Clinical trial results:
Simplifying the Rabies Pre-exposure Vaccination
Summary

EudraCT number	2011-001612-62
Trial protocol	BE
Global end of trial date	12 December 2015

Results information

Result version number	v1 (current)
This version publication date	31 October 2018
First version publication date	31 October 2018
Summary attachment (see zip file)	Publication_CID (2011-001612-62_publication_ciy513.pdf)

Trial information

Trial identification

Sponsor protocol code	ITMC0211

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01388985
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institute of Tropical Medicine
Sponsor organisation address	Nationalestraat 155, Antwerpen, Belgium, 2000
Public contact	Yven Van Herrewege, Institute of Tropical Medicine Antwerp, 0032 3247 6557, yvanherrewege@itg.be
Scientific contact	Yven Van Herrewege, Institute of Tropical Medicine Antwerp, 0032 3247 6557,

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	06 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 December 2015
Global end of trial reached?	Yes
Global end of trial date	12 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the clinical non-inferiority of an accelerated rabies vaccination schedule (of 2 two-sided intradermal injections on day 0 and 2 intradermal injections on day 7) to the standard schedule (of 3 one-side intradermal injections for pre-exposure immunization on day 0, day 7 and day 21 or 28) as assessed by "boostability" (% of subjects that have boostable rabies antibodies) after 1 to 3 years. Clinical non-inferiority is defined as a loss of no more than 10% of subjects that have boostable rabies antibody levels compared to standard treatment.

Protection of trial subjects:

All subjects were asked to report any side effects or adverse events from the time of the injection until 7 days after. No severe pain and distress were expected during the injections.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 September 2011
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: 498
Worldwide total number of subjects	498
EEA total number of subjects	498

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)	498
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at the Travel Clinic, Polyclinic department, in the Military Hospital Queen Astrid, Brussels. Subjects were recruited from the Belgian military settings (land deployment) before their departure on overseas deployment.

Pre-assignment

Screening details:

Inclusion:
- ICF
- age between 18 and 47 years
- rabies seronegative
- belgian soldiers or military students
- prepared to follow study schedule

Exclusion:
- previous rabies vaccination
- allergy to vaccine
- immune depression or immuno depressant medication
- intake of mefloquine
- planned deployment to overseas area within 35 days

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: One-month schedule

Arm description:

Classic intradermal schedule with 1 injection (0,1 ml) (one site) on day 0, day 7 and day 28 respectively.

Booster vaccination was done from 1 year after the first vaccination (day 365) on and before another deployment to rabies enzootic regions. If subjects were not deployed within the 3 years after the first rabies vaccination, booster vaccination was performed no later than 3 years after the first vaccination (day 1095 included).

Arm type	Experimental
Investigational medicinal product name	Rabipur
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Suspension for injection
Routes of administration	Intradermal use

Dosage and administration details:

One intradermal injection (0.1ml) was given on three different days (day 0, day 7 and day 28).

Booster vaccination was done from 1 year after the first vaccination (day 365) on and before another deployment to rabies enzootic regions. If subjects were not deployed within the 3 years after the first rabies vaccination, booster vaccination was performed no later than 3 years after the first vaccination (day 1095 included). Booster vaccination was done by one intradermal injection (0.1ml).

Arm title	Group 2: One-week schedule

Arm description:

Accelerated intradermal schedule with 2 injections (0,1 ml) (each 2 separate injection sites) on day 0 and 2 injections (0.1ml) (separate sites) on day 7.

Booster vaccination were done from 1 year after the first vaccination (day 365) on and before another deployment to rabies enzootic regions. If subjects were not deployed within the 3 years after the first rabies vaccination, booster vaccination was performed no later than 3 years after the first vaccination (day 1095 included).

Arm type	Experimental
Investigational medicinal product name	Rabipur
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Suspension for injection
Routes of administration	Intradermal use

Dosage and administration details:

Primary vaccination: Two injections (0.1ml) were given on the same day (day 0 and day 7): one on each forearm.

Booster vaccination was done from 1 year after the first vaccination (day 365) on and before another deployment to rabies enzootic regions. If subjects were not deployed within the 3 years after the first rabies vaccination, booster vaccination was performed no later than 3 years after the first vaccination (day 1095 included). Booster vaccination was done by one intradermal injection (0.1ml).

Number of subjects in period 1	Group 1: One-month schedule	Group 2: One-week schedule
Started	249	249
Completed	200	211
Not completed	49	38
Consent withdrawn by subject	13	4
Subject unavailable (on mission)	1	-
Death	-	1
Subject unavailable (mission)	-	1
Other	-	1
Error of nurse	5	1
Lost to follow-up	30	30

Baseline characteristics

Reporting groups	
Reporting group title	Group 1: One-month schedule
Reporting group description:	
Classic intradermal schedule with 1 injection (0,1 ml) (one site) on day 0, day 7 and day 28 respectively. Booster vaccination was done from 1 year after the first vaccination (day 365) on and before another deployment to rabies enzootic regions. If subjects were not deployed within the 3 years after the first rabies vaccination, booster vaccination was performed no later than 3 years after the first vaccination (day 1095 included).	
Reporting group title	Group 2: One-week schedule
Reporting group description:	
Accelerated intradermal schedule with 2 injections (0,1 ml) (each 2 separate injection sites) on day 0 and 2 injections (0.1ml) (separate sites) on day 7. Booster vaccination were done from 1 year after the first vaccination (day 365) on and before another deployment to rabies enzootic regions. If subjects were not deployed within the 3 years after the first rabies vaccination, booster vaccination was performed no later than 3 years after the first vaccination (day 1095 included).	

Reporting group values	Group 1: One-month schedule	Group 2: One-week schedule	Total
Number of subjects	249	249	498
Age categorical Units: Subjects			
20 years or less	11	17	28
21-30	138	136	274
31-40	71	60	131
41-50	29	35	64
more than 50	0	1	1
Age continuous Units: years			
median	29	28	
inter-quartile range (Q1-Q3)	24 to 35	23 to 34	-
Gender categorical Units: Subjects			
Female	12	8	20
Male	237	241	478
Serology at baseline			
RFFIT serology value at baseline (before first vaccine injection).			
Units: Subjects			
0.5 IU/ml or less	245	248	493
more than 0.5 IU/ml	4	1	5

End points

End points reporting groups

Reporting group title	Group 1: One-month schedule

Reporting group description:

Classic intradermal schedule with 1 injection (0,1 ml) (one site) on day 0, day 7 and day 28 respectively.

Booster vaccination was done from 1 year after the first vaccination (day 365) on and before another deployment to rabies enzootic regions. If subjects were not deployed within the 3 years after the first rabies vaccination, booster vaccination was performed no later than 3 years after the first vaccination (day 1095 included).

Reporting group title	Group 2: One-week schedule

Reporting group description:

Accelerated intradermal schedule with 2 injections (0,1 ml) (each 2 separate injection sites) on day 0 and 2 injections (0.1ml) (separate sites) on day 7.

Booster vaccination were done from 1 year after the first vaccination (day 365) on and before another deployment to rabies enzootic regions. If subjects were not deployed within the 3 years after the first rabies vaccination, booster vaccination was performed no later than 3 years after the first vaccination (day 1095 included).

Primary: Boostability (0.5 IU/ml or more) of the rabies antibodies after booster vaccination

End point title	Boostability (0.5 IU/ml or more) of the rabies antibodies after booster vaccination

End point description:

End point type	Primary

End point timeframe:

Assessed on day 7 after booster vaccination at year 1 to 3 after initial vaccination.

End point values	Group 1: One-month schedule	Group 2: One-week schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185	183		
Units: Subject counts	185	183		

Statistical analyses

Statistical analysis title	Efficacy analysis

Statistical analysis description:

The primary hypothesis will be assessed by calculating the two-sided 95% confidence interval (CI) for the difference in proportions of subjects boostable ("boostability rate") at 1 to 3 year. The CI will be calculated using Wilson's score method, pooled over the complete study population.

Comparison groups	Group 1: One-month schedule v Group 2: One-week schedule

Number of subjects included in analysis	368
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Proportion Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	2

Notes:

[1] - - if the two-sided 95% CI for the difference in boostability rates (accelerated schedule - standard schedule) lies entirely above -10% then non-inferiority of the accelerated schedule is concluded;
- if the 95% CI for the difference in boostability rates includes -10%, then non-inferiority cannot be established;
- if the 95% CI for the difference in boostability rates lies entirely below ¬-10%, then the accelerated regimen is clinically inferior to the standard regimen.

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

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

End point description:

End point type	Secondary

End point timeframe:

Assessed on day 35 after primary vaccination.

End point values	Group 1: One-month schedule	Group 2: One-week schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	238		
Units: Subject Counts	231	238		

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 endpoint by calculating differences in proportions and 95% CIs.

Comparison groups	Group 1: One-month schedule v Group 2: One-week schedule
Number of subjects included in analysis	469
Analysis specification	Post-hoc
Analysis type	other[2]
Parameter estimate	Proportion Difference
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	2

Notes:

[2] - No non-inferiority limits for the secondary endpoints are predefined, but the CIs will be interpreted in terms of clinical relevance of possible differences rather than statistical significance.

Secondary: Rabies serology more than 10 IU/ml after primary vaccination

End point title	Rabies serology more than 10 IU/ml after primary vaccination

End point description:

End point type	Secondary

End point timeframe:

Assessed on day 35 after primary vaccination and on day 7 after booster vaccination.

End point values	Group 1: One-month schedule	Group 2: One-week schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	238		
Units: Subject Counts	189	167		

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 endpoint by calculating differences in proportions and 95% CIs.

Comparison groups	Group 1: One-month schedule v Group 2: One-week schedule
Number of subjects included in analysis	469
Analysis specification	Post-hoc
Analysis type	other[3]
Parameter estimate	Difference
Point estimate	-12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19
upper limit	-4

Notes:

[3] - No non-inferiority limits for the secondary endpoints are predefined, but the CIs will be interpreted in terms of clinical relevance of possible differences rather than statistical significance.

Secondary: Adverse events and serious adverse events after primary and booster vaccinations

End point title	Adverse events and serious adverse events after primary and booster vaccinations

End point description:

End point type	Secondary

End point timeframe:

- Adverse events: within 7 days after initial and booster vaccinations.
- Serious adverse events: within 28 days after initial and booster vaccinations.

End point values	Group 1: One-month schedule	Group 2: One-week schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	249		
Units: number of subjects				
Any adverse event	190	190		
Possibly, probably or definitely drug-related AE	173	171		
Any Serious Adverse Event	1	2		
Local irritation of injection site	164	165		

Statistical analyses

Statistical analysis title	Safety analyses

Statistical analysis description:

All non-serious and serious adverse events will be grouped according to a pre-specified side-effect coding system and tabulated. The number of subjects experiencing any adverse event, any serious adverse event, and any drug-related serious adverse event will be compared between treatment groups using Fisher's exact test. Safety will be analyzed using the all-subjects-treated approach for the primary and booster vaccination periods separately.

Comparison groups	Group 1: One-month schedule v Group 2: One-week schedule
Number of subjects included in analysis	498
Analysis specification	Post-hoc
Analysis type	other[4]
P-value	= 1 [5]
Method	Fisher exact

Notes:

[4] - The number of subjects experiencing any adverse event, any serious adverse event, and any drug-related serious adverse event will be compared between treatment groups using Fisher's exact test.
[5] - adverse event: p-value=1
possibly, probably er definitely drug-related adverse event: p-value=0.92
serious adverse event: p-value=1
local irritation of injection sites: p-value=1
general discomfort related to injection sites: p-value=0.82

Secondary: Rabies serology more than 10 IU/ml after booster vaccination

End point title	Rabies serology more than 10 IU/ml after booster vaccination

End point description:

End point type	Secondary

End point timeframe:

Assessed at day 7 after booster vaccination.

End point values	Group 1: One-month schedule	Group 2: One-week schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185	183		
Units: Subject Counts	154	176		

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 endpoint by calculating differences in proportions and 95% CIs.	
Comparison groups	Group 1: One-month schedule v Group 2: One-week schedule
Number of subjects included in analysis	368
Analysis specification	Post-hoc
Analysis type	other
Parameter estimate	Proportion difference
Point estimate	13
Confidence interval	
level	95 %
sides	2-sided
lower limit	7
upper limit	19

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs occuring up to 7 days after each vaccination visit will be reported.
All SAE's occurring up to 28 days after each vaccination visit will be reported.

Adverse event reporting additional description:

Persons will receive an adverse event report form: one during primary vaccination and one after booster vaccination. This form needs to be completed and returned to the investigator at the serology visit.

All AEs will be reported on the source documents and in the eCRF.
All SAEs will be reported to the sponsor using the SAE form.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Group 1: One-month schedule

Reporting group description:

Classic intradermal schedule with 1 injection (0,1 ml) (one site) on day 0, day 7 and day 28 respectively.

Booster vaccination was done from 1 year after the first vaccination (day 365) on and before another deployment to rabies enzootic regions. If subjects were not deployed within the 3 years after the first rabies vaccination, booster vaccination was performed no later than 3 years after the first vaccination (day 1095 included).

Reporting group title	Group 2: One-week schedule

Reporting group description:

Accelerated intradermal schedule with 2 injections (0,1 ml) (each 2 separate injection sites) on day 0 and 2 injections (0.1ml) (separate sites) on day 7.

Booster vaccination were done from 1 year after the first vaccination (day 365) on and before another deployment to rabies enzootic regions. If subjects were not deployed within the 3 years after the first rabies vaccination, booster vaccination was performed no later than 3 years after the first vaccination (day 1095 included).

Serious adverse events	Group 1: One-month schedule	Group 2: One-week schedule	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 249 (0.40%)	2 / 249 (0.80%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Hemianopia			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Diplopia			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 249 (0.00%)	2 / 249 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Group 1: One-month schedule	Group 2: One-week schedule	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	156 / 249 (62.65%)	134 / 249 (53.82%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 249 (0.40%)	1 / 249 (0.40%)	
occurrences (all)	1	1	
Hot flush			

subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Peripheral vascular disorder			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Phlebitis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Suture insertion			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Tooth extraction			
subjects affected / exposed	0 / 249 (0.00%)	2 / 249 (0.80%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 249 (1.20%)	5 / 249 (2.01%)	
occurrences (all)	3	5	
Feeling hot			
subjects affected / exposed	1 / 249 (0.40%)	3 / 249 (1.20%)	
occurrences (all)	1	3	
Induration			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Inflammation			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	15 / 249 (6.02%)	11 / 249 (4.42%)	
occurrences (all)	15	11	
Injection site erythema			

subjects affected / exposed	130 / 249 (52.21%)	131 / 249 (52.61%)	
occurrences (all)	130	131	
Injection site haemorrhage			
subjects affected / exposed	2 / 249 (0.80%)	0 / 249 (0.00%)	
occurrences (all)	2	0	
Injection site hypersensitivity			
subjects affected / exposed	1 / 249 (0.40%)	2 / 249 (0.80%)	
occurrences (all)	1	2	
Injection site inflammation			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Injection site nodule			
subjects affected / exposed	4 / 249 (1.61%)	0 / 249 (0.00%)	
occurrences (all)	4	0	
Injection site pain			
subjects affected / exposed	14 / 249 (5.62%)	17 / 249 (6.83%)	
occurrences (all)	14	17	
Injection site pruritus			
subjects affected / exposed	3 / 249 (1.20%)	2 / 249 (0.80%)	
occurrences (all)	3	2	
injection site swelling			
subjects affected / exposed	43 / 249 (17.27%)	67 / 249 (26.91%)	
occurrences (all)	43	67	
Malaise			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	3 / 249 (1.20%)	2 / 249 (0.80%)	
occurrences (all)	3	2	
Pyrexia			
subjects affected / exposed	6 / 249 (2.41%)	2 / 249 (0.80%)	
occurrences (all)	6	2	
Thirst			

subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	2 / 249 (0.80%)	0 / 249 (0.00%)	
occurrences (all)	2	0	
Dyspnoea			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Respiratory disorder			
subjects affected / exposed	2 / 249 (0.80%)	0 / 249 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Fear			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 249 (0.80%)	4 / 249 (1.61%)	
occurrences (all)	2	4	
Frostbite			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Humerus fracture			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	

Meniscus injury			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Scratch			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Gilbert's syndrome			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Carpal tunnel syndrome			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	3 / 249 (1.20%)	1 / 249 (0.40%)	
occurrences (all)	3	1	
Dysgeusia			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	20 / 249 (8.03%)	20 / 249 (8.03%)	
occurrences (all)	20	20	
Syncope			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Lymphadenopathy			

subjects affected / exposed	6 / 249 (2.41%)	2 / 249 (0.80%)	
occurrences (all)	6	2	
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Photophobia			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 249 (0.80%)	0 / 249 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	4 / 249 (1.61%)	2 / 249 (0.80%)	
occurrences (all)	4	2	
Nausea			
subjects affected / exposed	6 / 249 (2.41%)	0 / 249 (0.00%)	
occurrences (all)	6	0	
Periodontitis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	2 / 249 (0.80%)	0 / 249 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			

subjects affected / exposed	0 / 249 (0.00%)	2 / 249 (0.80%)	
occurrences (all)	0	2	
Pruritus			
subjects affected / exposed	118 / 249 (47.39%)	119 / 249 (47.79%)	
occurrences (all)	118	119	
Rash			
subjects affected / exposed	5 / 249 (2.01%)	3 / 249 (1.20%)	
occurrences (all)	5	3	
Skin exfoliation			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	0 / 249 (0.00%)	2 / 249 (0.80%)	
occurrences (all)	0	2	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 249 (0.80%)	3 / 249 (1.20%)	
occurrences (all)	2	3	
Back pain			
subjects affected / exposed	4 / 249 (1.61%)	3 / 249 (1.20%)	
occurrences (all)	4	3	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	2 / 249 (0.80%)	0 / 249 (0.00%)	
occurrences (all)	2	0	
Pain in extremity			

subjects affected / exposed	4 / 249 (1.61%)	4 / 249 (1.61%)	
occurrences (all)	4	4	
Tendonitis			
subjects affected / exposed	3 / 249 (1.20%)	3 / 249 (1.20%)	
occurrences (all)	3	3	
Torticollis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 249 (0.40%)	2 / 249 (0.80%)	
occurrences (all)	1	2	
Bronchitis			
subjects affected / exposed	5 / 249 (2.01%)	1 / 249 (0.40%)	
occurrences (all)	5	1	
Ear infection			
subjects affected / exposed	2 / 249 (0.80%)	0 / 249 (0.00%)	
occurrences (all)	2	0	
Eye infection bacterial			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Furuncle			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Impetigo			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	2 / 249 (0.80%)	0 / 249 (0.00%)	
occurrences (all)	2	0	
Laryngitis			
subjects affected / exposed	2 / 249 (0.80%)	0 / 249 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
subjects affected / exposed	5 / 249 (2.01%)	4 / 249 (1.61%)	
occurrences (all)	5	4	

Onychomycosis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	2 / 249 (0.80%)	0 / 249 (0.00%)	
occurrences (all)	2	0	
Respiratory tract infection			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	2 / 249 (0.80%)	0 / 249 (0.00%)	
occurrences (all)	2	0	
Sinusitis			
subjects affected / exposed	2 / 249 (0.80%)	1 / 249 (0.40%)	
occurrences (all)	2	1	
Tooth abscess			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Tracheitis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 249 (0.40%)	0 / 249 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	0 / 249 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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/29939243