Clinical trial results:
Boostability for rabies in last-minute travelers: One Day Rabies Pre-exposure Intradermal Vaccination followed by one day Postexposure Intradermal Vaccination

Summary

EudraCT number	2014-001836-12
Trial protocol	BE
Global end of trial date	27 March 2017

Results information

Result version number	v1 (current)
This version publication date	05 June 2019
First version publication date	05 June 2019

Trial information

Trial identification

Sponsor protocol code	ITMC0414

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Institute of Tropical Medicine
Sponsor organisation address	Nationalestraat 155, Antwerpen, Belgium, 2000
Public contact	Clinical Trials Unit, Institute of Tropical Medicine, 0032 32476625, yvanherrewege@itg.be
Scientific contact	Clinical Trials Unit, Institute of Tropical Medicine, 0032 32476625, 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	26 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 March 2017
Global end of trial reached?	Yes
Global end of trial date	27 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To determine if a 2 x 0,1 ml priming dose results in an acceptable boostability (% of subjects that have boostable rabies antibodies) after 1 year.
- To determine the lowest booster dose (4 x 0,1 ml, or 2 x 0,1 ml) after a 2 x 0,1 ml priming dose needed to induce an acceptable boostability after 1 year.
- A vaccination regimen is considered to have an acceptable boostability if at least 90% of vaccinated subjects would reach a rabies titre of > 0.5 IU/mL 7 days after booster vaccination. This will be assessed by comparing the one-sided 95% confidence interval for the % of boostable subjects with the target value of 90%. If the one-sided 95% confidence interval excludes 90%, an acceptable boostability is considered to be established.

Protection of trial subjects:

This is a low risk clinical trial, investigating only registered vaccines. The main expected adverse reactions are the following common AE's;

- local reactions at the injection site, such as pain, erythema, swelling, or itching.
- mild systemic reactions, such as headache, nausea, abdominal pain, muscle aches, and dizziness.
- an immune complex-like reaction characterized by urticaria, pruritus, and malaise.

Serious Adverse Events, such as death or life threatening features, like anaphylactic shock, angioedema or hypovolemic shock (described in the literature as vaccine-related side effects) might occur as well.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	23 October 2014
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	Belgium: 303
Worldwide total number of subjects	303
EEA total number of subjects	303

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)	303
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started on 23 October 2014 and was completed on 25 June 2015. 303 subjects were recruited in total.

Pre-assignment

Screening details:

Inclusion:
- ICF
- Rabies seronegative
- Belgian soldiers or military students not deployable to high-risk areas
- Prepared to follow study schedule

Exclusion:
- Previous rabies vaccination
- Intake of mefloquine
- Planned deployment to overseas areas within 28 days
- Planned deployment to high rabies risk area within 2 years

Period 1

Period 1 title	Primary Vaccination Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Primary vaccination period
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Rabipur
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

Simulated Intradermal Post-exposure schedule with 2 x 1 injection (2 x 0,1 ml) (two sites) on day 0

Number of subjects in period 1	Primary vaccination period
Started	303
Completed	271
Not completed	32
Consent withdrawn by subject	12
On military mission	1
Lost to follow-up	14
Out of service	5

Period 2

Period 2 title	Post-Exposure Prophylaxis
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	4 doses

Arm description:

Simulated Intradermal Post-exposure schedule with 4 x 1 injection (4 x 0,1 ml) (two sites) on day 365

Arm type	Active comparator
Investigational medicinal product name	Rabipur
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

Simulated Intradermal Post-exposure schedule with 4 x 1 injection (4 x 0,1 ml) (two sites) on day 365

Arm title	2 doses

Arm description:

Simulated Intradermal Post-exposure schedule with 2 x 1 injection (2 x 0,1 ml) (two sites) on day 365

Arm type	Experimental
Investigational medicinal product name	Rabipur
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

Simulated Intradermal Post-exposure schedule with 2 x 1 injection (2 x 0,1 ml) (two sites) on day 365

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The primary vaccination period is not the main study period, so not considered the baseline.

Number of subjects in period 2[2]	4 doses	2 doses
Started	134	137
Completed	134	137

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The primary vaccination period is not the main study period, so not considered the baseline.

Baseline characteristics

Reporting groups	
Reporting group title	4 doses
Reporting group description:	
Simulated Intradermal Post-exposure schedule with 4 x 1 injection (4 x 0,1 ml) (two sites) on day 365	
Reporting group title	2 doses
Reporting group description:	
Simulated Intradermal Post-exposure schedule with 2 x 1 injection (2 x 0,1 ml) (two sites) on day 365	

Reporting group values	4 doses	2 doses	Total
Number of subjects	134	137	271
Age categorical Units: Subjects			
20 or less	7	3	10
21-30	39	42	81
31-40	40	28	68
41-50	31	45	76
more than 50	17	19	36
Age continuous Units: years			
median	35	39	
inter-quartile range (Q1-Q3)	26 to 46	27 to 47	-
Gender categorical Units: Subjects			
Female	15	15	30
Male	119	122	241

End points

End points reporting groups

Reporting group title	Primary vaccination period
Reporting group description: -	
Reporting group title	4 doses
Reporting group description:	
Simulated Intradermal Post-exposure schedule with 4 x 1 injection (4 x 0,1 ml) (two sites) on day 365	
Reporting group title	2 doses
Reporting group description:	
Simulated Intradermal Post-exposure schedule with 2 x 1 injection (2 x 0,1 ml) (two sites) on day 365	

Primary: Acceptable boostability of the rabies antibodies (more than 0.5 IU/ml) on day 7 after booster vaccination

End point title	Acceptable boostability of the rabies antibodies (more than 0.5 IU/ml) on day 7 after booster vaccination
End point description:	
End point type	Primary
End point timeframe:	
Assessed on day 7 after booster vaccination at 1 year after the initial vaccination.	

End point values	4 doses	2 doses		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	137		
Units: Subject counts	133	136		

Statistical analyses

Statistical analysis title	Efficacy analysis
Statistical analysis description:	
The proportion of subjects with serology results above 0.5 IU/mL was calculated and the one-sided confidence interval using the Wilson's score method was constructed. Acceptable boostability was inferred if the lower bound of the confidence interval was above 90%.	
Comparison groups	4 doses v 2 doses
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Wilson's confidence interval
Point estimate	99.3

Confidence interval	
level	95 %
sides	1-sided
lower limit	96.7

Statistical analysis title	Efficacy analysis

Statistical analysis description:

The proportion of subjects with serology results above 0.5 IU/mL was calculated and the one-sided confidence interval using the Wilson's score method was constructed. Acceptable boostability was inferred if the lower bound of the confidence interval was above 90%.

Comparison groups	2 doses v 4 doses
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Wilson's confidence interval
Point estimate	99.3
Confidence interval	
level	95 %
sides	1-sided
lower limit	96.8

Secondary: Rabies serology more than 3 IU/ml after primary vaccination

End point title	Rabies serology more than 3 IU/ml after primary vaccination

End point description:

End point type	Secondary

End point timeframe:

Assessed at day 14 after primary vaccination.

End point values	4 doses	2 doses		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	137		
Units: Subject count	2	2		

Statistical analyses

Statistical analysis title	Efficacy analysis

Statistical analysis description:

All secondary and tertiary endpoints are binary endpoints similar to the primary endpoint. They will be analyzed similarly to the primary. No target values for the secondary endpoints are predefined, but the CIs will be interpreted in terms of clinical relevance of possible differences rather than statistical significance.

Comparison groups	4 doses v 2 doses
Number of subjects included in analysis	271
Analysis specification	Post-hoc
Analysis type	other
Parameter estimate	Proportion above 3IU/mL
Point estimate	1.3
Confidence interval	
level	95 %
sides	1-sided
lower limit	0.6

Secondary: Rabies serology more than 3 IU/ml after booster vaccination

End point title	Rabies serology more than 3 IU/ml after booster vaccination

End point description:

End point type	Secondary

End point timeframe:

Assessed on day 7 after booster vaccination

End point values	4 doses	2 doses		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	137		
Units: Subject count	126	123		

Statistical analyses

Statistical analysis title	Efficacy analysis

Statistical analysis description:

All secondary and tertiary endpoints are binary endpoints similar to the primary endpoint. They will be analyzed similarly to the primary. No target values for the secondary endpoints are predefined, but the CIs will be interpreted in terms of clinical relevance of possible differences rather than statistical significance.

Comparison groups	4 doses v 2 doses
Number of subjects included in analysis	271
Analysis specification	Post-hoc
Analysis type	other
Parameter estimate	Proportion above 3 IU/mL
Point estimate	91.9
Confidence interval	
level	95 %
sides	1-sided
lower limit	88.7

Secondary: Long-lasting protection after primary vaccination (rabies serology more than 10 IU/ml)

End point title	Long-lasting protection after primary vaccination (rabies serology more than 10 IU/ml)

End point description:

End point type	Secondary

End point timeframe:

Assessed on day 14 after primary vaccination

End point values	4 doses	2 doses		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	137		
Units: Subject Count	25	25		

Statistical analyses

Statistical analysis title	Efficacy analysis

Statistical analysis description:

All secondary and tertiary endpoints are binary endpoints similar to the primary endpoint. They will be analyzed similarly to the primary. No target values for the secondary endpoints are predefined, but the CIs will be interpreted in terms of clinical relevance of possible differences rather than statistical significance.

Comparison groups	4 doses v 2 doses
Number of subjects included in analysis	271
Analysis specification	Post-hoc
Analysis type	other
Parameter estimate	Proportion above 10IU/mL
Point estimate	19.5
Confidence interval	
level	95 %
sides	1-sided
lower limit	16

Secondary: Long-lasting protection after booster vaccination (rabies serology more than 10 IU/ml)

End point title	Long-lasting protection after booster vaccination (rabies serology more than 10 IU/ml)

End point description:

End point type	Secondary

End point timeframe:

Assessed on day 7 after booster vaccination

End point values	4 doses	2 doses		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	137		
Units: Subject Count	107	95		

Statistical analyses

Statistical analysis title	Efficacy analysis

Statistical analysis description:

All secondary and tertiary endpoints are binary endpoints similar to the primary endpoint. They will be analyzed similarly to the primary. No target values for the secondary endpoints are predefined, but the CIs will be interpreted in terms of clinical relevance of possible differences rather than statistical significance.

Comparison groups	4 doses v 2 doses
Number of subjects included in analysis	271
Analysis specification	Post-hoc
Analysis type	other
Parameter estimate	Proportion above 10 IU/mL
Point estimate	74.5
Confidence interval	
level	95 %
sides	1-sided
lower limit	70

Secondary: Rabies serology of 0.5 IU/ml or more after primary vaccination

End point title	Rabies serology of 0.5 IU/ml or more after primary vaccination

End point description:

End point type	Secondary

End point timeframe:

Assessed on day 14 after primary vaccination

End point values	4 doses	2 doses		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	137		
Units: Subject Count	109	112		

Statistical analyses

Statistical analysis title	Efficacy analysis

Statistical analysis description:

All secondary and tertiary endpoints are binary endpoints similar to the primary endpoint. They will be analyzed similarly to the primary. No target values for the secondary endpoints are predefined, but the CIs will be interpreted in terms of clinical relevance of possible differences rather than statistical significance.

Comparison groups	4 doses v 2 doses
Number of subjects included in analysis	271
Analysis specification	Post-hoc
Analysis type	other
Parameter estimate	Proportion
Point estimate	82.5
Confidence interval	
level	95 %
sides	1-sided
lower limit	78.6

Secondary: Adverse Events and Serious Adverse Events

End point title	Adverse Events and Serious Adverse Events

End point description:

End point type	Secondary

End point timeframe:

- Adverse events within 7 days after primary and booster vaccination
- Serious Adverse Events within 7 days after primary and booster vaccination

End point values	4 doses	2 doses		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	137		
Units: number of events				
adverse event	73	70		
serious adverse event	0	0		
possibly, probably or definitely drug-related AE	72	68		
local irritation of injection site	71	68		
general discomfort related to injections	6	11		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported within 7 days of the vaccination.
Serious adverse events are reported within 14 days of the vaccination.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	All participants (Whole study period)

Reporting group description: -

Serious adverse events	All participants (Whole study period)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 303 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	All participants (Whole study period)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	156 / 303 (51.49%)		
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 303 (0.33%)		
occurrences (all)	1		
Ligament sprain			
subjects affected / exposed	1 / 303 (0.33%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 303 (0.33%)		
occurrences (all)	1		

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 303 (1.65%)		
occurrences (all)	5		
Influenza like illness			
subjects affected / exposed	3 / 303 (0.99%)		
occurrences (all)	3		
Injection site erythema			
subjects affected / exposed	144 / 303 (47.52%)		
occurrences (all)	144		
Injection site pain			
subjects affected / exposed	1 / 303 (0.33%)		
occurrences (all)	1		
Injection site pruritus			
subjects affected / exposed	49 / 303 (16.17%)		
occurrences (all)	49		
Injection site swelling			
subjects affected / exposed	25 / 303 (8.25%)		
occurrences (all)	25		
Pyrexia			
subjects affected / exposed	1 / 303 (0.33%)		
occurrences (all)	1		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 303 (0.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 303 (0.99%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	2 / 303 (0.66%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Blister			

subjects affected / exposed	1 / 303 (0.33%)		
occurrences (all)	1		
Photosensitivity reaction			
subjects affected / exposed	1 / 303 (0.33%)		
occurrences (all)	1		
Pruritus generalised			
subjects affected / exposed	1 / 303 (0.33%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 303 (0.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 303 (0.33%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	1 / 303 (0.33%)		
occurrences (all)	1		
Bursitis			
subjects affected / exposed	1 / 303 (0.33%)		
occurrences (all)	1		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 303 (0.33%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	2 / 303 (0.66%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	1 / 303 (0.33%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 303 (0.33%)		
occurrences (all)	1		
Vestibular neuronitis			

subjects affected / exposed	1 / 303 (0.33%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 303 (0.66%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 March 2016	The objective of this amendment was to carry out an interim analysis, including more data than foreseen in the initial protocol [v 2.0]. As mentioned in the protocol version 2.0 we will analyse serology data of day 0 and day 14 for all subjects (N=303), because they finished their primary vaccination. The proposed interim analysis would include boostability data (primary endpoint) of the first 53 participants who have completed their study procedures (by protocol) by the end of 2015. The interim analysis would thus concern the results of the serology tests performed at Day 365 and 372, are separately analysed for this 53 subjects, without waiting for the results (Day 365 and 372) of the whole group of 303 subjects.

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/30566636