Clinical trial results:
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

Summary

EudraCT number	2022-004181-37
Trial protocol	Outside EU/EEA
Global end of trial date	21 February 2022

Results information

Result version number	v1 (current)
This version publication date	03 March 2023
First version publication date	03 March 2023

Trial information

Trial identification

Sponsor protocol code	B9371039

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04648241
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 October 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the immunogenicity of Tick-borne Encephalitis (TBE) vaccine 0.5 mL and 0.25 mL by NT

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 January 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 165
Worldwide total number of subjects	165
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	2
Children (2-11 years)	52
Adolescents (12-17 years)	16
Adults (18-64 years)	80
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted as part of the Phase 3 clinical development plan to support the use of TBE vaccine 0.5 milliliter (mL) in healthy Japanese adults (greater than or equal to [>=] 16 years old) and 0.25 mL in pediatric subjects (>=1 and less than [<] 16 years old) at investigator sites in Japan.

Pre-assignment

Screening details:

The study was conducted in single country from 18 January 2021 to 21 February 2022. A total of 165 subjects were enrolled.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Adults (>=16 years old)

Arm description:

Subjects aged >=16 years old received three doses of 0.5 mL TBE vaccine intramuscularly as Dose 1 on Day 1, Dose 2 between 21 to 35 days after Dose 1 and Dose 3 between 150-365 days after Dose 2. Subjects were followed up for safety for 21-35 days after Dose 3.

Arm type	Experimental
Investigational medicinal product name	Tick-borne encephalitis vaccine
Investigational medicinal product code	PF-06830414
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received three doses of 0.5 mL TBE vaccine intramuscularly.

Arm title	Pediatric (1 to <16 Years Old)

Arm description:

Subjects aged 1 to <16 years old received three doses of 0.25 mL TBE vaccine intramuscularly as Dose 1 on Day 1, Dose 2 between 21 to 35 days after Dose 1 and Dose 3 between 150-365 days after Dose 2. Subjects were followed up for safety for 21-35 days after Dose 3.

Arm type	Experimental
Investigational medicinal product name	Tick-borne encephalitis vaccine
Investigational medicinal product code	PF-06830414
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received three doses of 0.25 mL TBE vaccine intramuscularly.

Number of subjects in period 1	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)
Started	100	65
Completed	99	65
Not completed	1	0
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Adults (>=16 years old)
Reporting group description:	
Subjects aged >=16 years old received three doses of 0.5 mL TBE vaccine intramuscularly as Dose 1 on Day 1, Dose 2 between 21 to 35 days after Dose 1 and Dose 3 between 150-365 days after Dose 2. Subjects were followed up for safety for 21-35 days after Dose 3.	
Reporting group title	Pediatric (1 to <16 Years Old)
Reporting group description:	
Subjects aged 1 to <16 years old received three doses of 0.25 mL TBE vaccine intramuscularly as Dose 1 on Day 1, Dose 2 between 21 to 35 days after Dose 1 and Dose 3 between 150-365 days after Dose 2. Subjects were followed up for safety for 21-35 days after Dose 3.	

Reporting group values	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)	Total
Number of subjects	100	65	165
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	2	2
Children (2-11 years)	0	52	52
Adolescents (12-17 years)	5	11	16
Adults (18-64 years)	80	0	80
From 65-84 years	15	0	15
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	44.3	6.9	
standard deviation	± 16.02	± 3.89	-
Sex: Female, Male Units: Subjects			
Female	55	19	74
Male	45	46	91
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	100	65	165
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	0	0	0
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	100	65	165

Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Adults (>=16 years old)

Reporting group description:

Subjects aged >=16 years old received three doses of 0.5 mL TBE vaccine intramuscularly as Dose 1 on Day 1, Dose 2 between 21 to 35 days after Dose 1 and Dose 3 between 150-365 days after Dose 2. Subjects were followed up for safety for 21-35 days after Dose 3.

Reporting group title	Pediatric (1 to <16 Years Old)

Reporting group description:

Subjects aged 1 to <16 years old received three doses of 0.25 mL TBE vaccine intramuscularly as Dose 1 on Day 1, Dose 2 between 21 to 35 days after Dose 1 and Dose 3 between 150-365 days after Dose 2. Subjects were followed up for safety for 21-35 days after Dose 3.

Subject analysis set title	Pediatric (3 to 15 Years Old)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects aged 3 to 15 years old received three doses of 0.25 mL TBE vaccine intramuscularly as Dose 1 on Day 1, Dose 2 in between 21 to 35 days after Dose 1 and Dose 3 between 150-365 days after Dose 2. Subjects were followed up for safety for 21-35 days after Dose 3.

Subject analysis set title	Pediatric (1 to 2 Years Old)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects aged 1 to 2 years received three doses of 0.25 mL TBE vaccine intramuscularly as Dose 1 on Day 1, Dose 2 between 21 to 35 days after Dose 1 and Dose 3 in between 150-365 days after Dose 2. Subjects were followed up for safety for 21-35 days after Dose 3.

Primary: Percentage of Seropositive Subjects at 4 Weeks After Dose 3

End point title	Percentage of Seropositive Subjects at 4 Weeks After Dose 3[1]

End point description:

Seropositivity rate based on the immune response was determined by neutralization test (NT). Subjects who achieved tick-borne encephalitis virus (TBEV) NT titers greater than or equal to (>=) 1:10 were considered as seropositive. Exact 2-sided 95% confidence interval (CI) based on the Clopper and Pearson method was presented. Evaluable immunogenicity (EI) population: Subjects who received all 3 doses of the investigational product(IP), had blood drawn for assay testing within the specified time frame for baseline and 4 weeks after the third vaccination, had valid and determinate assay result (NT titer) at baseline and 4 weeks after the third vaccination visit, were NT seronegative at baseline, and had no major protocol violations. Number of subjects analysed=subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

4 weeks after Dose 3

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	65		
Units: Percentage of subjects				
number (confidence interval 95%)	98.0 (92.9 to 99.8)	100 (94.5 to 100)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Local Reactions (LR) Within 7 Days After Dose 1

End point title	Percentage of Subjects With Local Reactions (LR) Within 7 Days After Dose 1[2]

End point description:

LR:subject or legally acceptable representative/parent/legal guardian using an electronic diary (e-diary).LR:redness, swelling & pain at injection site.Redness & swelling measured using measuring device units.1 measuring device unit=0.5 centimeter(cm).Redness & swelling were graded as: for subjects >=12 years of age, mild(greater than[>] 2.0 to 5.0 cm), moderate(>5.0 to 10.0 cm) and severe (>10.0 cm); for subjects less than (<)12 years of age, mild(>0 to 2.0 cm), moderate(>2.0 to7.0 cm) and severe(>7.0 cm). Pain at injection site was graded as: for subjects >2 years of age, mild(does not interfere with activity),moderate(interferes with activity) and severe(prevents daily activity); for subjects less than or equal to(<=)2 years of age, mild(hurts if gently touched) moderate(hurts if gently touched with crying)and severe(causes limitation of limb movement). Safety analysis included all enrolled subjects who received at least 1 dose of IP.

End point type	Primary

End point timeframe:

Within 7 days after Dose 1

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	65		
Units: Percentage of subjects				
number (confidence interval 95%)				
Redness: Mild	2.0 (0.2 to 7.0)	3.1 (0.4 to 10.7)		
Redness: Moderate	0 (0.0 to 3.6)	1.5 (0.0 to 8.3)		
Redness: Severe	0 (0.0 to 3.6)	0 (0.0 to 5.5)		
Swelling: Mild	3.0 (0.6 to 8.5)	3.1 (0.4 to 10.7)		
Swelling: Moderate	0 (0.0 to 3.6)	0 (0.0 to 5.5)		
Swelling: Severe	0 (0.0 to 3.6)	0 (0.0 to 5.5)		
Pain at the injection site: Mild	52.0 (41.8 to 62.1)	36.9 (25.3 to 49.8)		
Pain at the injection site: Moderate	7.0 (2.9 to 13.9)	6.2 (1.7 to 15.0)		
Pain at the injection site: Severe	0 (0.0 to 3.6)	0 (0.0 to 5.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Local Reactions Within 7 Days After Dose 2

End point title	Percentage of Subjects With Local Reactions Within 7 Days After Dose 2[3]

End point description:

LR:subject or legally acceptable representative/parent/legal guardian using an e-diary. Local reactions included redness, swelling and pain at the injection site. Redness and swelling were measured using measuring device units. 1 measuring device unit =0.5 cm. Redness and swelling were graded as: for subjects >=12 years of age, mild (>2.0 to 5.0 cm), moderate(>5.0 to 10.0 cm) and severe (>10.0 cm); for subjects <12 years of age, mild(>0 to 2.0 cm), moderate(>2.0 to7.0 cm) and severe(>7.0 cm). Pain at the injection site was graded as: for subjects >2 years of age, mild(does not interfere with activity), moderate(interferes with activity) and severe(prevents daily activity); for subjects <=2 years of age, mild(hurts if gently touched) moderate(hurts if gently touched with crying) and severe(causes limitation of limb movement). Exact 2-sided 95% CI based on the Clopper and Pearson method was presented. Safety set analysed.

End point type	Primary

End point timeframe:

Within 7 days after Dose 2

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	65		
Units: Percentage of subjects				
number (confidence interval 95%)				
Redness: Mild	0.0 (0.0 to 3.6)	3.1 (0.4 to 10.7)		
Redness: Moderate	0 (0.0 to 3.6)	0 (0.0 to 5.5)		
Redness: Severe	0 (0.0 to 3.6)	0 (0.0 to 5.5)		
Swelling: Mild	0 (0.0 to 3.6)	1.5 (0.0 to 8.3)		
Swelling: Moderate	0 (0.0 to 3.6)	0 (0.0 to 5.5)		
Swelling: Severe	0 (0.0 to 3.6)	0 (0.0 to 5.5)		
Pain at the injection site: Mild	40.0 (30.3 to 50.3)	24.6 (14.8 to 36.9)		
Pain at the injection site: Moderate	4.0 (1.1 to 9.9)	1.5 (0.0 to 8.3)		
Pain at the injection site: Severe	0 (0.0 to 3.6)	0 (0.0 to 5.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Local Reactions Within 7 Days After Dose 3

End point title	Percentage of Subjects With Local Reactions Within 7 Days After Dose 3[4]

End point description:

LR:subject or legally acceptable representative/parent/legal guardian using an e-diary. Local reactions included redness, swelling and pain at the injection site. Redness and swelling were measured using measuring device units. 1 measuring device unit =0.5 cm. Redness and swelling were graded as: for subjects >=12 years of age, mild (>2.0 to 5.0 cm), moderate(>5.0 to 10.0 cm) and severe (>10.0 cm); for subjects <12 years of age, mild(>0 to 2.0 cm), moderate(>2.0 to7.0 cm) and severe(>7.0 cm). Pain at the injection site was graded as: for subjects >2 years of age, mild(does not interfere with activity), moderate(interferes with activity) and severe(prevents daily activity); for subjects <=2 years of age, mild(hurts if gently touched) moderate(hurts if gently touched with crying) and severe(causes limitation of limb movement). Exact 2-sided 95% CI based on the Clopper and Pearson method was presented. Safety set analyzed.

End point type	Primary

End point timeframe:

Within 7 days after Dose 3

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	65		
Units: Percentage of subjects				
number (confidence interval 95%)				
Redness: Mild	2.0 (0.2 to 7.1)	7.7 (2.5 to 17.0)		
Redness: Moderate	0 (0.0 to 3.7)	0 (0.0 to 5.5)		
Redness: Severe	0 (0.0 to 3.7)	0 (0.0 to 5.5)		
Swelling: Mild	1.0 (0.0 to 5.5)	6.2 (1.7 to 15.0)		
Swelling: Moderate	1.0 (0.0 to 5.5)	3.1 (0.4 to 10.7)		
Swelling: Severe	0 (0.0 to 3.7)	0 (0.0 to 5.5)		
Pain at the injection site: Mild	33.3 (24.2 to 43.5)	30.8 (19.9 to 43.4)		
Pain at the injection site: Moderate	3.0 (0.6 to 8.6)	4.6 (1.0 to 12.9)		
Pain at the injection site: Severe	0 (0.0 to 3.7)	0 (0.0 to 5.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Systemic Events (SE) Within 7 Days After Dose 1

End point title	Percentage of Subjects With Systemic Events (SE) Within 7 Days After Dose 1[5][6]

End point description:

SE:subjects/legally acceptable representative/parent/legal guardian using e-diary,fever:temperature >=37.5 degree(deg)Celsius (C),categorized:37.5to38.4, 38.5to38.9, 39.0to40.0, >40.0degC.Fatigue, headache, muscle pain, joint pain: mild(didn't interfere with activity),moderate(mod)(some interference with activity),severe(prevented daily activity).Vomiting: mild(1-2 times in 24 hours[hrs]),mod(>2 times in 24hrs),severe(required IV hydration).Diarrhea: mild(2-3 loose stools in 24hrs),mod(4-5 loose stools in 24hrs), severe(6 or more loose stools in 24hrs). Decreased appetite: mild(decreased interest in eating), mod(decreased oral intake), severe(refusal to feed).Drowsiness: mild(Increased sleeping bouts), mod(slightly subdued interfering with daily activity), severe(disabling not interested in usual daily activity). Irritability: mild(easily consolable),mod(required increased attention), severe(inconsolable).Safety set . 99999=not applicable.n=subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Within 7 days after Dose 1

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Adults (>=16 years old)	Pediatric (3 to 15 Years Old)	Pediatric (1 to 2 Years Old)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	100	57	8	
Units: Percentage of subjects				
number (confidence interval 95%)				
Fever: >=37.5 degree C(n=100,57,8)	2.0 (0.2 to 7.0)	5.3 (1.1 to 14.6)	25.0 (3.2 to 65.1)	
Fever: 37.5 to 38.4 degree C(n=100,57,8)	2.0 (0.2 to 7.0)	3.5 (0.4 to 12.1)	25.0 (3.2 to 65.1)	
Fever: 38.5 to 38.9 degree C(n=100,57,8)	0 (0.0 to 3.6)	1.8 (0.0 to 9.4)	0 (0.0 to 36.9)	
Fever: 39.0 to 40.0 degree C(n=100,57,8)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	0 (0.0 to 36.9)	
Fever: >40.0 degree C(n=100,57,8)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	0 (0.0 to 36.9)	
Fatigue: Mild(n=100,57,0)	11.0 (5.6 to 18.8)	8.8 (2.9 to 19.3)	99999 (99999 to 99999)	
Fatigue: Moderate(n=100,57,0)	5.0 (1.6 to 11.3)	1.8 (0.0 to 9.4)	99999 (99999 to 99999)	
Fatigue: Severe(n=100,57,0)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Headache: Mild(n=100,57,0)	7.0 (2.9 to 13.9)	7.0 (1.9 to 17.0)	99999 (99999 to 99999)	
Headache: Moderate(n=100,57,0)	6.0 (2.2 to 12.6)	1.8 (0.0 to 9.4)	99999 (99999 to 99999)	
Headache: Severe(n=100,57,0)	0 (0.0 to 3.6)	1.8 (0.0 to 9.4)	99999 (99999 to 99999)	
Vomiting: Mild(n=100,57,0)	1.0 (0.0 to 5.4)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Vomiting: Moderate(n=100,57,0)	1.0 (0.0 to 5.4)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Vomiting: Severe(n=100,57,0)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Diarrhea: Mild(n=100,57,0)	7.0 (2.9 to 13.9)	8.8 (2.9 to 19.3)	99999 (99999 to 99999)	
Diarrhea: Moderate(n=100,57,0)	2.0 (0.2 to 7.0)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Diarrhea: Severe(n=100,57,0)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Muscle pain: Mild(n=100,57,0)	16.0 (9.4 to 24.7)	5.3 (1.1 to 14.6)	99999 (99999 to 99999)	
Muscle pain: Moderate(n=100,57,0)	3.0 (0.6 to 8.5)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Muscle pain: Severe(n=100,57,0)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Joint pain: Mild(n=100,57,0)	4.0 (1.1 to 9.9)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Joint pain: Moderate(n=100,57,0)	3.0 (0.6 to 8.5)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Joint pain: Severe(n=100,57,0)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Decreased appetite: Mild(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	
Decreased appetite: Moderate(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	12.5 (0.3 to 52.7)	

Decreased appetite: Severe(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	
Drowsiness: Mild(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	25.0 (3.2 to 65.1)	
Drowsiness: Moderate(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	
Drowsiness: Severe(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	
Irritability: Mild(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	12.5 (0.3 to 52.7)	
Irritability: Moderate(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	12.5 (0.3 to 52.7)	
Irritability: Severe(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Systemic Events Within 7 Days After Dose 2

End point title	Percentage of Subjects With Systemic Events Within 7 Days After Dose 2[7][8]

End point description:

SE: subjects/legally acceptable representative/parent/legal guardian using e-diary. It included fever: temperature >=37.5 deg C and categorised as 37.5 to 38.4, 38.5 to 38.9, 39.0 to 40.0, >40.0 deg C. Fatigue, headache, muscle pain, joint pain: mild(didn't interfere with activity),mod(some interference with activity),severe(prevented daily activity). Vomiting: mild(1-2 times in 24 hours[hrs]),mod(>2 times in 24hrs), severe(required intravenous hydration).Diarrhea: mild(2-3 loose stools in 24hrs),moderate(4-5 loose stools in 24hrs), severe(6 or more loose stools in 24hrs). Decreased appetite: mild(decreased interest in eating), moderate(decreased oral intake),severe(refusal to feed) .Safety set .99999=not applicable.n=subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Within 7 days after Dose 2

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be analyzed for Overall Study Adults (>=16 years old), Pediatric (3 to 15 Years Old) and Pediatric (1 to 2 Years Old) arms.

End point values	Adults (>=16 years old)	Pediatric (3 to 15 Years Old)	Pediatric (1 to 2 Years Old)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	100	57	8	
Units: Percentage of subjects				
number (confidence interval 95%)				
Fever: >=37.5 degree C(n=100,57,8)	1.0 (0.0 to 5.4)	7.0 (1.9 to 17.0)	0 (0.0 to 36.9)	
Fever: 37.5 to 38.4 degree C(n=100,57,8)	1.0 (0.0 to 5.4)	3.5 (0.4 to 12.1)	0 (0.0 to 36.9)	
Fever: 38.5 to 38.9 degree C(n=100,57,8)	0 (0.0 to 3.6)	3.5 (0.4 to 12.1)	0 (0.0 to 36.9)	
Fever: 39.0 to 40.0 degree C(n=100,57,8)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	0 (0.0 to 36.9)	

Fever: >40.0 degree C(n=100,57,8)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	0 (0.0 to 36.9)	
Fatigue: Mild(n=100,57,0)	7.0 (2.9 to 13.9)	1.8 (0.0 to 9.4)	99999 (99999 to 99999)	
Fatigue: Moderate(n=100,57,0)	1.0 (0.0 to 5.4)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Fatigue: Severe(n=100,57,0)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Headache: Mild(n=100,57,0)	10.0 (4.9 to 17.6)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Headache: Moderate(n=100,57,0)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Headache: Severe(n=100,57,0)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Vomiting: Mild(n=100,57,0)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Vomiting: Moderate(n=100,57,0)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Vomiting: Severe(n=100,57,0)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Diarrhea: Mild(n=100,57,0)	4.0 (1.1 to 9.9)	7.0 (1.9 to 17.0)	99999 (99999 to 99999)	
Diarrhea: Moderate(n=100,57,0)	1.0 (0.0 to 5.4)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Diarrhea: Severe(n=100,57,0)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Muscle pain: Mild(n=100,57,0)	2.0 (0.2 to 7.0)	1.8 (0.0 to 9.4)	99999 (99999 to 99999)	
Muscle pain: Moderate(n=100,57,0)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Muscle pain: Severe(n=100,57,0)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Joint pain: Mild(n=100,57,0)	1.0 (0.0 to 5.4)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Joint pain: Moderate(n=100,57,0)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Joint pain: Severe(n=100,57,0)	0 (0.0 to 3.6)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Decreased appetite: Mild(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	
Decreased appetite: Moderate(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	
Decreased appetite: Severe(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	
Drowsiness: Mild(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	12.5 (0.3 to 52.7)	
Drowsiness: Moderate(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	
Drowsiness: Severe(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	
Irritability: Mild(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	
Irritability: Moderate(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	
Irritability: Severe(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Systemic Events Within 7 Days After Dose 3

End point title	Percentage of Subjects With Systemic Events Within 7 Days After Dose 3[9][10]

End point description:

SE: subjects/legally acceptable representative/parent/legal guardian using e-diary. It included fever: temperature >=37.5 deg C and categorised as 37.5 to 38.4, 38.5 to 38.9, 39.0 to 40.0, >40.0 deg C. Fatigue, headache, muscle pain, joint pain: mild(didn't interfere with activity),mod(some interference with activity),severe(prevented daily activity). Vomiting: mild(1-2 times in 24 hours[hrs]),mod(>2 times in 24hrs), severe(required intravenous hydration).Diarrhea: mild(2-3 loose stools in 24hrs),moderate(4-5 loose stools in 24hrs), severe(6 or more loose stools in 24hrs). Decreased appetite: mild(decreased interest in eating), moderate(decreased oral intake),severe(refusal to feed) .Safety set .99999=not applicable.n=subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Within 7 days after Dose 3

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Adults (>=16 years old)	Pediatric (3 to 15 Years Old)	Pediatric (1 to 2 Years Old)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	99	57	8	
Units: Percentage of subjects				
number (confidence interval 95%)				
Fever: >=37.5 degree C(n=99,57,8)	1.0 (0.0 to 5.5)	10.5 (4.0 to 21.5)	12.5 (0.3 to 52.7)	
Fever: 37.5 to 38.4 degree C(n=99,57,8)	0 (0.0 to 3.7)	8.8 (2.9 to 19.3)	12.5 (0.3 to 52.7)	
Fever: 38.5 to 38.9 degree C(n=99,57,8)	1.0 (0.0 to 5.5)	0 (0.0 to 6.3)	0 (0.0 to 36.9)	
Fever: 39.0 to 40.0 degree C(n=99,57,8)	0 (0.0 to 3.7)	1.8 (0.0 to 9.4)	0 (0.0 to 36.9)	
Fever: >40.0 degree C(n=99,57,8)	0 (0.0 to 3.7)	0 (0.0 to 6.3)	0 (0.0 to 36.9)	
Fatigue: Mild(n=99,57,0)	9.1 (4.2 to 16.6)	1.8 (0.0 to 9.4)	99999 (99999 to 99999)	
Fatigue: Moderate(n=99,57,0)	2.0 (0.2 to 7.1)	5.3 (1.1 to 14.6)	99999 (99999 to 99999)	
Fatigue: Severe(n=99,57,0)	0 (0.0 to 3.7)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Headache: Mild(n=99,57,0)	9.1 (4.2 to 16.6)	5.3 (1.1 to 14.6)	99999 (99999 to 99999)	
Headache: Moderate(n=99,57,0)	1.0 (0.0 to 5.5)	3.5 (0.4 to 12.1)	99999 (99999 to 99999)	
Headache: Severe(n=99,57,0)	1.0 (0.0 to 5.5)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Vomiting: Mild(n=99,57,0)	2.0 (0.2 to 7.1)	1.8 (0.0 to 9.4)	99999 (99999 to 99999)	
Vomiting: Moderate(n=99,57,0)	0 (0.0 to 3.7)	1.8 (0.0 to 9.4)	99999 (99999 to 99999)	
Vomiting: Severe(n=99,57,0)	0 (0.0 to 3.7)	0 (0.0 to 6.3)	99999 (99999 to 99999)	

Diarrhea: Mild(n=99,57,0)	5.1 (1.7 to 11.4)	5.3 (1.1 to 14.6)	99999 (99999 to 99999)	
Diarrhea: Moderate(n=99,57,0)	0 (0.0 to 3.7)	3.5 (0.4 to 12.1)	99999 (99999 to 99999)	
Diarrhea: Severe(n=99,57,0)	1.0 (0.0 to 5.5)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Muscle pain: Mild(n=99,57,0)	3.0 (0.6 to 8.6)	1.8 (0.0 to 9.4)	99999 (99999 to 99999)	
Muscle pain: Moderate(n=99,57,0)	1.0 (0.0 to 5.5)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Muscle pain: Severe(n=99,57,0)	0 (0.0 to 3.7)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Joint pain: Mild(n=99,57,0)	0 (0.0 to 3.7)	5.3 (1.1 to 14.6)	99999 (99999 to 99999)	
Joint pain: Moderate(n=99,57,0)	1.0 (0.0 to 5.5)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Joint pain: Severe(n=99,57,0)	1.0 (0.0 to 5.5)	0 (0.0 to 6.3)	99999 (99999 to 99999)	
Decreased appetite: Mild(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	12.5 (0.3 to 52.7)	
Decreased appetite: Moderate(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	
Decreased appetite: Severe(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	
Drowsiness: Mild(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	25.0 (3.2 to 65.1)	
Drowsiness: Moderate(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	
Drowsiness: Severe(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	
Irritability: Mild(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	
Irritability: Moderate(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	
Irritability: Severe(n=0,0,8)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0.0 to 36.9)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Adverse Events (AEs) Within 1 Month After Dose 1

End point title	Percentage of Subjects With Adverse Events (AEs) Within 1 Month After Dose 1[11]

End point description:

An AE was defined as any untoward medical occurrence in a clinical study subject, temporally associated with the use of study intervention, whether considered related to the study intervention. Exact 2-sided 95% CI based on the Clopper and Pearson method was presented. Safety analysis population included all enrolled subjects who received at least 1 dose of the investigational product.

End point type	Primary

End point timeframe:

Within 1 month after Dose 1

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	65		
Units: Percentage of subjects				
number (confidence interval 95%)	6.0 (2.2 to 12.6)	21.5 (12.3 to 33.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Adverse Events (AEs) Within 1 Month After Dose 2

End point title	Percentage of Subjects With Adverse Events (AEs) Within 1 Month After Dose 2[12]

End point description:

An AE was defined as any untoward medical occurrence in a clinical study subject, temporally associated with the use of study intervention, whether considered related to the study intervention. Exact 2-sided 95% CI based on the Clopper and Pearson method was presented. Safety analysis population included all enrolled subjects who received at least 1 dose of the investigational product. Number of subjects analysed= subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Within 1 month after Dose 2

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint was planned to be analyzed for Overall Study Adults (>=16 years old), Pediatric (3 to 15 Years Old) and Pediatric (1 to 2 Years Old) arms.

End point values	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	65		
Units: Percentage of subjects				
number (confidence interval 95%)	2.0 (0.2 to 7.0)	10.8 (4.4 to 20.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Adverse Events (AEs) Within 1 Month After any Dose

End point title	Percentage of Subjects With Adverse Events (AEs) Within 1 Month After any Dose[13]

End point description:

An AE was defined as any untoward medical occurrence in a clinical study subject, temporally associated with the use of study intervention, whether considered related to the study intervention. Exact 2-sided 95% CI based on the Clopper and Pearson method was presented. Safety analysis population included all enrolled subjects who received at least 1 dose of the investigational product.

End point type	Primary

End point timeframe:

Within 1 month after any Dose

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	65		
Units: Percentage of subjects				
number (confidence interval 95%)	14.0 (7.9 to 22.4)	41.5 (29.4 to 54.4)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Adverse Events (AEs) Within 1 Month After Dose 3

End point title	Percentage of Subjects With Adverse Events (AEs) Within 1 Month After Dose 3[14]

End point description:

An AE was defined as any untoward medical occurrence in a clinical study subject, temporally associated with the use of study intervention, whether considered related to the study intervention. Exact 2-sided 95% CI based on the Clopper and Pearson method was presented. Safety analysis population included all enrolled subjects who received at least 1 dose of the investigational product.

End point type	Primary

End point timeframe:

Within 1 month after Dose 3

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint was planned to be analyzed for Overall Study Adults (>=16 years old), Pediatric (3 to 15 Years Old) and Pediatric (1 to 2 Years Old) arms.

End point values	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	65		
Units: Percentage of subjects				
number (confidence interval 95%)	6.1 (2.3 to 12.7)	29.2 (18.6 to 41.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Serious Adverse Events (SAEs) Throughout the Study

End point title	Percentage of Subjects With Serious Adverse Events (SAEs) Throughout the Study[15]

End point description:

An SAE was defined as any untoward medical occurrence that, at any dose that resulted in death; was life-threatening (immediate risk of death); required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent disability/incapacity (substantial disruption of the ability to conduct normal life functions); resulted in congenital anomaly/birth defect or that is considered to be an important medical event. Percentage of subjects with SAEs and the exact 2-sided 95% CI based on the Clopper and Pearson method was presented. Safety analysis population included all enrolled subjects who received at least 1 dose of the investigational product.

End point type	Primary

End point timeframe:

From Day 1 up to 35 days after Dose 3 (up to approximately 15 months)

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	65		
Units: Percentage of subjects				
number (confidence interval 95%)	2.0 (0.2 to 7.0)	1.5 (0.0 to 8.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Seropositive Subjects at 4 Weeks After Dose 2

End point title	Percentage of Seropositive Subjects at 4 Weeks After Dose 2

End point description:

Seropositivity rate based on the immune response was determined by NT. Subjects who achieved TBEV NT titers >=1:10 were considered as seropositive. Exact 2-sided 95% CI based on the Clopper and Pearson method was presented. Evaluable immunogenicity population for the second dose: Subjects who received the first 2 doses of the investigational product, had blood drawn for assay testing within the specified time frame for baseline and 4 weeks after the second vaccination, had valid and determinate assay result (NT titer) at baseline and 4 weeks after the second vaccination visit, were NT seronegative at baseline, and had no major protocol violations.

End point type	Secondary

End point timeframe:

4 weeks after Dose 2

End point values	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	65		
Units: Percentage of subjects				
number (confidence interval 95%)	93.0 (86.1 to 97.1)	92.3 (83.0 to 97.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers (GMTs) of TBEV Neutralizing Antibody Titers at 4 Weeks After Dose 2 and Dose 3

End point title	Geometric Mean Titers (GMTs) of TBEV Neutralizing Antibody Titers at 4 Weeks After Dose 2 and Dose 3

End point description:

GMTs and associated 2-sided 95% CIs were calculated as the mean of the assay results on the natural logarithmic scale based on Student’s t distribution and then exponentiating the results. The lower limit of quantitation (LLOQ) value for NT was 5. Assay results below the LLOQ were set to 0.5 × LLOQ. EI population: Subjects who received all 3 doses of the investigational product, had blood drawn for assay testing within specified time frame for baseline and 4 weeks after the third vaccination, had valid and determinate assay result (NT titer) at baseline and 4 weeks after the third vaccination visit, were NT seronegative at baseline, and had no major protocol violations. Here, “Number of Subjects Analysed” signifies subjects who were evaluable for this end point.

End point type	Secondary

End point timeframe:

4 weeks after Dose 2 and Dose 3

End point values	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	65		
Units: Titer				
geometric mean (confidence interval 95%)				
4 Weeks after Dose 2	28.2 (23.5 to 33.8)	29.4 (23.3 to 37.0)		
4 Weeks after Dose 3	80.1 (65.1 to 98.5)	233.1 (187.9 to 289.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Fold Rise (GMFR) of TBEV Neutralizing Antibody Titers at 4 Weeks After Dose 3 as Compared to Baseline

End point title	Geometric Mean Fold Rise (GMFR) of TBEV Neutralizing Antibody Titers at 4 Weeks After Dose 3 as Compared to

	Baseline

End point description:

GMFRs and the corresponding 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). The LLOQ value for NT was 5. Assay results below the LLOQ were set to 0.5 × LLOQ. EI population: Subjects who received all 3 doses of the investigational product, had blood drawn for assay testing within specified time frame for baseline and 4 weeks after the third vaccination, had valid and determinate assay result (NT titer) at baseline and 4 weeks after the third vaccination visit, were NT seronegative at baseline, and had no major protocol violations. Here, "Number of subjects analysed" signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline to 4 weeks after Dose 3

End point values	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	65		
Units: Fold rise				
geometric mean (confidence interval 95%)	32.0 (26.0 to 39.4)	93.2 (75.2 to 115.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Fold Rise (GMFR) of TBEV Neutralizing Antibody Titers at 4 Weeks After Dose 2 as Compared to Baseline

End point title	Geometric Mean Fold Rise (GMFR) of TBEV Neutralizing Antibody Titers at 4 Weeks After Dose 2 as Compared to Baseline

End point description:

GMFRs and the corresponding 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). The LLOQ value for NT was 5. Assay results below the LLOQ were set to 0.5 × LLOQ. Evaluable immunogenicity population for the second dose: Subjects who received the first 2 doses of the investigational product, had blood drawn for assay testing within the specified time frame for baseline and 4 weeks after the second vaccination, had valid and determinate assay result (NT titer) at baseline and 4 weeks after the second vaccination visit, were NT seronegative at baseline, and had no major protocol violations.

End point type	Secondary

End point timeframe:

From Baseline to 4 weeks after Dose 2

End point values	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	65		
Units: Fold rise				
geometric mean (confidence interval 95%)	11.2 (9.3 to 13.4)	11.8 (9.3 to 14.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Neutralizing Antibody Titers >= Lower Limit of Quantification (LLOQ)

End point title	Percentage of Subjects with Neutralizing Antibody Titers >= Lower Limit of Quantification (LLOQ)

End point description:

The LLOQ value for NT was 5. Assay results below the LLOQ were set to 0.5 × LLOQ. Percentage of subjects with NT>=LLOQ and exact 2-sided 95% CI based on the Clopper and Pearson method was presented. EI population: Subjects who received all 3 doses of the investigational product, had blood drawn for assay testing within specified time frame for baseline and 4 weeks after the third vaccination, had valid and determinate assay result (NT titer) at baseline and 4 weeks after the third vaccination visit, were NT seronegative at baseline, and had no major protocol violations. Here, "Number of subjects analysed" signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Before Dose 1, 4 weeks after Dose 2, Before Dose 3 and 4 weeks after Dose 3

End point values	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	65		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Before Dose 1	0 (0.0 to 3.7)	0 (0.0 to 5.5)		
4 Weeks after Dose 2	96.0 (90.0 to 98.9)	98.5 (91.7 to 100.0)		
Before Dose 3	63.6 (53.4 to 73.1)	86.2 (75.3 to 93.5)		
4 Weeks after Dose 3	99.0 (94.5 to 100.0)	100.0 (94.5 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Fold Rise (GMFR) of TBEV Neutralizing Antibody Titers at 4 Weeks After Dose 3 as Compared to 4 Weeks After Dose 2

End point title	Geometric Mean Fold Rise (GMFR) of TBEV Neutralizing Antibody Titers at 4 Weeks After Dose 3 as Compared to 4 Weeks After Dose 2

End point description:

GMFRs and the corresponding 2-sided 95% CIs were calculated by exponentiating the mean logarithm of fold rises and the corresponding CIs (based on the Student t distribution). The LLOQ value for NT was 5. Assay results below the LLOQ were set to 0.5 × LLOQ. EI population: Subjects who received all 3 doses of the investigational product, had blood drawn for assay testing within specified time frame for baseline and 4 weeks after the third vaccination, had valid and determinate assay result (NT titer) at baseline and 4 weeks after the third vaccination visit, were NT seronegative at baseline, and had no major protocol violations. Here, "Number of subjects analysed" signifies subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From 4 weeks after Dose 2 to 4 weeks after Dose 3

End point values	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	65		
Units: Fold rise				
geometric mean (confidence interval 95%)	2.8 (2.3 to 3.5)	7.9 (6.2 to 10.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-Cause mortality: from Day(D)1 up to 35D after Dose3(up to approximately 15months([M]); SAEs:from D1 up to 35D after Dose3(up to approx.15M);Other AEs(non-systematic assessment[SA]):up to 1M after each Dose;LR&SE(SA,other AEs):within 7Dafter each Dose)

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. However, what is presented are distinct events. An event may be categorised as serious in one subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	v 24.1

Reporting groups

Reporting group title	Adults (>=16 years old)

Reporting group description:

Subjects aged >=16 years old received three doses of 0.5 mL TBE vaccine intramuscularly as Dose 1 on Day 1, Dose 2 between 21 to 35 days after Dose 1 and Dose 3 between 150-365 days after Dose 2. Subjects were followed up for safety for 21-35 days after Dose 3.

Reporting group title	Pediatric (1 to <16 Years Old)

Reporting group description:

Subjects aged 1 to <16 years old received three doses of 0.25 mL TBE vaccine intramuscularly as Dose 1 on Day 1, Dose 2 between 21 to 35 days after Dose 1 and Dose 3 between 150-365 days after Dose 2. Subjects were followed up for safety for 21-35 days after Dose 3.

Serious adverse events	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 100 (2.00%)	1 / 65 (1.54%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 100 (1.00%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 100 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			

subjects affected / exposed	1 / 100 (1.00%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Adults (>=16 years old)	Pediatric (1 to <16 Years Old)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 100 (76.00%)	59 / 65 (90.77%)	
Injury, poisoning and procedural complications			
Cartilage injury			
subjects affected / exposed	1 / 100 (1.00%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Arthropod sting			
subjects affected / exposed	0 / 100 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Ankle fracture			
subjects affected / exposed	0 / 100 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	2 / 100 (2.00%)	1 / 65 (1.54%)	
occurrences (all)	2	1	
Joint injury			
subjects affected / exposed	1 / 100 (1.00%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	1 / 100 (1.00%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache (HEADACHE)			
alternative assessment type: Systematic			
subjects affected / exposed	23 / 100 (23.00%)	9 / 65 (13.85%)	
occurrences (all)	39	12	
Hypersomnia (INCREASED SLEEP)			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 100 (0.00%)	3 / 65 (4.62%)	
occurrences (all)	0	5	
General disorders and administration site conditions			
Fatigue (FATIGUE)			
alternative assessment type: Systematic			
subjects affected / exposed	27 / 100 (27.00%)	9 / 65 (13.85%)	
occurrences (all)	42	11	
Injection site erythema (REDNESS)			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 100 (3.00%)	7 / 65 (10.77%)	
occurrences (all)	4	12	
Injection site swelling (SWELLING)			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 100 (4.00%)	9 / 65 (13.85%)	
occurrences (all)	5	10	
Injection site pain (PAIN)			
alternative assessment type: Systematic			
subjects affected / exposed	68 / 100 (68.00%)	43 / 65 (66.15%)	
occurrences (all)	141	71	
Pyrexia (FEVER)			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 100 (3.00%)	13 / 65 (20.00%)	
occurrences (all)	6	20	
Vessel puncture site bruise			
subjects affected / exposed	1 / 100 (1.00%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Conjunctivitis allergic			
subjects affected / exposed	0 / 100 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Myopia			

subjects affected / exposed	0 / 100 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Vomiting (VOMITING)			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 100 (4.00%)	2 / 65 (3.08%)	
occurrences (all)	4	2	
Diarrhoea (DIARRHEA)			
alternative assessment type: Systematic			
subjects affected / exposed	15 / 100 (15.00%)	12 / 65 (18.46%)	
occurrences (all)	22	16	
Dental caries			
subjects affected / exposed	0 / 100 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 100 (0.00%)	2 / 65 (3.08%)	
occurrences (all)	0	2	
Asthma			
subjects affected / exposed	0 / 100 (0.00%)	2 / 65 (3.08%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 100 (0.00%)	3 / 65 (4.62%)	
occurrences (all)	0	3	
Dermatitis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	0 / 100 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Psychiatric disorders			
Irritability (IRRITABILITY)			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 100 (0.00%)	2 / 65 (3.08%)	
occurrences (all)	0	2	

Musculoskeletal and connective tissue disorders			
Arthralgia (JOINT PAIN)			
alternative assessment type: Systematic			
subjects affected / exposed	10 / 100 (10.00%)	3 / 65 (4.62%)	
occurrences (all)	10	3	
Myalgia (MUSCLE PAIN)			
alternative assessment type: Systematic			
subjects affected / exposed	22 / 100 (22.00%)	4 / 65 (6.15%)	
occurrences (all)	26	6	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 100 (0.00%)	3 / 65 (4.62%)	
occurrences (all)	0	3	
Gastroenteritis			
subjects affected / exposed	1 / 100 (1.00%)	8 / 65 (12.31%)	
occurrences (all)	1	8	
Upper respiratory tract infection			
subjects affected / exposed	1 / 100 (1.00%)	2 / 65 (3.08%)	
occurrences (all)	1	2	
Parotitis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 65 (1.54%)	
occurrences (all)	0	1	
Otitis externa			
subjects affected / exposed	1 / 100 (1.00%)	0 / 65 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	3 / 100 (3.00%)	11 / 65 (16.92%)	
occurrences (all)	3	13	
Gastroenteritis viral			
subjects affected / exposed	1 / 100 (1.00%)	2 / 65 (3.08%)	
occurrences (all)	1	2	
Empyema			
subjects affected / exposed	1 / 100 (1.00%)	1 / 65 (1.54%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			

Decreased appetite (DECREASED APPETITE) alternative assessment type: Systematic subjects affected / exposed occurrences (all)	 0 / 100 (0.00%) 0	 2 / 65 (3.08%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2020	Added fever to prespecified systemic events in primary safety endpoints for subjects 1 to <=2 years of age.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported