# 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.<br><br>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.<br><br>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<br>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<br>Units: years | | | |
| median | 29 | 28 | |
| inter-quartile range (Q1-Q3) | 24 to 35 | 23 to 34 | - |
| Gender categorical<br>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