, France, Germany, and other European countries, as well as Russia. About 140 million doses of the vaccine have been supplied, including ≥75 million doses of the current formulation, which has been available since 2001. Many clinical studies in adults and children have been conducted overseas, which have demonstrated the safety and immunogenicity of investigational product in both adults and children. The field effectiveness of investigational product has also been demonstrated in Austria, where high vaccine coverage led to a decline in TBE incidence.[7,8,9]

2.2.3. Status of TBE in Japan and the Development Request for TBE Vaccine

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.[10] However, as no commercially available diagnostic ELISA kit for TBE is available in Japan to date, and since patients with CNS symptoms in Japan are not systematically tested for TBE infection, underdiagnosis is a possibility. At the same time, it has been reported in epizootiological surveys that the virus is circulating in nature in Japan.[11]

As described above, there have recently been cases of TBE reported in Japan. Further, as described in Section 2.2.1, there is a medical need for immunization based on the 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. CCI [redacted]

2.2.4. Clinical Overview

Overseas Clinical Study Data

TBE vaccine has to date been investigated in numerous clinical studies in adults and children, all of which were conducted in Europe. Data from these studies were used to select the dose and administration schedule with which TBE vaccine was confirmed to be safe and immunogenic and, accordingly, approved in European countries.

Furthermore, the benefit/risk of TBE vaccine for adult and pediatric populations remains positive for individuals at risk of exposure to TBEV based on the database of postmarketing adverse drug reactions.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of TBE vaccine may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) [TBE Vaccine]		
Potential risks associated with TBE vaccine include but are not limited to the following: local reactions (injection site pain or tenderness, redness, and swelling) and systemic events (fever, irritability, decreased appetite, and increased sleep). As with any vaccine, an allergic reaction can occur. The allergic reaction can vary from skin rash to swelling of the face or lips, wheezing, and/or shortness of breath. A severe allergic reaction (anaphylactic shock, collapse, or shock-like state [hypotonic-hyporesponsive episode]) may also occur. There may also be additional risks related to the vaccines administered in the study that are not known at this time.	The potential risks are based on the IB for TBE vaccine.	Safety assessments (ie, local reactions, systemic events, AEs [including observation for 30 minutes after vaccination], and SAEs) described in the protocol and ongoing review of safety data by the investigator and sponsor study team will serve to monitor and mitigate these risks.
Study Procedures		
Risks that may be associated with study procedures include risks from blood draws, including pain, swelling, bruising, and infection where blood is taken.	Risks and possible discomforts from the study procedures such as pain, swelling, bruising, infection around the vein where the child's blood is collected may also occur, although this is very uncommon.	The volume and frequency of blood draws required during the study has been minimized as far as possible.

2.3.2. Benefit Assessment

TBE is a rare but potentially fatal disease in Japan.[10,11] In endemic countries where the vaccine has been approved, field effectiveness studies of TBE vaccine have demonstrated its efficacy.[7,8,9] Thus, participants are expected to be protected from TBEV infection by receiving TBE vaccine in this study. Moreover, TBE vaccine is a vaccine requested by MHLW for development in Japan because of high medical need.[12] Participants will contribute to a growing body of knowledge regarding the effectiveness and safety of this vaccine in an area of high medical need.

2.3.3. Overall Benefit/Risk Conclusion

The potential risks and benefits demonstrated with TBE vaccine reflect a positive benefit/risk profile.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Primary Immunogenicity Objectives	**Estimands**	**Primary Immunogenicity Endpoints**
• 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 Objectives	**Estimands**	**Primary Safety Endpoints**
• To evaluate the safety profile of TBE vaccine 0.5 mL. • To evaluate the safety profile of TBE vaccine 0.25 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 • The percentage of participants reporting systemic events within 7 days after each vaccination.	• Prespecified local reactions (redness, swelling, and pain at the injection site). • Prespecified systemic events (fever, decreased 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.

	• The percentage of participants reporting AEs within 1 month after each dose. • The percentage of participants reporting SAEs during the study period.	• SAEs throughout the study.
Secondary Immunogenicity Objectives	**Estimands**	**Secondary Immunogenicity Endpoints**
• 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. • 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.	TBEV-neutralizing antibody titers.


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4. STUDY DESIGN

4.1. Overall Design

This Phase 3, multicenter, single-arm, open-label study will be conducted at investigator sites in Japan. This study is part of the Phase 3 clinical development plan to support use of TBE vaccine 0.5 mL 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 is to provide key safety and immunogenicity data in Japanese participants. Study duration is approximately 7 to 15 months for each participant.

Approximately 100 adults (≥16 years of age at the time of consent) and 65 children (≥1 to <16 years of age at the time of consent) will be enrolled to receive study intervention such that approximately 150 evaluable participants complete the study.

4.2. Scientific Rationale for Study Design

TBE vaccine has been approved in many countries for adults (≥16 years of age) and children (≥1 to <16 years of age) at the 2 dosages assessed in this study. This study will assess TBE vaccine in Japanese adult and pediatric populations at the dose and administration schedule equivalent to what has been approved overseas.

Human reproductive safety data are limited for TBE vaccine; however, based on the few cases of exposure during pregnancy and lactation, no overt safety signal was identified. Therefore, given the paucity of information regarding safety of vaccination during pregnancy or lactation, the use of a highly effective method of contraception is required for this trial (see Appendix 4).

4.3. Justification for Dose

TBE vaccine is the inactivated vaccine containing formaldehyde-inactivated TBEV. As mentioned in Section 2.2.4, based on abundant clinical study data, the approved dosage and administration of TBE vaccine has been demonstrated to be safe and immunogenic. Pfizer considers that the same dosage and administration is appropriate in the Japanese population because there is no precedent where an inactivated vaccine, introduced from overseas, has needed an alternate dosage in Japanese as compared to non-Japanese participants.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Pfizer will review eligibility criteria verified by the investigator or qualified designee to confirm that participants meet study eligibility criteria before they are enrolled into the study. The enrollment approval process will be initiated for a participant after an informed consent document has been signed and the investigator or qualified designee has assessed the participant as eligible. The enrollment approval will be based on review of CRF/system data.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Group 1: Participants ≥16 Years of Age

Age and Sex:

1. Japanese male or female participants ≥16 years of age at Visit 1 (the time of consent).

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants (and a legally acceptable representative/parent/legal guardian if the participant is 16 to <20 years of age) who are willing and able to comply with all scheduled visits, vaccination plan, and other study procedures including completion of the e-diary for 7 days for participants after each of 3 vaccinations.

3. Participants (and/or a legally acceptable representative/parent/legal guardian if the participant is 16 to <20 years of age) must be able to be contacted by telephone during study participation.

Informed Consent:

4. Participants (and a legally acceptable representative/parent/legal guardian if the participant is 16 to <20 years of age) are capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Group 2: Participants 1 to <16 Years of Age

1. Japanese male or female participants between the ages of ≥1 and <16 years, inclusive (ie, <16 years), at Visit 1 (the time of consent).

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Type of Participant and Disease Characteristics:

2. Participants whose parent(s)/legal guardian(s) is willing and able to comply with all scheduled visits, vaccination plan, and other study procedures including completion of the e-diary for 7 days for participants after each of 3 vaccinations.

3. The legally acceptable representative/parent/legal guardian must be able to be contacted by telephone during study participation.

Informed Consent:

4. Participants whose parent(s)/legal guardian(s) are capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Common for Groups 1 and 2

Medical Conditions:

1. Medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the vaccines being administered in the study. History of severe hypersensitivity to egg and chicken proteins (anaphylactic reaction after oral ingestion of egg protein).

3. Significant neurological disorder or history of seizure including febrile seizure, or significant stable or evolving disorders such as cerebral palsy, encephalopathy, hydrocephalus, or other significant neurological disorders. Does not include history of resolving syndromes due to birth trauma, such as Erb's palsy and/or hypotonic-hyporesponsive episodes.

4. Major known congenital malformation or serious chronic disorder.

5. Known history of TBEV infection.

6. Known history of other flavivirus infection (eg, dengue fever, yellow fever, JEV, West Nile virus).

7. Known history of infection with HIV, HCV, or HBV.

8. Immunocompromised participants with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

9. History of autoimmune disease or an active autoimmune disease requiring therapeutic intervention including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and/or insulin-dependent diabetes mellitus (type 1).

10. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participants inappropriate for entry into this study.

11. Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate any type of injection.

Prior/Concomitant Therapy:

12. Previous vaccination with any licensed or investigational TBE vaccine, or planned receipt of other flavivirus vaccines apart from JEV vaccine (eg, yellow fever, dengue fever) during the study. (Note: Administration of JEV vaccine is prohibited during a participant's participation in this study.)

13. Participants who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before investigational product administration. Intra-articular, intrabursal, inhaled/nebulized, or topical (skin or eyes) corticosteroids are permitted.

14. Receipt of blood/plasma products or immunoglobulin, from 60 days before investigational product administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

15. Previous administration with an investigational drug within 30 days prior to study entry and/or during study participation. Participation in purely observational studies is acceptable.

Diagnostic Assessments:

Not applicable.

Other Exclusions:

16. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

17. Females who are pregnant or breastfeeding.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his/her partner(s) CCI [redacted] and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent (or whose legally acceptable representative/parent/legal guardian consent if the participant is 1 to <20 years of age) to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions may allow a participant to be enrolled/started on study intervention once the conditions have resolved and the participant is otherwise eligible:

- Current febrile illness (axillary temperature 37.5°C) or other acute illness within 48 hours before investigational product administration.
- Receipt of systemic antibiotic therapy for other acute illness within 72 hours before investigational product administration.
- Receipt of any inactivated vaccine within 14 days or any live vaccine within 28 days before or anticipated receipt of any vaccine within the 14 days (in the case of inactivated vaccine) or 28 days (in the case of live vaccine) after investigational product administration.
- Receipt of short-term (<14 days) systemic corticosteroids. Investigational product administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

<table>
<tr><td>Intervention Name</td><td>Tick-borne encephalitis vaccine, PF-06830414</td></tr>
<tr><td>Type</td><td>Biologic</td></tr>
<tr><td>Dose Formulation</td><td>Suspension for injection in a pre-filled syringe

Composition of TBE Vaccines
<table>
<tr><th>Composition of a Single Dose</th><th>FSME-IMMUN 0.25 mL</th><th>FSME-IMMUN 0.5 mL</th></tr>
<tr><td>Formaldehyde-inactivated TBEV[a]</td><td>Target 1.2 µg (range 1.00-1.38 µg)</td><td>Target 2.4 µg (range 2.00-2.75 µg)</td></tr>
<tr><td>Aluminum hydroxide, hydrated</td><td>0.17 mg Al^{3+}</td><td>0.35 mg Al^{3+}</td></tr>
<tr><td>Human serum albumin</td><td>0.25 mg</td><td>0.5 mg</td></tr>
<tr><td>Sodium chloride</td><td>1.725 mg</td><td>3.45 mg</td></tr>
<tr><td>Disodium hydrogen phosphate</td><td>0.11 mg</td><td>0.22.mg</td></tr>
<tr><td>Potassium dihydrogen phosphate</td><td>0.023 mg</td><td>0.045 mg</td></tr>
<tr><td>Water for injection</td><td>ad 0.25 mL</td><td>ad 0.5 mL</td></tr>
</table>
a. Produced using a CC working virus seed and consisting of a sterile suspension of formaldehyde-inactivated and sucrose gradient purified TBEV antigen.</td></tr>
<tr><td>Unit Dose Strength(s)</td><td>• 2.4 µg/0.5 mL (for participants ≥16 years of age)
• 1.2 µg/0.25 mL (for participants ≥1 to <16 years of age)</td></tr>
<tr><td>Dosage Level(s)</td><td>1st dose 0.5 mL or 0.25 mL
2nd dose (21-35 days after 1st dose) 0.5 mL or 0.25 mL
3rd dose (150-365 days after 2nd dose) 0.5 mL or 0.25 mL</td></tr>
<tr><td>Route of Administration</td><td>Intramuscular</td></tr>
<tr><td>IMP or NIMP</td><td>IMP</td></tr>
<tr><td>Sourcing</td><td>Provided centrally by the sponsor</td></tr>
<tr><td>Packaging and Labeling</td><td>Study intervention will be provided in an open-label carton that includes 1 prefilled syringe. Each carton will be labeled as required per country requirement.</td></tr>
</table>

6.1.1. Administration

Participants will receive 1 dose of TBE vaccine at each vaccination visit (Visits 1, 2, and 4) in accordance with the study's SoA.

TBE Vaccine 2.4 µg/0.5 mL

In participants ≥16 years of age, TBE vaccine should be administered intramuscularly by injecting 0.5 mL into the deltoid muscle of the right or left arm (preferably the nondominant arm).

TBE Vaccine 1.2 µg/0.25 mL

In participants <16 years of age, TBE vaccine should be administered intramuscularly by injecting 0.25 mL into the deltoid muscle of the right or left arm (preferably the nondominant arm), except for children up to 18 months of age or when dependent on a child's development and nutrition status. For children ≤18 months of age, TBE vaccine should be

administered intramuscularly by injecting 0.25 mL into the anterolateral thigh muscle of the leg at the vaccination visits.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.1.2. Medical Devices

1. Instructions for medical device use as a prefilled syringe are provided in the IP manual.

2. All medical device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.9) and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

CCI

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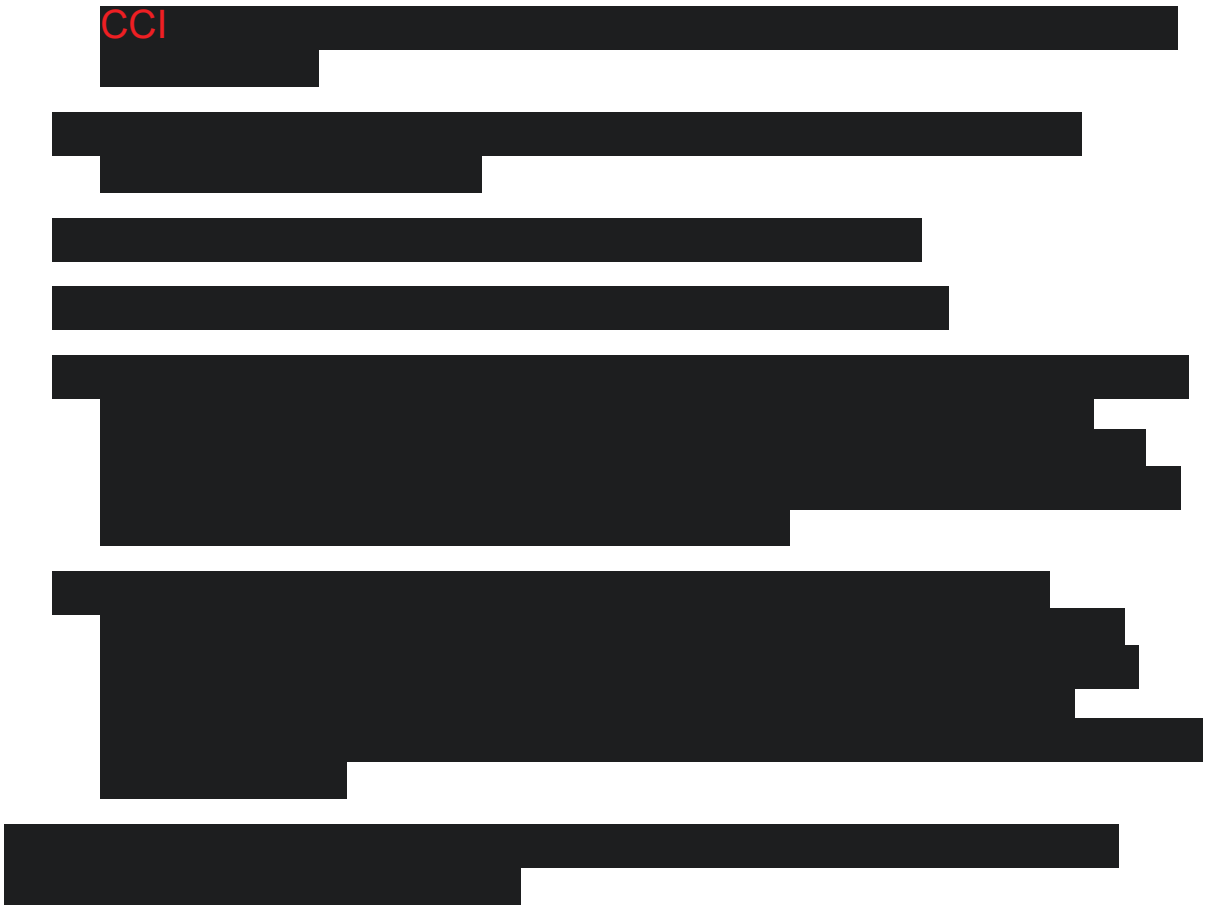
[redacted]



[redacted]

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

This is an open-label study; however, the specific study intervention dispensed to the participant will be assigned using an IRT. The site will contact the IRT prior to the start of study intervention administration for each participant. The site will record the study intervention assignment on the applicable CRF, if required.

The investigator's knowledge of the study intervention should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

Study intervention will be dispensed at the study visits summarized in the SoA.

Dispensed and unused study intervention must not be redispensed to other participants.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The site will complete the required dosage preparation record located in the IP manual. The use of the preparation record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the preparation record after approval from the sponsor and/or designee.

6.5. Concomitant Therapy

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

6.5.1. Prohibited Concomitant Vaccines and Treatments Prior to the Study

- Licensed or investigational TBE vaccines.
- Any inactivated vaccine within 14 days or any live vaccine within 28 days before or after investigational product administration.
- Prior receipt of flavivirus vaccines (eg, yellow fever, dengue fever) apart from JEV vaccine, which is permitted if received prior to the study.

6.5.2. Prohibited Concomitant Vaccines and Treatments During the Study

- Nonstudy investigational vaccines, investigational drugs, or investigational medical devices.
- Licensed or investigational TBE vaccines.
- Blood/plasma products or immunoglobulins.
- Other flavivirus vaccines (eg, yellow fever, dengue fever, JEV) during the study.

- Systemic immunosuppressive therapy is prohibited during the study; however, topical corticosteroids (eg, intra-articular, inhaled/nebulized, intrabursal, skin, or eyes, etc) is permitted.

- Unless administration is considered immediately medically necessary, no vaccines should be administered until at least 14 days after investigational product administration in the case of inactivated vaccines, or at least 28 days after in the case of live vaccines.

6.5.3. Permitted Concomitant Vaccines and Treatments During the Study

- If medically necessary (eg, pandemic or outbreak with pandemic potential), influenza or other pandemic vaccines may be given at any time (however, an interval of >14 days prior to or >14 days after investigational product administration is preferred).

- Any licensed vaccine other than flavivirus vaccine is permitted but may not be administered concurrently with the investigational product. Whenever possible, any licensed vaccine should be administered at least 14 days for inactivated vaccines, or at least 28 days for live vaccines, before or after study vaccination.

- The use of antipyretics and other pain medication to treat symptoms associated with investigational product administration is permitted during participation in the study. The use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of vaccination.

- A topical anesthetic is permitted only for blood sample collection.

- Medications other than those described as prohibited are permitted.

6.5.4. Recording Prior and Concomitant Vaccines and Treatments

The name and date of administration for any nonstudy vaccinations received from the time of signing of the ICD until the final visit will be collected and recorded in the CRF.

History of JEV vaccination of participants will be collected at Visit 1 as far as possible.

6.6. Dose Modification

Not applicable.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following: a participant no longer meets the eligibility criteria during the vaccination period of the study (eg, pregnancy).

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety. See the SRM for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, postvaccination study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant (or legally acceptable representative/parent/legal guardian if the participant is 1 to <20 years of age) may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs/SAEs;
- Protocol deviation;
- Physician decision;
- Request by the participant or participant's legally acceptable representative/parent/legal guardian;
- No longer meets eligibility criteria;
- Pregnancy.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant or participant's parent(s)/legal guardian(s). All attempts to contact the participant or participant's parent(s)/legal guardian(s) and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

At the time of discontinuation, please refer to the ISF and SRM for assessments to be collected at the time of study discontinuation and follow up and for any further evaluations that need to be completed.

The participant should be requested to return for a final visit, if applicable, and the investigator will perform the procedures indicated for the next visit. Any AEs or SAEs that are continuing at the time of withdrawal from the study should be followed until resolution or, in case of permanent impairment, until the condition stabilizes.

If a participant withdraws from the study, he/she or the participant's parent(s)/legal guardian(s) may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or postvaccination study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD (and assent, if applicable) before performing any study-specific procedures.

The date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 10 mL (for participants ≥1 to <16 years of age; the minimum is 5 mL). The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.1.1. Immunogenicity Assessments

Blood samples will be collected from all participants at Visit 1 (Day 1), Visit 3 (21-35 days after the second vaccination), Visit 4 (150-365 days after the second vaccination), and Visit 5 (21-35 days after the third vaccination). These are the immunogenicity time points.

Group 1: Participants ≥16 Years of Age
The volume of the blood sample is approximately 10 mL at each blood sample collection visit.

Group 2: Participants ≥1 to <16 Years of Age
Considering the difficulty of blood sample collection, the volume of the blood sample is approximately 10 mL (the minimum is 5 mL) at each blood sample collection visit.

8.1.1.1. TBEV Antibody Testing

Sera will be assayed for TBEV-neutralizing antibody levels, CCI at baseline, 4 weeks after the second vaccination, and prior to and 4 weeks after the third vaccination. At the third vaccination visit, the blood sample will be collected prior to vaccination.

NT titers ≥10 CCI are considered seropositive.[13] CCI

TBE antibody response will be determined CCI by means of NT.[15]

CCI

The tests will be performed at the following laboratories:

- Serological and Biochemical Control, Quality Control Vaccines, Pfizer QC / Biological Lab I, Austria.

CCI

8.1.2. Biological Samples

Blood samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. CCI No testing of the participant's genetic material will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's genetic material is performed.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues. Medical history, temperature, physical examination (as clinically indicated for the second and third doses), and assessment of eligibility will be conducted for all participants before administration of each dose of TBE vaccine. The participants will be observed for at least 30 minutes after vaccination and any acute (immediate) reactions will be assessed and recorded.

Common for Groups 1 and 2

Local reactions, systemic events, temperature, and antipyretic and/or pain medication use will be prompted for and collected daily in an e-diary from Day 1 to Day 7 after each dose of vaccination.

8.2.1. Participant Electronic Diary

The participant (or participant's parent[s]/legal guardian[s] if the participants is ≥1 to <16 years of age) will be asked to record the use of antipyretic/pain medication (yes/no) in the e-diary (in a provisioned device or application on a personal device) in the evening, daily, for 7 days after each dose of investigational product. The use of prophylactic antipyretic/pain medication, while permitted to treat symptoms associated with investigational product administration, is not recommended on the day of investigational product administration (before or after vaccination). For participants 16 to <20 years of age, the participant's parent(s)/legal guardian(s) should monitor the participant's compliance with data entry.

8.2.2. Grading Scale for Prompted Events

The grading scales used in this study to assess prompted events as described below are based on concepts outlined in the FDA CBER guidelines on toxicity grading scales for adults and adolescent volunteers enrolled in preventive vaccine clinical trials, but have been adapted for applicability to healthy infants.

8.2.2.1. Local Reactions

Local reactions, including pain, redness, and swelling at the injection site on the deltoid or anterolateral thigh, will be prompted for and collected daily for the first 7 days following each vaccination (Days 1 through 7, where Day 1 is the day of vaccination) in an e-diary according to the grading scale in Table 1 (≥16 years of age), Table 2 (1 to ≤2 years of age), Table 3 (>2 to <12 years of age), or Table 4 (≥12 to <16 years of age). The participant or participant's parent(s)/legal guardian(s) will be prompted to contact the investigator if the participant experiences a severe (Grade 3 or above) local reaction to assess the reaction and perform an unscheduled assessment or visit as appropriate.

Only an investigator is able to classify a participant's local reaction as Grade 4, after physical examination of the participant or documentation from another medically qualified source (eg, emergency room or hospital record). If a participant experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. Site staff will educate the participant's parent(s)/legal guardian(s) regarding signs and symptoms that would prompt site contact.

The procedure for notification of the sponsor is provided in the ISF or equivalent.

Group 1: Participants ≥16 Years of Age

Redness and swelling will be measured and recorded in caliper units (range: 1 to >21) by the participant, and then categorized as mild, moderate, or severe based on the grading scale in Table 1 for participants ≥16 years of age. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. Participants' legally acceptable representative/parent/legal guardian should monitor the participants' compliance of data entry for participants 16 through 19 years of age.

Table 1. Grading Scale for Local Reactions (Participants ≥16 Years of Age)

	Mild Grade 1	Moderate Grade 2	Severe Grade 3[a]	Grade 4[b]
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (>20 measuring device units)	Necrosis or exfoliative dermatitis[b]
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (>20 measuring device units)	Necrosis[b]
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain at the injection site

a. Participants experiencing local reactions >20 caliper units (>10 cm) are to be seen by or contact the study site; an unscheduled visit may be required.
b. Grade 4 assessment must be made by an investigator; Grade 4 will not be collected in the e-diary but will be collected in the case report form. The severity of the local reaction should be graded using the AE severity grading scale provided in the protocol.

Group 2: Participants ≥1 to <16 Years of Age

Participants 1 to ≤2 Years of Age

Redness and swelling will be measured and recorded in caliper units (range: 1 to >14) by the participant's legally acceptable representative/parent/legal guardian, and then categorized as mild, moderate, or severe based on the grading scale in Table 2 for participants 1 to ≤2 years of age. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm.

Table 2. Grading Scale for Local Reactions (Participants 1 to ≤2 Years of Age)

	Mild Grade 1	Moderate Grade 2	Severe Grade 3[a]	Grade 4[b]
Redness	>0.5 cm to 2.0 cm (1 to 4 measuring device units)	>2.0 cm to 7.0 cm (5 to 14 measuring device units)	>7.0 cm (>14 measuring device units)	Necrosis or exfoliative dermatitis[b]
Swelling	>0.5 cm to 2.0 cm (1 to 4 measuring device units)	>2.0 cm to 7.0 cm (5 to 14 measuring device units)	>7.0 cm (>14 measuring device units)	Necrosis[b]
Pain at the injection site (tenderness)	Hurts if gently touched (eg, whimpers, winces, protests or withdraws)	Hurts if gently touched with crying	Causes limitation of limb movement	Emergency room visit or hospitalization for severe pain at the injection site

a. Participants experiencing local reactions >14 caliper units (>7.0 cm) are to be seen by or contact the study site; an unscheduled visit may be required.
b. Grade 4 assessment must be made by an investigator; Grade 4 will not be collected in the e-diary but will be collected in the case report form. The severity of the local reaction should be graded using the AE severity grading scale provided in the protocol.

Participants >2 to <12 Years of Age

Redness and swelling will be measured and recorded in caliper units (range: 1 to >14) by the participant's legally acceptable representative/parent/legal guardian, and then categorized as mild, moderate, or severe based on the grading scale in Table 3 for participants >2 to <12 years of age. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm.

Table 3. Grading Scale for Local Reactions (Participants >2 to <12 Years of Age)

	Mild Grade 1	Moderate Grade 2	Severe Grade 3[a]	Grade 4[b]
Redness	>0.5 cm to 2.0 cm (1 to 4 measuring device units)	>2.0 cm to 7.0 cm (5 to 14 measuring device units)	>7.0 cm (>14 measuring device units)	Necrosis or exfoliative dermatitis[b]
Swelling	>0.5 cm to 2.0 cm (1 to 4 measuring device units)	>2.0 cm to 7.0 cm (5 to 14 measuring device units)	>7.0 cm (>14 measuring device units)	Necrosis[b]
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain at the injection site

a. Participants experiencing local reactions >14 caliper units (>7.0 cm) are to be seen by or contact the study site; an unscheduled visit may be required.
b. Grade 4 assessment must be made by an investigator; Grade 4 will not be collected in the e-diary but will be collected in the case report form. The severity of the local reaction should be graded using the AE severity grading scale provided in the protocol.

Participants ≥12 to <16 Years of Age

Redness and swelling will be measured and recorded in caliper units (range: 1 to >20) by the participant's legally acceptable representative/parent/legal guardian, and then categorized as mild, moderate, or severe based on the grading scale in Table 4 for participants ≥12 to <16 years of age. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm.

Table 4. Grading Scale for Local Reactions (Participants ≥12 to <16 Years of Age)

	Mild Grade 1	Moderate Grade 2	Severe Grade 3[a]	Grade 4[b]
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (>20 measuring device units)	Necrosis or exfoliative dermatitis[b]
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units))	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (>20 measuring device units)	Necrosis[b]
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain at the injection site

a. Participants experiencing local reactions >20 caliper units (>10 cm) are to be seen by or contact the study site; an unscheduled visit may be required.
b. Grade 4 assessment must be made by an investigator; Grade 4 will not be collected in the e-diary but will be collected in the case report form. The severity of the local reaction should be graded using the AE severity grading scale provided in the protocol.

8.2.2.2. Systemic Events

Group 1: Participants ≥16 Years of Age

For 7 consecutive days starting on the day of each vaccination (eg, study Day 1 to Day 7), participants are to assess fatigue, headache, vomiting, diarrhea, muscle pain, and joint pain in the e-diary according to the grading scale in Table 5. Participants' legally acceptable representative/parent/legal guardian should monitor the participants' compliance of data entry for participants 16 through 19 years of age. Participants will also be instructed to contact site staff if the participant experiences any possible Grade 4 prompted systemic event (ie, emergency room visit or hospitalization for severe fatigue, headache, vomiting, diarrhea, muscle pain, or joint pain) within 7 days after vaccination. Study staff may also contact the participant to obtain additional information on Grade 3 events entered into the e-diary.

Only an investigator is able to classify a participant's systemic event as Grade 4, after physical examination of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. If a participant experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor.

The procedure for notification of the sponsor is provided in the ISF or equivalent.

Table 5. Grading Scale for Systemic Events (Participants ≥16 Years of Age)

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Fatigue (= tiredness in diaries)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires intravenous hydration	Emergency room visit or hospitalization for severe vomiting
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe muscle pain
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe joint pain

a. Grade 4 assessment must be made by an investigator; Grade 4 will not be collected in the e-diary but will be collected in the case report form.

The participant will be asked to record the use of antipyretic and/or pain medication in the e-diary from Day 1 to Day 7 after vaccination. Participants' legally acceptable representative/parent/legal guardian should monitor the participants' compliance of data entry for participants 16 through 19 years of age.

Group 2: Participants ≥1 to <16 Years of Age

For 7 consecutive days starting on the day of vaccination (eg, study Day 1 to Day 7), participants' parent(s)/legal guardian(s) are to assess fatigue, headache, vomiting, diarrhea, muscle pain, joint pain, decreased appetite, drowsiness, and irritability in the e-diary according to the grading scale in Table 6, Table 7, or Table 8 according to the participant's age. The participant's parent(s)/legal guardian(s) will also be instructed to contact site staff if the participant experiences any possible Grade 4 prompted systemic event (ie, emergency room visit or hospitalization for severe fatigue, headache, vomiting, diarrhea, muscle pain, or joint pain) within 7 days after vaccination. Study staff may also contact the participant to obtain additional information on Grade 3 events entered into the e-diary.

Only an investigator is able to classify a participant's systemic event as Grade 4, after physical examination of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or telephone contact with the participant. If a participant experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor.

The procedure for notification of the sponsor is provided in the ISF or equivalent.

The participant's parent(s)/legal guardian(s) will be asked to record the use of antipyretic and/or pain medication in the e-diary from Day 1 to Day 7 after vaccination in an e-diary.

Participants 1 to ≤2 Years of Age

Table 6. Grading Scale for Systemic Events (Participants 1 to ≤2 Years of Age)

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Decreased appetite (Loss of appetite)	Decreased interest in eating	Decreased oral intake	Refusal to feed	Emergency room visit or hospitalization for severe decreased appetite (loss of appetite)
Drowsiness (increased sleep)	Increased or prolonged sleeping bouts	Slightly subdued interfering with daily activity	Disabling not interested in usual daily activity.	Emergency room visit or hospitalization for severe drowsiness (increased sleep)
Irritability (fussiness) (synonymous with restless sleep; decreased sleep)	Easily consolable	Requiring increased attention	Inconsolable; crying cannot be comforted	Emergency room visit or hospitalization for severe irritability (fussiness)

a. Grade 4 assessment must be made by an investigator; Grade 4 will not be collected in the e-diary but will be collected in the case report form.

Participants >2 to <12 Years of Age

Table 7. Grading Scale for Systemic Events (Participants >2 to <12 Years of Age)

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Fatigue (= tiredness in diaries)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires intravenous hydration	Emergency room visit or hospitalization for severe vomiting

Table 7. Grading Scale for Systemic Events (Participants >2 to <12 Years of Age)

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe muscle pain
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe joint pain

a. Grade 4 assessment must be made by an investigator; Grade 4 will not be collected in the e-diary but will be collected in the case report form.

Participants ≥12 to <16 Years of Age

Table 8. Grading Scale for Systemic Events (Participants ≥12 to <16 Years of Age)

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
Fatigue (= tiredness in diaries)	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires intravenous hydration	Emergency room visit or hospitalization for severe vomiting
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe muscle pain
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe joint pain

a. Grade 4 assessment must be made by an investigator; Grade 4 will not be collected in the e-diary but will be collected in the case report form.

8.2.2.2.1. Fever

Common for Groups 1 and 2

In order to record information on fever, a digital thermometer will be given to the participant or participant's parent(s)/legal guardian(s) with instructions on how to measure axillary temperature at home. Temperature will be prompted for and collected in the evening, daily, in the e-diary for 7 days following each study vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination) and at any time during the 7 days that fever is suspected. The highest temperature for each day will be recorded in the e-diary. Temperature will be collected daily until fever has resolved (1 day of temperature less than 37.5°C) in order to collect a stop date in the CRF. A participant or participant's parent(s)/legal guardian(s) will be prompted to contact the investigator if the participant experiences a fever >40.0°C within the 7 days following vaccination to assess the fever and perform an unscheduled assessment, as applicable (see Section 8.11.6). Study staff may also contact the participant's parent(s)/legal guardian(s) to obtain additional information if a temperature of >38.9°C is entered into an e-diary. Temperature measured by the axillary route will be recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 9 below.

Table 9. Ranges for Fever

	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4
Fever	≥37.5°C; ≤38.4°C	≥38.5°C; ≤38.9°C	≥39.0°C; ≤40.0°C	>40.0°C

8.2.3. Physical Examinations

Physical examination (at Visit 1) will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.

Prior to subsequent vaccination (at Visits 2 and 4), physical examination should be performed if the clinical assessment indicates that it is necessary to comprehensively evaluate the participant.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.4. Vital Signs

Axillary temperature will be assessed prior to vaccination and recorded in the CRF. If multiple measurements are taken at the same time point, the most out-of-range (eg, highest) value must be recorded.

8.2.5. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will not be collected for this study.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 8. Device deficiencies are covered in Section 8.3.9.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant/parent/legal guardian/legally authorized representative will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant /parent(s)/legal guardian/legally authorized representative provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 3, and from Visit 4 to Visit 5. Between Visit 3 and Visit 4, only SAEs will be reported.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Reporting Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Reporting Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the Vaccine SAE Reporting Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.

- A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Reporting Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until delivery.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Reporting Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the ISF.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Reporting Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Reporting Form is maintained in the ISF.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Reporting Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Reporting Form is maintained in the ISF.

8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Not applicable.

8.3.9. Medical Device Deficiencies

Medical devices are being provided for use in this study as the study intervention is supplied in prefilled syringes. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 8.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.1 through 8.3.4 and Appendix 3 of the protocol.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies or malfunctions of the device will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Appendix 8.

8.3.9.2. Follow-up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on a follow-up form with all changes signed and dated by the investigator.

8.3.9.3. Prompt Reporting of Device Deficiencies to Sponsor

Device deficiencies will be reported to the sponsor within 1 day after the investigator determines that the event meets the protocol definition of a medical device deficiency. Information will be provided to the sponsor as described in the IP manual. The medical device complaint CRF will also be completed.

Any device deficiency that is associated with an SAE must be reported to Pfizer Safety within 24 hours upon the investigator's awareness as outlined in Sections 8.3.1.1 and 8.3.1.2.

The sponsor will be the contact for the receipt of device deficiency information.

8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength. Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	**Recorded on the CRF**	**Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness**
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Reporting Form **only when associated with an SAE.**

- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

8.4. Treatment of Overdose

For this study, any dose of TBE vaccine greater than 1 dose (0.5 mL for participants ≥16 years of age, 0.25 mL for participants ≥1 to <16 years of age) within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

CCI [redacted]

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.1.1.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

The study procedures are summarized in the SoA. The day of Dose 1 is considered to be Day 1.

Unless specified in the sections below, the order of key procedures within a given visit may have some flexibility.

8.11.1. Visit 1 (Dose 1 Visit, Day 1)

Prior to vaccination:

- For participants ≥20 years of age: Obtain a personally signed and dated ICD indicating that the participant has been informed of all pertinent aspects of the study before performing any study-specific procedures.
- For participants <20 years of age: Obtain a personally signed and dated ICD indicating that the participant's parent(s)/legal guardian(s) has been informed of all pertinent aspects of the study before performing any study-specific procedures. Considering the participant's age and the capacity to understand, assent from participant should be obtained.
- Assign a participant number via the IRT.
- Obtain and record the participant's demographic information (including date of birth, sex, race, and ethnicity). The complete date of birth (ie, DD-MMM-YYYY) will be collected to critically evaluate the immune response and safety profile by age.
- Perform a clinical assessment, including medical history (including significant birth history) and physical examination; record any findings on the medical history CRF.

- Record vaccine history.
- Record concomitant medications used to treat SAEs.
- Measure and record the participant's axillary temperature (°C).
- Collect a blood sample of approximately 10 mL (for participants ≥1 to <16 years of age; the minimum is 5 mL) for immunogenicity (a topical anesthetic is permitted).
- For female participants of childbearing potential: Discuss contraceptive use and perform a urine pregnancy test. The result of the pregnancy test must be confirmed before administration of investigational product.
- Ensure that all inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met.
- Assign an investigational product container number via the IRT. This must be the last step before proceeding. A site staff member will prepare the investigational product according to the IP manual.

After enrollment:

- The investigator or delegated site staff will administer a single 0.5-mL or 0.25-mL injection of TBE vaccine into the deltoid muscle (or anterolateral thigh, if the participant is <18 months of age).
- The investigator or delegated site staff will observe the participant for 30 minutes after vaccination for any reactions.
- Record any AEs on the CRF and on an SAE form as applicable. Record concomitant medications used to treat SAEs.
- Issue the participant or participant's parent(s)/legal guardian(s) a measuring device to measure TBE vaccine injection site reactions and a digital thermometer and provide instructions on their use.
- Issue the participant or participant's parent(s)/legal guardian(s) an e-diary (device or application).
- Provide instructions on use and completion of the e-diary. Ask the participant or participant's parent(s)/legal guardian(s) to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant or participant's parent(s)/legal guardian(s) to contact the investigator site staff or investigator as soon as possible during the 7-day postvaccination period if the participant has a fever >40.0°C, redness and/or swelling at the TBE vaccine injection site measuring >20 measuring device units (if the participant is ≥12 years of age) or >14 measuring device units (>7 cm, if the participant is <12 years of age), or severe TBE vaccine injection site pain (prevents daily activity [in participants >2 years of age] or causes limitation of limb movement [in participants ≤2 years of age]) to determine if the event requires further assessment by the investigator.

- Ask the participant/participant's parent(s)/legal guardian(s) to contact the investigator or investigator site staff as soon as possible if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs.

- Provide the participant or participant's parent(s)/legal guardian(s) with the participant contact card containing the study and investigator information (see Section 10.1.10).

- Inform the participant or participant's parent(s)/legal guardian(s) that the use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).

- The investigator or an authorized designee completes the CRF and the source documents and the site staff will update the investigational product accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of the ongoing safety review.

8.11.2. Visit 2 (Dose 2 Visit, 21-35 Days After Visit 1 [Dose 1])

- Ensure and document that the participant continues to be eligible for the study (see Section 7.2 for participant discontinuation/withdrawal) and none of the temporary delay criteria are met (Section 5.5).

- Record nonstudy vaccinations administered since Visit 1, as described in Section 6.5.

- Record concomitant medications used to treat SAEs since Visit 1, as described in Section 6.5.

- Review the participant's e-diary data with the participant or participant's parent(s)/legal guardian(s); collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.

- Determine whether any AEs (includes nonserious AEs and SAEs) have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in Section 10.3, and record concomitant medications used to treat SAEs.

- Measure and record the participant's axillary temperature (°C).

- For female participants of childbearing potential: Discuss contraceptive use and perform a urine pregnancy test. The result of pregnancy test must be confirmed before administration.

- Investigator or delegated site staff will administer a single 0.5-mL or 0.25-mL injection of TBE vaccine into the deltoid muscle (or anterolateral thigh, if the participant is <18 months of age).

After vaccination:

- Investigator or delegated site staff will observe the participant for 30 minutes after vaccination for any reactions.

- Record any AEs on the CRF and on an SAE form as applicable. Record concomitant medications used to treat SAEs.

- Confirm that the e-diary is working and review instructions if necessary. Remind the participant or participant's parent(s)/legal guardian(s) to complete the e-diary for 7 days after the day of vaccination. Provide a thermometer or measuring device if needed.

- Ask the participant or participant's parent(s)/legal guardian(s) to contact the investigator site staff or investigator as soon as possible during the 7-day postvaccination period if the participant has a fever >40.0°C, redness and/or swelling at the TBE vaccine injection site measuring >20 measuring device units (if the participant is ≥12 years of age) or >14 measuring device units (>7 cm, if the participant is <12 years of age), or severe TBE vaccine injection site pain (prevents daily activity [in participants >2 years of age] or causes limitation of limb movement [in participants ≤2 years of age]) to determine if the event requires further assessment by the investigator.

- Remind the participant or participant's parent(s)/legal guardian(s) to contact the investigator or investigator site staff as soon as possible if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.

- Confirm whether the participant or participant's parent(s)/legal guardian(s) still possesses the participant contact card. Provide a participant contact card if needed.

- Remind the participant or participant's parent(s)/legal guardian(s) that the use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).

- The investigator or an authorized designees completes the CRF and the source documents and the site staff will update the investigational product accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of the ongoing safety review.

8.11.3. Visit 3 (Blood Draw Visit, 21-35 Days After Visit 2 [Dose 2])

- Ensure and document that the participant continues to be eligible for the study (see Section 7.2 for participant discontinuation/withdrawal).
- Record nonstudy vaccinations administered since Visit 2, as described in Section 6.5.
- Record concomitant medications used to treat SAEs since Visit 2, as described in Section 6.5.
- Review the participant's e-diary data with the participant or participant's parent(s)/legal guardian(s); collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.
- Determine whether any AEs (includes nonserious AEs and SAEs) have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in Section 10.3, and record concomitant medications used to treat SAEs.
- Collect a blood sample of approximately 10 mL (for participants ≥1 to <16 years; the minimum is 5 mL) for immunogenicity (a topical anesthetic is permitted).
- Remind the participant or participant's parent(s)/legal guardian(s) to contact the investigator or investigator site staff as soon as possible if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.
- Confirm whether the participant's parent(s)/legal guardian(s) still possesses the participant contact card. Provide a participant contact card if needed.
- The investigator or an authorized designee completes the CRF and the source documents and updates the investigational product accountability records.

8.11.4. Visit 4 (Dose 3 Visit, 150-365 Days After Dose 2)

- Ensure and document that the participant continues to be eligible for the study (see Section 7.2 for participant discontinuation/withdrawal) and none of the temporary delay criteria are met (Section 5.5).
- Record nonstudy vaccinations administered since Visit 3, as described in Section 6.5.
- Record concomitant medications used to treat SAEs since Visit 1, as described in Section 6.5.

- Determine whether any SAEs have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in Section 10.3, and record concomitant medications used to treat SAEs.

- Measure and record the participant's axillary temperature (°C).

- Collect a blood sample of approximately 10 mL (for participants ≥1 to <16 years; the minimum is 5 mL) for immunogenicity (a topical anesthetic is permitted).

- For female participants of childbearing potential: Discuss contraceptive use and perform a urine pregnancy test. The result of the pregnancy test must be confirmed before administration.

- The investigator or delegated site staff will administer a single 0.5-mL or 0.25-mL injection of TBE vaccine into the deltoid muscle (or anterolateral thigh, if the participant is <18 months of age).

After vaccination:

- The investigator or delegated site staff will observe the participant for 30 minutes after vaccination for any reactions.

- Record any AEs on the CRF and on an SAE form as applicable. Record concomitant medications used to treat SAEs.

- Issue the participant or participant's parent(s)/legal guardian(s) an e-diary (device or application).

- Provide instructions on use and completion of the e-diary. Ask the participant or participant's parent(s)/legal guardian(s) to complete the e-diary for 7 days after the day of vaccination.

- Ask the participant or participant's parent(s)/legal guardian(s) to contact the investigator site staff or investigator as soon as possible during the 7-day postvaccination period if the participant has a fever >40.0°C, redness and/or swelling at the TBE vaccine injection site measuring >20 measuring device units (if the participant is ≥12 years of age) or >14 measuring device units (>7 cm, if the participant is <12 years of age), or severe TBE vaccine injection site pain (prevents daily activity [in participants >2 years of age] or causes limitation of limb movement [in participants ≤2 years of age]) to determine if the event requires further assessment by the investigator.

- Remind the participant or participant's parent(s)/legal guardian(s) to contact the investigator or investigator site staff as soon as possible if any significant illness or medical event (eg, emergency room visit or hospitalization) occurs during the study period.

- Confirm whether the participant or participant's parent(s)/legal guardian(s) still possesses the participant contact card. Provide a participant contact card if needed.

- Remind the participant or participant's parent(s)/legal guardian(s) that the use of prophylactic antipyretic/pain medication, while permitted, is not recommended on the day of investigational product administration (before or after vaccination).

- The investigator or an authorized designees completes the CRF and the source documents and updates the investigational product accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online at frequent intervals for the 7 days following vaccination to evaluate participant compliance and as part of the ongoing safety review.

8.11.5. Visit 5 (Dose 3 Follow-up Visit, 21-35 Days After Visit 4 [Dose 3])

- Ensure and document that the participant continues to be eligible for the study (see Section 7.2 for participant discontinuation/withdrawal) and none of the temporary delay criteria are met (Section 5.5).

- Record nonstudy vaccinations administered since Visit 5, as described in Section 6.5.

- Record concomitant medications used to treat SAEs since Visit 1, as described in Section 6.5.

- Review the participant's e-diary data with the participant's parent(s)/legal guardian(s); collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF.

- Collect the e-diary (if a device was provided).

- Determine whether any AEs (includes nonserious AEs and SAEs) have occurred since the previous visit and follow up on any previously reported events to determine the outcome (ie, record stop dates or confirm if they are still continuing) and record as described in Section 10.3, and record concomitant medications used to treat SAEs.

- Collect a blood sample of approximately 10 mL (for participants ≥1 to <16 years of age; the minimum is 5 mL) for immunogenicity (a topical anesthetic is permitted).

- The investigator or an authorized designee completes the CRF and the source documents.

8.11.6. Unscheduled Visits

If the participant or participant's parent(s)/legal guardian(s) reports redness and/or swelling at the TBE vaccine injection site measuring >20 measuring device units (if the participant is ≥12 years of age) or >14 measuring device units (>7 cm, if the participant is <12 years of age), severe injection site pain, or a fever >40.0°C during the 7-day postvaccination period, a telephone contact must occur as soon as possible between the investigator or medically qualified designee and the participant/participant's parent(s)/legal guardian(s) to assess if an unscheduled investigator site visit is required. Note that for a fever >40.0°C, the participant or participant's parent(s)/legal guardian(s) should be instructed not to delay seeking medical care, as appropriate, while arranging for an unscheduled visit if applicable. A visit should be scheduled as soon as possible to assess the extent of the injection site reaction, unless any of the following is true:

- The participant is unable to visit the site for unscheduled visit.
- The participant's parent(s)/legal guardian(s) is unable to bring the participant to the unscheduled visit.
- The reaction is no longer present at the time of the telephone contact.
- The participant or participant's parent(s)/legal guardian(s) recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error).
- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to visit the site for unscheduled visit, the participant's parent(s)/legal guardian(s) is unable to bring the participant to an unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing reactions must be assessed at the next study visit.

During the investigator site visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure axillary temperature (°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain in accordance with the grades provided in Section 8.2.2 (if present).

- Assess other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

The participant or participant's parent(s)/legal guardian(s) will also be instructed to contact investigator site staff if the participant experiences any emergency room visit or hospitalization for decreased appetite, drowsiness/increased sleep, irritability, or local reaction within 7 days of vaccination.

The participant or participant's parent(s)/legal guardian(s) will also be instructed to contact the investigator site to report any significant illness, medical event, or hospitalization that occurs during the study period. The investigator site should determine if an unscheduled visit to further evaluate the event is warranted in all such cases.

Additionally, study staff may contact the participant or participant's parent(s)/legal guardian(s) to obtain additional information on Grade 3 events entered into the e-diary.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

The primary immunogenicity objective of the study is to assess the immunogenicity of the investigational product by NT in healthy Japanese adults (16 years of age and older) and children (≥1 to <16 years of age) when administered in a 3-dose schedule. The null hypothesis to be tested concerns the seropositivity rate for the primary endpoint in each age group. The immune response induced by TBE vaccine will be evaluated in each age group, testing the hypotheses H_0: seropositivity rate ≤90% vs H_1: seropositivity rate >90%. These hypotheses will be tested by age group separately and no adjustment of multiplicity will be considered. For each age group, if the lower bound of the 95% CI on the NT seropositivity rate among the evaluable population is >90%, the objective is achieved.

9.1.1. Estimands

9.1.1.1. Immunogenicity

9.1.1.1.1. Primary Estimand

The primary estimand is seropositivity rate based on TBEV-neutralizing antibody levels (achieving NT titer ≥1:10) 4 weeks after the third dose for the evaluable population (Section 9.3).

This estimand estimates the immunogenicity in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing serology results are not imputed, as MCAR is assumed. For participants who discontinue the study or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.

9.1.1.1.2. Secondary Estimands

The secondary estimands of this study are following for the evaluable population.

- Seropositivity rate based on TBEV-neutralizing antibody levels (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.

These estimands estimate the immunogenicity in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing serology results are not imputed, as MCAR is assumed. For participants who discontinue the study or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.

9.1.1.2. Safety

In participants receiving at least 1 dose of investigational product:

- The percentage of participants reporting local reactions within 7 days following each vaccination.
- The percentage of participants reporting systemic events within 7 days following each vaccination.
- The percentage of participants reporting AEs within 1 month after each vaccination.
- The percentage of participants reporting SAEs throughout the study.

Missing e-diary data are not imputed. Imputation of missing AE dates and missing AE severity will be applied following Pfizer safety rules.

9.2. Sample Size Determination

Sample sizes are determined as the number of participants to be enrolled that is expected to achieve the criterion of immunogenicity in which the lower limit of 95% CI (Clopper-Pearson method) for the seropositivity rate for the primary endpoint is higher than

90% for each age population. Considering 10% dropouts, approximately 65 child participants and approximately 100 adult participants are intended to be enrolled as in the following, which shows sufficiently high statistical power.

- Adults
  Assuming the expected seropositivity rate among 90 evaluable adults to be 99.4%, the statistical power to demonstrate that the lower limit of the 95% CI of the estimate will exceed 90% is computed to be >99%.

- Children
  Assuming the expected seropositivity rate among 60 evaluable children to be 99.6%, the statistical power to demonstrate that the lower limit of the 95% CI of the estimate will exceed 90% is computed to be 97.3%.

9.3. Analysis Sets

For purposes of analysis, the following populations are defined by age group:

Population	Description
Enrolled	"Enrolled" means that a participant, or his or her legally authorized representative, has agreed to participate in a clinical study following completion of the informed consent process and is deemed eligible to participate. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Evaluable immunogenicity	All participants who are eligible, receive all 3 doses of the investigational product, have blood drawn for assay testing within the specified time frame for baseline and 4 weeks after the third vaccination, have valid and determinate assay result (NT titer) at baseline and 4 weeks after the third vaccination visit, are NT seronegative at baseline, and have no major protocol violations.
All-available immunogenicity	All enrolled participants who receive at least the first 2 doses of the investigational product and have valid and determinate assay results (NT titer CCI [redacted]) 4 weeks after the second and/or the third vaccination.
Safety	All enrolled participants who receive at least 1 dose of the investigational product.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary, CCI [redacted] endpoints. All analyses are conducted by age groups.

9.4.1. Immunogenicity Analyses

Endpoint	Statistical Analysis Methods
Primary	Point estimate and the exact 2-sided 95% CI will be calculated using the Clopper-Pearson method for the seropositivity rate based on the immune response determined by NT 4 weeks after the third vaccination. NT titers ≥1:10 are considered seropositive. The evaluable immunogenicity population will be the primary population for the analysis.
Secondary	Point estimate and the exact 2-sided 95% CI will be calculated using the Clopper-Pearson method for the seropositivity rate based on the immune response determined by NT 4 weeks after the second vaccination. Neutralizing antibody GMT 4 weeks after the second vaccination and 4 weeks after the third vaccination will be calculated. Two-sided 95% CIs for the mean of the logarithmically transformed assay results will be computed based on the Student t distribution. GMFRs and associated 2-sided 95% CIs will be provided for neutralizing antibody titer from baseline to 4 weeks after the second and 4 weeks the third vaccinations. In addition, GMFR will be provided for neutralizing antibody titer from 4 weeks after the second vaccination to 4 weeks after the third vaccination. The GMFR will be calculated as the mean of the difference of logarithmically transformed antibody titers (postvaccination minus prevaccination for each participant) and transformed back to the original scale. Two-sided 95% CIs will be obtained by constructing CIs using 1-sample Student's t distribution for the mean difference of measures on the logarithmically transformed assay results, and transforming the limits back to the original scale. Empirical RCDCs by time points will be presented for neutralizing antibody titer. Titers below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. The above analyses are based on the evaluable immunogenicity population. An additional analysis will be performed based on all-available immunogenicity population if there is enough difference between the all-available immunogenicity population and the evaluable immunogenicity population. Missing serology data are not imputed.

Endpoint	Statistical Analysis Methods
CCI	[redacted]

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

Endpoint	Statistical Analysis Methods
Primary	Point estimate and the exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the percentage of participants reporting each event (local reactions, systemic events, AEs, and SAEs). AEs and SAEs will be categorized according to MedDRA terms. The safety analyses are based on safety population. Missing e-diary data are not imputed; handling missing AE dates and missing AE severity will be applied following the Pfizer safety rules.
Secondary	N/A
CCI	[redacted]

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, and supporting clinical development.

CCI [redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally acceptable representative/parent/legal guardian and answer all questions regarding the study. The participant or his/her legally acceptable representative/parent/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally acceptable representative/parent/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally acceptable representative/parent/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally acceptable representative/parent/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally acceptable representative/parent/legal guardian.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 Jan 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 Jul 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the ISF.

Description of the use of computerized system is documented in the data management plan.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor’s Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the ISF.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant’s participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or

problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol.

- Pregnancy testing
    - Conducted at Visits 1, 2, and 4 (prior to vaccination).

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  - Is associated with accompanying symptoms.
  - Requires additional diagnostic testing or medical/surgical intervention.
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or

convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Reporting Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Reporting Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Reporting Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the Vaccine SAE Reporting Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Reporting Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Reporting Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form

- Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames.

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10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

Not applicable.

10.8. Appendix 8: Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

Both the investigator and the sponsor will comply with all local medical device reporting requirements.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.2 for the list of sponsor medical devices).

10.8.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator for study participants, users, and other persons. This definition also includes events considered related to procedures for study participants only. • An ADE is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.8.2. Definition of SAE, SADE, and Unanticipated Serious Adverse Device Effect

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is an AE that:
a. Led to death.
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term "life-threatening" in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a preexisting condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect.
SADE Definition
• An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
USADE Definition
• A USADE is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.8.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

10.8.4. Recording/Reporting and Follow-up of AEs and/or SAEs and Device Deficiencies

AE, SAE, and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the IP manual and completing the Medical Device Complaint CRF.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/Device Deficiency
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.8.5. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via Vaccine SAE Reporting Form
• Facsimile transmission of the Vaccine SAE Reporting Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Reporting Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Reporting Form pages within the designated reporting time frames.

10.8.6. Reporting of SADEs

SADE Reporting to Pfizer Safety
NOTE: There are additional reporting obligations for medical device incidents that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.9. Appendix 9: Country-Specific Requirements

10.9.1. Japan-Specific Regulatory Requirements

10.9.1.1. Definitions of Serious Adverse Event, Serious Adverse Event Caused by Medical Device, and Unanticipated Serious Adverse Event Caused by Medical Device

Definition of Serious Adverse Event Caused by Medical Device

An SAE caused by medical device is defined as an AE caused by a medical device that led to an outcome characteristic of SAEs, or a device-related incident whose recurrence might lead to death or serious deterioration in health.

10.10. Appendix 10: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
CBER	Center for Biologics Evaluation and Research
CC	chick-chick
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DILI	drug-induced liver injury
DMC	data monitoring committee
DRE	drug-related event
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
CCI	[redacted]
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
CCI	[redacted]
GMFR	geometric mean fold rise
GMT	geometric mean titer
HBV	hepatitis B virus

Abbreviation	Term
HCV	hepatitis C virus
HI	hemagglutination inhibition
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
CCI	[redacted]
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRT	interactive response technology
ISF	investigator site file
ISO	International Organization for Standardization
JEV	Japanese encephalitis virus
LFT	liver function test
LLOQ	lower limit of quantitation
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
N/A	not applicable
NIMP	noninvestigational medicinal product
NT	neutralization test
PI	principal investigator
PT	prothrombin time
RCDC	reverse cumulative distribution curve
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOP	standard operating procedure
SRM	study reference manual
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBE	tick-borne encephalitis
TBEV	tick-borne encephalitis virus

Abbreviation	Term
TBili	total bilirubin
UK	United Kingdom
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
VIE U	Vienna units
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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