Clinical trial results:
Immunological responses after concomitant vaccination with the yellow fever-vaccine Stamaril and the TBE-vaccine FSME Immun, or JE-vaccine Ixiaro

Summary

EudraCT number	2017-002137-32
Trial protocol	SE
Global end of trial date	16 April 2019

Results information

Result version number	v1 (current)
This version publication date	08 April 2022
First version publication date	08 April 2022

Trial information

Trial identification

Sponsor protocol code	FV001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Karolinska Institutet, Department of Medicine, Center for Infectious Medicine
Sponsor organisation address	Alfred Nobels Allé 8, Huddinge, Sweden, 14152
Public contact	Hans-Gustaf Ljunggren, Karolinska Institutet, Department of Medicine, Center for Infectious Medicine, hans-gustaf.ljunggren@ki.se
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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	16 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To study if individuals that have received concomittant vaccinations with FSME Immun and Stamaril generate a better immune response against TBE compared to individuals that only received FSME Immun and to study if individuals that have received concomittant vaccinations with Ixiaro and Stamaril generate a better immune response against JE compared to individuals that only received Ixiaro.

Protection of trial subjects:

The study was conducted in compliance with the protocol, regulatory requirements, good clinical practice (GCP) and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

Background therapy:

Concomitant medications not mentioned in the exclusion criteria were permitted. Medications that were not permitted were those that have a lasting effect on the individual's immune response and those that may endanger the individual during vaccination. Examples of the above are long-term antiviral treatment, such as treatment for HIV and HCV infection, chronic immunosuppressive treatment or anticoagulants.

Concomitant medications were recorded in the CRF.

Evidence for comparator: -

Actual start date of recruitment	15 November 2017
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	Sweden: 145
Worldwide total number of subjects	145
EEA total number of subjects	145

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)	145
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 161 subjects who wanted vaccination against TBE, JE and/or Yellow fever were screened in order to reach the planned number of subjects for the trial. 16 of the 161 screened subjects dit not meet the inclusion criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A1 TBE and Yellow fever

Arm description:

Individuals that were vaccinated against TBE and Yellow fever. The vaccinations were administered in different arms.

Arm type	Experimental
Investigational medicinal product name	FSME-IMMUN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0,5 mL administered day 0, day 30 and day 180

Investigational medicinal product name	Stamaril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0,5 mL administered day 0 (single dose)

Arm title	Cohort A2 TBE and Yellow fever

Arm description:

Individuals that were vaccinated against TBE and Yellow fever. The vaccinations were administered in the same arm.

Arm type	Experimental
Investigational medicinal product name	FSME-IMMUN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0,5 mL administered day 0, day 30 and day 180

Investigational medicinal product name	Stamaril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0,5 mL administered day 0 (single dose)

Arm title	Cohort B1 JE and Yellow fever

Arm description:

Individuals that were vaccinated against JE and Yellow fever. The vaccinations were administered in different arms.

Arm type	Experimental
Investigational medicinal product name	IXIARO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0,5 mL administered day 0 and day 30

Investigational medicinal product name	Stamaril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0,5 mL administered day 0 (single dose)

Arm title	Cohort B2 JE and Yellow fever

Arm description:

Individuals that were vaccinated against JE and Yellow fever. The vaccinations were administered in the same arm.

Arm type	Experimental
Investigational medicinal product name	IXIARO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0,5 mL administered day 0 and day 30

Investigational medicinal product name	Stamaril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0,5 mL administered day 0 (single dose)

Arm title	Cohort C TBE

Arm description:

Individuals that were vaccinated against TBE.

Arm type	Active comparator

Investigational medicinal product name	FSME-IMMUN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0,5 mL administered day 0, day 30 and day 180

Arm title	Cohort D JE

Arm description:

Individuals that were vaccinated against JE.

Arm type	Active comparator
Investigational medicinal product name	IXIARO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0,5 mL administered day 0 and day 30

Arm title	Cohort E Yellow fever

Arm description:

Individuals that were vaccinated against Yellow fever.

Arm type	Active comparator
Investigational medicinal product name	Stamaril
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0,5 mL administered day 0 (single dose)

Number of subjects in period 1	Cohort A1 TBE and Yellow fever	Cohort A2 TBE and Yellow fever	Cohort B1 JE and Yellow fever
Started	23	20	21
Completed	20	20	20
Not completed	3	0	1
Adverse event, non-fatal	1	-	-
Poor compliance	2	-	1
Subject moved to another location	-	-	-

Number of subjects in period 1	Cohort B2 JE and Yellow fever	Cohort C TBE	Cohort D JE
Started	21	20	20
Completed	20	19	20
Not completed	1	1	0
Adverse event, non-fatal	1	-	-
Poor compliance	-	-	-

Subject moved to another location	-	1	-

Number of subjects in period 1	Cohort E Yellow fever
Started	20
Completed	20
Not completed	0
Adverse event, non-fatal	-
Poor compliance	-
Subject moved to another location	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A1 TBE and Yellow fever
Reporting group description:	
Individuals that were vaccinated against TBE and Yellow fever. The vaccinations were administered in different arms.	
Reporting group title	Cohort A2 TBE and Yellow fever
Reporting group description:	
Individuals that were vaccinated against TBE and Yellow fever. The vaccinations were administered in the same arm.	
Reporting group title	Cohort B1 JE and Yellow fever
Reporting group description:	
Individuals that were vaccinated against JE and Yellow fever. The vaccinations were administered in different arms.	
Reporting group title	Cohort B2 JE and Yellow fever
Reporting group description:	
Individuals that were vaccinated against JE and Yellow fever. The vaccinations were administered in the same arm.	
Reporting group title	Cohort C TBE
Reporting group description:	
Individuals that were vaccinated against TBE.	
Reporting group title	Cohort D JE
Reporting group description:	
Individuals that were vaccinated against JE.	
Reporting group title	Cohort E Yellow fever
Reporting group description:	
Individuals that were vaccinated against Yellow fever.	

Reporting group values	Cohort A1 TBE and Yellow fever	Cohort A2 TBE and Yellow fever	Cohort B1 JE and Yellow fever
Number of subjects	23	20	21
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 is reported for the subjects that completed the study.			
Units: years arithmetic mean standard deviation	 31.3 ± 9.0	 28.9 ± 7.1	 28.3 ± 10.2

Gender categorical			
Gender is reported for the subjects that completed the study.			
Units: Subjects			
Female	13	14	11
Male	7	6	9
Not recorded	3	0	1

Reporting group values	Cohort B2 JE and Yellow fever	Cohort C TBE	Cohort D JE
Number of subjects	21	20	20
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 is reported for the subjects that completed the study.			
Units: years			
arithmetic mean	27.8	24.4	26.0
standard deviation	± 4.6	± 5.9	± 6.3
Gender categorical			
Gender is reported for the subjects that completed the study.			
Units: Subjects			
Female	10	13	13
Male	10	6	7
Not recorded	1	1	0

Reporting group values	Cohort E Yellow fever	Total	
Number of subjects	20	145	
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 is reported for the subjects that completed the study.			
Units: years			

arithmetic mean	29.7		
standard deviation	± 9.5	-	

Gender categorical			
Gender is reported for the subjects that completed the study.			
Units: Subjects			
Female	12	86	
Male	8	53	
Not recorded	0	6	

End points

End points reporting groups

Reporting group title	Cohort A1 TBE and Yellow fever
Reporting group description: Individuals that were vaccinated against TBE and Yellow fever. The vaccinations were administered in different arms.	
Reporting group title	Cohort A2 TBE and Yellow fever
Reporting group description: Individuals that were vaccinated against TBE and Yellow fever. The vaccinations were administered in the same arm.	
Reporting group title	Cohort B1 JE and Yellow fever
Reporting group description: Individuals that were vaccinated against JE and Yellow fever. The vaccinations were administered in different arms.	
Reporting group title	Cohort B2 JE and Yellow fever
Reporting group description: Individuals that were vaccinated against JE and Yellow fever. The vaccinations were administered in the same arm.	
Reporting group title	Cohort C TBE
Reporting group description: Individuals that were vaccinated against TBE.	
Reporting group title	Cohort D JE
Reporting group description: Individuals that were vaccinated against JE.	
Reporting group title	Cohort E Yellow fever
Reporting group description: Individuals that were vaccinated against Yellow fever.	

Primary: Neutralizing antibodies against TBEV

End point title	Neutralizing antibodies against TBEV[1]
End point description: Number of subjects with neutralizing antibodies (nAbs) against TBE virus	
End point type	Primary
End point timeframe: Final time point, 30 (+14) days after last dose of vaccine	

Notes:

[1] - 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: This endpoint is only applicable for subjects receiving vaccine against TBE, hence only applicable for cohorts A1, A2 and C.

End point values	Cohort A1 TBE and Yellow fever	Cohort A2 TBE and Yellow fever	Cohort C TBE	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	19	
Units: subjects	17	19	16	

Statistical analyses

Statistical analysis title	Comparison of nAbs (TBEV) titers between cohorts
Comparison groups	Cohort A1 TBE and Yellow fever v Cohort A2 TBE and Yellow fever v Cohort C TBE
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Kruskal-wallis

Primary: Neutralizing antibodies against JEV

End point title	Neutralizing antibodies against JEV[2]

End point description:

Number of subjects with neutralizing antibodies (nAbs) against JE virus

End point type	Primary

End point timeframe:

Final time point, 30 (+14) days after last dose of vaccine

Notes:

[2] - 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: This endpoint is only applicable for subjects receiving vaccine against JE, hence only applicable for cohorts B1, B2 and D.

End point values	Cohort B1 JE and Yellow fever	Cohort B2 JE and Yellow fever	Cohort D JE	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	20	
Units: subjects	17	11	12	

Statistical analyses

Statistical analysis title	Comparison of nAbs (JEV) titers between cohorts
Comparison groups	Cohort B1 JE and Yellow fever v Cohort B2 JE and Yellow fever v Cohort D JE

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Kruskal-wallis

Primary: Neutralizing antibodies against YFV

End point title	Neutralizing antibodies against YFV[3]

End point description:

Number of subjects with neutralizing antibodies (nAbs) against YF virus

End point type	Primary

End point timeframe:

Final time point: for cohort A1, A2, B1 and B2 30 (+14) days after last dose of vaccine, for cohort E 60 (+14) days after vaccination

Notes:

[3] - 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: This endpoint is only applicable for subjects receiving vaccine against YF, hence only applicable for cohorts A1, A2, B1, B2 and E.

End point values	Cohort A1 TBE and Yellow fever	Cohort A2 TBE and Yellow fever	Cohort B1 JE and Yellow fever	Cohort B2 JE and Yellow fever
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	20	20	20
Units: subjects	20	20	20	20

End point values	Cohort E Yellow fever			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: subjects	20			

Statistical analyses

Statistical analysis title	Comparison of nAbs (YFV) titers between cohorts
Comparison groups	Cohort A1 TBE and Yellow fever v Cohort A2 TBE and Yellow fever v Cohort B1 JE and Yellow fever v Cohort B2 JE and Yellow fever v Cohort E Yellow fever
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Kruskal-wallis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the time point of the first vaccination until end of study for each subject.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Cohort A1 TBE and Yellow fever

Reporting group description:

Individuals that were vaccinated against TBE and Yellow fever. The vaccinations were administered in different arms.

Reporting group title	Cohort A2 TBE and Yellow fever

Reporting group description:

Individuals that were vaccinated against TBE and Yellow fever. The vaccinations were administered in the same arm.

Reporting group title	Cohort B1 JE and Yellow fever

Reporting group description:

Individuals that were vaccinated against JE and Yellow fever. The vaccinations were administered in different arms.

Reporting group title	Cohort B2 JE and Yellow fever

Reporting group description:

Individuals that were vaccinated against JE and Yellow fever. The vaccinations were administered in the same arm.

Reporting group title	Cohort C TBE

Reporting group description:

Individuals that were vaccinated against TBE.

Reporting group title	Cohort D JE

Reporting group description:

Individuals that were vaccinated against JE.

Reporting group title	Cohort E Yellow fever

Reporting group description:

Individuals that were vaccinated against Yellow fever.

Serious adverse events	Cohort A1 TBE and Yellow fever	Cohort A2 TBE and Yellow fever	Cohort B1 JE and Yellow fever
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)	1 / 20 (5.00%)	0 / 21 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	1 / 23 (4.35%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Dislocation of hip, baby			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 23 (0.00%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort B2 JE and Yellow fever	Cohort C TBE	Cohort D JE
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Dislocation of hip, baby			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort E Yellow fever		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Dislocation of hip, baby			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			

subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort A1 TBE and Yellow fever	Cohort A2 TBE and Yellow fever	Cohort B1 JE and Yellow fever
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 23 (82.61%)	16 / 20 (80.00%)	12 / 21 (57.14%)
General disorders and administration site conditions			
Flu like symtoms			
subjects affected / exposed	1 / 23 (4.35%)	3 / 20 (15.00%)	3 / 21 (14.29%)
occurrences (all)	1	3	3
Injection site abscess			
subjects affected / exposed	1 / 23 (4.35%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Pain/redness at site			
subjects affected / exposed	7 / 23 (30.43%)	7 / 20 (35.00%)	1 / 21 (4.76%)
occurrences (all)	7	7	1
Fatigue			
subjects affected / exposed	2 / 23 (8.70%)	2 / 20 (10.00%)	0 / 21 (0.00%)
occurrences (all)	2	2	0
Fever			
subjects affected / exposed	0 / 23 (0.00%)	3 / 20 (15.00%)	3 / 21 (14.29%)
occurrences (all)	0	4	3
Reproductive system and breast disorders			
Scrotal pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Pregnancy			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Dysmenorrhoea			
subjects affected / exposed	0 / 23 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 23 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Sore throat			
subjects affected / exposed	3 / 23 (13.04%)	0 / 20 (0.00%)	2 / 21 (9.52%)
occurrences (all)	3	0	2
Asthma			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
allergic rhinitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 23 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	0 / 23 (0.00%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	1 / 23 (4.35%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Cut			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	1 / 23 (4.35%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 23 (13.04%)	4 / 20 (20.00%)	2 / 21 (9.52%)
occurrences (all)	4	6	2
Dizziness			

subjects affected / exposed	0 / 23 (0.00%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Lymph node pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Middle ear inflammation			
subjects affected / exposed	1 / 23 (4.35%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	1 / 23 (4.35%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Nausea/vomiting			
subjects affected / exposed	1 / 23 (4.35%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Stomac flu			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Gastric ulcer			
subjects affected / exposed	0 / 23 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 23 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Localised infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Joint pain			

subjects affected / exposed	1 / 23 (4.35%)	0 / 20 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2
Back pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Muscle (body) pain			
subjects affected / exposed	2 / 23 (8.70%)	1 / 20 (5.00%)	1 / 21 (4.76%)
occurrences (all)	2	1	1
Heel spur			
subjects affected / exposed	0 / 23 (0.00%)	0 / 20 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Infections and infestations			
Upper respiratory infection			
subjects affected / exposed	8 / 23 (34.78%)	7 / 20 (35.00%)	3 / 21 (14.29%)
occurrences (all)	12	12	4
Urinary tract infection			
subjects affected / exposed	0 / 23 (0.00%)	2 / 20 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Vaginal infection			
subjects affected / exposed	0 / 23 (0.00%)	3 / 20 (15.00%)	0 / 21 (0.00%)
occurrences (all)	0	3	0
Herpes simplex			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Diabetes type 2			
subjects affected / exposed	1 / 23 (4.35%)	0 / 20 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Iron deficiency			
subjects affected / exposed	0 / 23 (0.00%)	1 / 20 (5.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Cohort B2 JE and Yellow fever	Cohort C TBE	Cohort D JE
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 21 (47.62%)	16 / 20 (80.00%)	16 / 20 (80.00%)
General disorders and administration site conditions			

Flu like symtoms			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	1 / 20 (5.00%)
occurrences (all)	2	0	1
Injection site abscess			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Pain/redness at site			
subjects affected / exposed	2 / 21 (9.52%)	3 / 20 (15.00%)	3 / 20 (15.00%)
occurrences (all)	2	4	3
Fatigue			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Fever			
subjects affected / exposed	2 / 21 (9.52%)	2 / 20 (10.00%)	0 / 20 (0.00%)
occurrences (all)	2	2	0
Reproductive system and breast disorders			
Scrotal pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Pregnancy			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Dysmenorrhoea			
subjects affected / exposed	0 / 21 (0.00%)	2 / 20 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	4	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Sore throat			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Asthma			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
allergic rhinitis			

subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Cut			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 21 (9.52%)	3 / 20 (15.00%)	2 / 20 (10.00%)
occurrences (all)	2	3	5
Dizziness			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Lymph node pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Middle ear inflammation			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Toothache			
subjects affected / exposed	2 / 21 (9.52%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Nausea/vomiting			
subjects affected / exposed	1 / 21 (4.76%)	2 / 20 (10.00%)	0 / 20 (0.00%)
occurrences (all)	1	2	0
Stomac flu			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	2 / 20 (10.00%)
occurrences (all)	0	1	2
Gastric ulcer			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Localised infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Joint pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Muscle (body) pain			
subjects affected / exposed	1 / 21 (4.76%)	1 / 20 (5.00%)	2 / 20 (10.00%)
occurrences (all)	2	1	2
Heel spur			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Upper respiratory infection			
subjects affected / exposed	5 / 21 (23.81%)	10 / 20 (50.00%)	11 / 20 (55.00%)
occurrences (all)	6	12	13
Urinary tract infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Vaginal infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Herpes simplex			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Diabetes type 2			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Iron deficiency			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Cohort E Yellow fever		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 20 (55.00%)		
General disorders and administration site conditions			
Flu like symtoms			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Injection site abscess			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Pain/redness at site			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		

Fever			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Scrotal pain			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Pregnancy			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Dysmenorrhoea			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Sore throat			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Asthma			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
allergic rhinitis			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			

Bruising subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Cut subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Fall subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Dizziness subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Blood and lymphatic system disorders Lymph node pain subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Ear and labyrinth disorders Middle ear inflammation subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Gastrointestinal disorders Toothache subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Nausea/vomiting subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Stomac flu subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Gastric ulcer subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		

Diarrhoea subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Skin and subcutaneous tissue disorders Skin hyperpigmentation subjects affected / exposed occurrences (all) Localised infection subjects affected / exposed occurrences (all)	 0 / 20 (0.00%) 0 0 / 20 (0.00%) 0		
Musculoskeletal and connective tissue disorders Joint pain subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Muscle (body) pain subjects affected / exposed occurrences (all) Heel spur subjects affected / exposed occurrences (all)	 0 / 20 (0.00%) 0 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 0 / 20 (0.00%) 0		
Infections and infestations Upper respiratory infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Vaginal infection subjects affected / exposed occurrences (all) Herpes simplex subjects affected / exposed occurrences (all)	 7 / 20 (35.00%) 9 0 / 20 (0.00%) 0 0 / 20 (0.00%) 0 0 / 20 (0.00%) 0		

Metabolism and nutrition disorders			
Diabetes type 2			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Iron deficiency			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2018	Changes in protocol version 3 compared to version 2: - Introduced the possibility of recruiting subjects to more than one cohort at a time. - Subjects receiving dose 2 and 3 should stay 30 minutes instead of 60 minutes. The risk of an allergic reaction is very small after receiving the second and third dose of the same vaccine. - Extended the time window for the third dose TBE vaccine from 5 months (+/- 14 days) after the second dose to 5-12 months after the second dose (according to SmPC). - The use of corticosteroids may be permitted, but not orally or if it is used so frequently or in such doses that it can be considered to significantly affect the effect of the vaccine. - Introduced the possibility for a subject to continue in the study with blood sampling only, if vaccination has been stopped due to safety reasons. - Discontinued subjects will be offered a final follow-up visit. - Introduced the possibility to replace a subject that has dropped out before visit 4.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported