Clinical trial results:
Toward an optimal accelerated Tick-Borne Encephalitis (TBE) vaccination schedule for the last-minute traveler

Summary

EudraCT number	2019-000801-61
Trial protocol	BE
Global end of trial date	11 October 2021

Results information

Result version number	v1 (current)
This version publication date	23 November 2023
First version publication date	23 November 2023
Summary attachment (see zip file)	Poster (TBE.NETCM.NBR.final.pdf) Statistical Analysis Report (20220310_SAR_FASTBEPROTECT_Final_PS_signed.pdf) Publication (Final publication JTM.pdf)

Trial information

Trial identification

Sponsor protocol code	ITM201901

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Insitute of Tropical Medicine
Sponsor organisation address	Nationalestraat 155, Antwerpen, Belgium, 2000
Public contact	Yven Van Herrewege, ITM Clinical Trial Unit, +32 33455557, yvanherrewege@itg.be
Scientific contact	Yven Van Herrewege, ITM Clinical Trial Unit, +32 33455557, yvanherrewege@itg.be

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 October 2021
Global end of trial reached?	Yes
Global end of trial date	11 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the time to seroconversion of the different schedules of accelerated TBE vaccination based on reactogenicity data up to 28 days after the first dose.

Protection of trial subjects:

Since this can be considered a low-risk clinical trial; testing only a registered vaccine, a Data and Safety Monitoring Board will not be installed for this study. However, an Independent Expert Group will be set-up to review and advise on any SAE reported in the study. This Independent Expert Group will consist of at least 2 medical doctors with relevant experience who are not part of the study team.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 77
Worldwide total number of subjects	77
EEA total number of subjects	77

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	77
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Ninety-six (96) patients were screened, and 77 patients were enrolled. Nineteen (19) patients were excluded at enrolment. All 77 patients completed the primary vaccination. Sixty-seven (67) patients completed the booster vaccination, 4 were lost to follow-up and 6 withdrew consent.

Pre-assignment

Screening details:

Ninety-six (96) patients were screened, and 77 patients were enrolled. Nineteen (19) patients were excluded at enrolment.

Period 1

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

Blinding implementation details:

NA. Open-label study

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Classic accelerated schedule
Day 0: 1 dose 0.5ml IM
Day 14: 1 dose 0,5 ml IM

Arm type	Active comparator
Investigational medicinal product name	FSME Immun ® vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Day 0: 1 dose 0.5ml intra-muscular
Day 14: 1 dose 0,5 ml intra-muscular

Arm title	Group 2

Arm description:

Day 0: 2 doses 0.5ml IM

Arm type	Experimental
Investigational medicinal product name	FSME Immun ® vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Day 0: 2 doses 0.5ml IM

Arm title	Group 3

Arm description:

Day 0: 2 doses 0.1ml ID

Arm type	Experimental

Investigational medicinal product name	FSME Immun ® vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intradermal use

Dosage and administration details:

Day 0: 2 doses 0.1ml intra-dermal

Arm title	Group 4

Arm description:

Day 0: 2 doses 0.1ml ID
Day 7: 2 doses 0,1 ml ID

Arm type	Experimental
Investigational medicinal product name	FSME Immun ® vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intradermal use

Dosage and administration details:

Day 0: 2 doses 0.1ml ID
Day 7: 2 doses 0,1 ml ID

Arm title	Group 5

Arm description:

Day 0: 2 doses 0.1ml ID
Day 14: 2 doses 0,1 ml ID

Arm type	Experimental
Investigational medicinal product name	FSME Immun ® vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intradermal use

Dosage and administration details:

Day 0: 2 doses 0.1ml ID
Day 14: 2 doses 0,1 ml ID

Number of subjects in period 1	Group 1	Group 2	Group 3
Started	15	16	15
Completed	15	15	13
Not completed	0	1	2
Consent withdrawn by subject	-	-	1
Lost to follow-up	-	1	1

Number of subjects in period 1	Group 4	Group 5
Started	15	16
Completed	11	13
Not completed	4	3
Consent withdrawn by subject	3	2
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Classic accelerated schedule Day 0: 1 dose 0.5ml IM Day 14: 1 dose 0,5 ml IM	
Reporting group title	Group 2
Reporting group description:	
Day 0: 2 doses 0.5ml IM	
Reporting group title	Group 3
Reporting group description:	
Day 0: 2 doses 0.1ml ID	
Reporting group title	Group 4
Reporting group description:	
Day 0: 2 doses 0.1ml ID Day 7: 2 doses 0,1 ml ID	
Reporting group title	Group 5
Reporting group description:	
Day 0: 2 doses 0.1ml ID Day 14: 2 doses 0,1 ml ID	

Reporting group values	Group 1	Group 2	Group 3
Number of subjects	15	16	15
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age (in year): median			
Units: years median inter-quartile range (Q1-Q3)	 19 18 to 20	 19 18 to 19.5	 19 18 to 20
Gender categorical Units: Subjects			
Female Male	2 13	4 12	2 13

Reporting group values	Group 4	Group 5	Total
Number of subjects	15	16	77

Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age (in year): median			
Units: years			
median	19	19.5	
inter-quartile range (Q1-Q3)	18 to 21	18 to 21.5	-
Gender categorical Units: Subjects			
Female	3	2	13
Male	12	14	64

End points

End points reporting groups	
Reporting group title	Group 1
Reporting group description: Classic accelerated schedule Day 0: 1 dose 0.5ml IM Day 14: 1 dose 0,5 ml IM	
Reporting group title	Group 2
Reporting group description: Day 0: 2 doses 0.5ml IM	
Reporting group title	Group 3
Reporting group description: Day 0: 2 doses 0.1ml ID	
Reporting group title	Group 4
Reporting group description: Day 0: 2 doses 0.1ml ID Day 7: 2 doses 0,1 ml ID	
Reporting group title	Group 5
Reporting group description: Day 0: 2 doses 0.1ml ID Day 14: 2 doses 0,1 ml ID	

Primary: Time to seropositivity	
End point title	Time to seropositivity[1]
End point description: ITT analysis	
End point type	Primary
End point timeframe: Up to day 28 after the first injection	

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: Due to the nature of this pilot study, and the relatively small sample size, no formal statistical comparisons were planned.

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	15	15
Units: Days				
number (not applicable)				
Quartile 25	21	28	14	14
Quartile 50	28	0.0	28	14
Quartile 75	0.0	0.0	0.0	17

End point values	Group 5			

Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Days				
number (not applicable)				
Quartile 25	18			
Quartile 50	21			
Quartile 75	0.0			

Attachments (see zip file)	1/Figure 2..pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with neutralizing antibodies

End point title	Proportion of subjects with neutralizing antibodies

End point description:

Secondary objectives: To estimate the proportion of subjects with neutralizing antibodies (≥ 10) at day 7, day 14, day 21, day 28, month 3, month 6, 1 year and 1 year + 21 days after the start of the primary vaccination with 95% Wilson confidence interval for the five vaccination regimens (ITT analysis).

End point type	Secondary

End point timeframe:

at day 7, day 14, day 21, day 28, month 3, month 6, 1 year and 1 year + 21 days after the start of the primary vaccination

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	16	14	15
Units: Percentage				
number (confidence interval 95%)				
Day 7	0.0 (0.0 to 20.4)	0.0 (0.0 to 19.4)	7.1 (1.3 to 31.5)	6.7 (1.2 to 29.8)
Day 14	0.0 (0.0 to 20.4)	6.7 (1.2 to 29.8)	40.0 (19.8 to 64.3)	78.6 (52.4 to 92.4)
Day 21	40.0 (19.8 to 64.3)	18.8 (6.6 to 43.0)	26.7 (10.9 to 52.0)	71.4 (45.4 to 88.3)
Day 28	53.3 (30.1 to 75.2)	25.0 (10.2 to 49.5)	46.7 (24.8 to 69.9)	69.2 (42.4 to 87.3)
Month 3	0.0 (0.0 to 20.4)	6.3 (1.1 to 28.3)	6.7 (1.2 to 29.8)	6.7 (1.2 to 29.8)
Month 6	0.0 (0.0 to 20.4)	6.3 (1.1 to 28.3)	13.3 (3.7 to 37.9)	13.3 (3.7 to 37.9)
Month 12	0.0 (0.0 to 20.4)	6.7 (1.2 to 29.8)	7.7 (1.4 to 33.3)	45.5 (21.3 to 72.0)
Month 12 + 21 days	100.0 (79.6 to 100.0)	93.3 (70.2 to 98.8)	100.0 (77.2 to 100.0)	90.9 (62.3 to 98.4)

End point values	Group 5			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Percentage				
number (confidence interval 95%)				
Day 7	0.0 (0.0 to 19.4)			
Day 14	26.7 (10.9 to 52.0)			
Day 21	56.3 (33.2 to 76.9)			
Day 28	56.3 (33.2 to 76.9)			
Month 3	0.0 (0.0 to 19.4)			
Month 6	6.7 (1.2 to 29.8)			
Month 12	30.8 (12.7 to 57.6)			
Month 12 + 21 days	100 (77.2 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

- Occurrence of solicited local and general symptoms within 7 days after each vaccination.
- Occurrence of (vaccine-related) AEs for 7 days after each vaccination.
- Occurrence of (vaccine-related) SAEs for 14 days after each vaccination.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Group 1
Reporting group description:	
Classic accelerated schedule Day 0: 1 dose 0.5ml IM Day 14: 1 dose 0,5 ml IM	
Reporting group title	Group 2
Reporting group description:	
Day 0: 2 doses 0.5ml IM	
Reporting group title	Group 3
Reporting group description:	
Day 0: 2 doses 0.1ml ID	
Reporting group title	Group 4
Reporting group description:	
Day 0: 2 doses 0.1ml ID Day 7: 2 doses 0,1 ml ID	
Reporting group title	Group 5
Reporting group description:	
Day 0: 2 doses 0.1ml ID Day 14: 2 doses 0,1 ml ID	

Serious adverse events	Group 1	Group 2	Group 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Group 4	Group 5	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Group 1	Group 2	Group 3
Total subjects affected by non-serious adverse events subjects affected / exposed	4 / 15 (26.67%)	2 / 16 (12.50%)	3 / 15 (20.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Axillary pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Chills			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			

Dermatitis allergic			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Axillary mass			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Muscle rigidity			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Torticollis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Infections and infestations			
Mumps			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Group 4	Group 5	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)	4 / 16 (25.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Axillary pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Influenza like illness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Chills			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Hyperhidrosis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Axillary mass			
subjects affected / exposed	2 / 15 (13.33%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Back pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Muscle rigidity			

subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Torticollis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Mumps			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2019	The protocol was amended in response to a comment from the FAGG on the initial submission. Changes: - Addition of the inclusion criterium "willing to take contraception until the last vaccination (for women of childbearing potential)" - Addition of pregnancy testing (urine) at every vaccination visit
28 October 2019	According to version 1.2 of the protocol, the intradermal injections would be prepared by the study nurses, just before administration to the patient. However, to provide a more controlled setting the intradermal syringes will be created by the hospital pharmacist or a delegated person at the Hospital pharmacy. It will be possible to trace the created intradermal syringes back to the batch number of the original vials.
14 July 2020	Changes: - Extra follow-up assessment on local reactions during month 3 and month 6 visit. - Including interim safety analysis after month 6 visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37074147