



## Clinical trial results:

### Switch To RltuXimab in MS

**A phase 2 open label study of Rituximab in MS patients previously treated with self-injectibles using a target based therapy approach**

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2010-023021-38 |
| Trial protocol           | SE             |
| Global end of trial date | 31 March 2015  |

#### Results information

|                                   |                                                           |
|-----------------------------------|-----------------------------------------------------------|
| Result version number             | v1                                                        |
| This version publication date     | 31 December 2017                                          |
| First version publication date    | 31 December 2017                                          |
| Summary attachment (see zip file) | Assessment of Safety (Clinical Study Report_20151015.pdf) |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | STRIX-MS001 |
|-----------------------|-------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |                                                                                                   |
|------------------------------|---------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Västerbottens läns landsting                                                                      |
| Sponsor organisation address | Dept of Neurology, Norrlands University Hospital, Umeå, Sweden, 90185                             |
| Public contact               | Anders Svenningsson, Norrlands University Hospital, Dept of Neurology, anders.svenningsson@me.com |
| Scientific contact           | Anders Svenningsson, Norrlands University Hospital, Dept of Neurology, anders.svenningsson@me.com |

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:

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**Results analysis stage**

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|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 15 October 2015 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 31 March 2015   |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 31 March 2015   |
| Was the trial ended prematurely?                     | No              |

Notes:

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**General information about the trial**

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Main objective of the trial:

To evaluate the feasibility and safety of switching from injectible MS treatments to Mabthera in stable relapsing-remitting multiple sclerosis (RRMS)

To study the effects on inflammatory parameters on magnetic resonance imaging when switching MS therapy to Mabthera in RRMS

To study the development of neurodegenerative processes after therapy switch to Rituximab using quantitative MRI measurements and analysis of biomarkers for axonal damage in the cerebrospinal fluid (CSF)

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Protection of trial subjects:

Baseline measurements with high sensitivity MRI (with double dose contrast) will be done twice with 3 months apart to collect enough data for comparison of effect on inflammatory parameters between first line DMD:s and Rituximab. Lumbar puncture will be performed once during this period in close connection with the second MRI, immediately before the therapy switch. The Rituximab therapy will be performed on an outpatient basis and require approximately 6 hours per infusion with two weeks apart. Follow-up examinations will be performed at month 3 and 6 and thereafter 6-monthly up to two years. High sensitivity MRI will be performed 3 and 6 months after start of Rituximab treatment and thereafter regular MRI including qMRI every 6 month. Lumbar puncture will be performed in close connection to the MRI examinations after one and two years, respectively.

Tests and endpoints during the study:

Blood chemistry Safety

Flow cytometry Safety, exploratory

MRI, double dose contrast + qMRI Safety, disease activity inflammation

MRI, standard + qMRI Safety, neurodegeneration

LP Biomarkers, neurodegeneration

EDSS Disease progression

MSIS29 Social activity measure, QoL

SDMT Cognitive function

FSMC Fatigue

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Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 01 November 2011 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Sweden: 77 |
|--------------------------------------|------------|

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|                                    |    |
|------------------------------------|----|
| Worldwide total number of subjects | 77 |
| EEA total number of subjects       | 77 |

Notes:

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**Subjects enrolled per age group**

|                                           |    |
|-------------------------------------------|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 77 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Inclusion criteria: Between the age of 18 and 55 years (inclusive) of age, Diagnosis of Relapsing Remitting MS, Treatment with any of the first line injectable DMD:s, In fertile females, willing to comply with effective contraceptive methods. Clinically stable on first line injectable therapies for 6 months.

### Pre-assignment

Screening details:

Patients fulfilling inclusion criteria were offered participation in the study according to a randomisation procedure in the Swedish MS registry.

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 77 |
| Number of subjects completed | 77 |

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | Baseline period             |
| Is this the baseline period? | Yes                         |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

### Arms

|           |                    |
|-----------|--------------------|
| Arm title | Baseline treatment |
|-----------|--------------------|

Arm description:

Baseline period of three months with the present first line DMD:s (disease-modifying drugs).

|                                        |                                   |
|----------------------------------------|-----------------------------------|
| Arm type                               | Disease-modifying drugs           |
| Investigational medicinal product name | Avonex                            |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Injection                         |
| Routes of administration               | Intramuscular and intravenous use |

Dosage and administration details:

Patients continued their unchanged, prescribed, drug treatment during the run-in period. First line treatment includes treatments that involve self-administered injections interferons, once a week.

|                                        |                  |
|----------------------------------------|------------------|
| Investigational medicinal product name | Copaxone         |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

Patients continued their unchanged, prescribed, drug treatment during the run-in period. First line treatment includes treatments that involve self-administered injections with Glatiramere, daily.

|                                        |                                   |
|----------------------------------------|-----------------------------------|
| Investigational medicinal product name | Rebif                             |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Injection                         |
| Routes of administration               | Intramuscular and intravenous use |

Dosage and administration details:

Patients continued their unchanged, prescribed, drug treatment during the run-in period. First line treatment includes treatments that involve self-administered injections interferons, once a week.

| <b>Number of subjects in period 1</b> | Baseline treatment |
|---------------------------------------|--------------------|
| Started                               | 77                 |
| Completed                             | 75                 |
| Not completed                         | 2                  |
| Consent withdrawn by subject          | 2                  |

## Period 2

|                              |                             |
|------------------------------|-----------------------------|
| Period 2 title               | Treatment period            |
| Is this the baseline period? | No                          |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

## Arms

| <b>Arm title</b> | Treatment period |
|------------------|------------------|
|------------------|------------------|

### Arm description:

After a run-in period of 3 months with unchanged injection therapy, treatment was shifted to rituximab (Mabthera®; Roche AB, Stockholm, Sweden).

|                                        |                       |
|----------------------------------------|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Rituximab (Mabthera®) |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Infusion              |
| Routes of administration               | Intravenous use       |

### Dosage and administration details:

Two doses of rituximab (1000 mg intravenous (IV)) were given 2 weeks apart.

If inflammatory activity occurred during the second year, the patient received a re-treatment with 1000 mg rituximab IV.

| <b>Number of subjects in period 2</b> | Treatment period |
|---------------------------------------|------------------|
| Started                               | 75               |
| Completed                             | 72               |
| Not completed                         | 3                |
| Pregnancy                             | 1                |
| Planning for pregnancy                | 1                |
| Lack of efficacy                      | 1                |



## Baseline characteristics

### Reporting groups

| Reporting group title          | Baseline period |
|--------------------------------|-----------------|
| Reporting group description: - |                 |

| Reporting group values                                | Baseline period | Total |  |
|-------------------------------------------------------|-----------------|-------|--|
| Number of subjects                                    | 77              | 77    |  |
| Age categorical                                       |                 |       |  |
| Adults 18-55 years.                                   |                 |       |  |
| Units: Subjects                                       |                 |       |  |
| In utero                                              | 0               | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0               | 0     |  |
| Newborns (0-27 days)                                  | 0               | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0               | 0     |  |
| Children (2-11 years)                                 | 0               | 0     |  |
| Adolescents (12-17 years)                             | 0               | 0     |  |
| Adults (18-64 years)                                  | 77              | 77    |  |
| From 65-84 years                                      | 0               | 0     |  |
| 85 years and over                                     | 0               | 0     |  |
| Gender categorical                                    |                 |       |  |
| Units: Subjects                                       |                 |       |  |
| Female                                                | 52              | 52    |  |
| Male                                                  | 25              | 25    |  |

## End points

### End points reporting groups

|                                                                                                                                                  |                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Reporting group title                                                                                                                            | Baseline treatment |
| Reporting group description:                                                                                                                     |                    |
| Baseline period of three months with the present first line DMD:s (disease-modifying drugs).                                                     |                    |
| Reporting group title                                                                                                                            | Treatment period   |
| Reporting group description:                                                                                                                     |                    |
| After a run-in period of 3 months with unchanged injection therapy, treatment was shifted to rituximab (Mabthera®; Roche AB, Stockholm, Sweden). |                    |

### Primary: To study safety and efficacy in reducing inflammatory activity upon switch from injectable first-line treatments to rituximab in patients with clinically stable relapsing-remitting MS (RRMS)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | To study safety and efficacy in reducing inflammatory activity upon switch from injectable first-line treatments to rituximab in patients with clinically stable relapsing-remitting MS (RRMS) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                |
| The primary endpoints are                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                |
| <ul style="list-style-type: none"><li>•To document the safety of Rituximab treatment in a non-selected population of RRMS patients using a new target based treatment protocol.</li><li>•The number of Gd-enhancing active lesions in two MRI scans performed three months apart in a run-in period before therapy switch compared with two MRI scans three months apart with the first scan performed three months after therapy switch. The MRI scans will be performed with double dose contrast and 15 minutes delay to maximize the sensitivity.</li><li>•The change in the marker for axonal damage NFL in the CSF before treatment switch and after one year of Rituximab treatment. We have previously shown that treatment with natalizumab will lead to a significant reduction of this value when changing therapy from first line DMD:s.</li></ul> |                                                                                                                                                                                                |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Primary                                                                                                                                                                                        |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                |
| The patients were followed up through regular clinical visits, MRI and lumbar punctures for a period of 24 months.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                |

| End point values            | Baseline treatment | Treatment period  |  |  |
|-----------------------------|--------------------|-------------------|--|--|
| Subject group type          | Reporting group    | Reporting group   |  |  |
| Number of subjects analysed | 75 <sup>[1]</sup>  | 72 <sup>[2]</sup> |  |  |
| Units: Results of MRI       | 75                 | 72                |  |  |

Notes:

[1] - Two persons withdrew their consent.

[2] - Reasons for premature stop: pregnancy, planned pregnancy and lack of efficacy.

|                                   |                                                                                                                          |
|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Published article/Improved treatment satisfaction after<br>Published article/Reduced inflammation in relapsing-remitting |
|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------|

### Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Comparative statistics |
|----------------------------|------------------------|

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**Statistical analysis description:**

All statistical testing were done as two-sided on a 5 % level of significance, all confidence intervals 95 % intervals.

The Wilcoxon signed-rank test was used to test paired significance between the separate time points. Descriptive statistics were reported for all variables with calculation of mean values, median values, standard deviation (SD) and range. Missing values were not replaced.

|                                         |                                       |
|-----------------------------------------|---------------------------------------|
| Comparison groups                       | Baseline treatment v Treatment period |
| Number of subjects included in analysis | 147                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority <sup>[3]</sup>            |
| P-value                                 | < 0.05                                |
| Method                                  | Wilcoxon signed-rank test             |

**Notes:**

[3] - Each patient was its own control, which resulted in perfect matching and stronger statistical analysis. With a baseline period including two high-sensitivity MRI scans regarding active inflammation made a comparison of efficacy regarding this aspect of the disease possible. The comparison of NFL (Neurofilament light chains) levels in the CSF (Cerebrospinal fluid) will provide information of treatment effects on the neurodegenerative part of the disease possible.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the time a patient consents to participate in the trial until he/she has completed the trial.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |       |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

|                    |     |
|--------------------|-----|
| Dictionary version | 4.0 |
|--------------------|-----|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Treatment period |
|-----------------------|------------------|

Reporting group description: -

| Serious adverse events                            | Treatment period                                                                                            |  |  |
|---------------------------------------------------|-------------------------------------------------------------------------------------------------------------|--|--|
| Total subjects affected by serious adverse events |                                                                                                             |  |  |
| subjects affected / exposed                       | 6 / 75 (8.00%)                                                                                              |  |  |
| number of deaths (all causes)                     | 0                                                                                                           |  |  |
| number of deaths resulting from adverse events    | 0                                                                                                           |  |  |
| Nervous system disorders                          |                                                                                                             |  |  |
| Stroke                                            |                                                                                                             |  |  |
| subjects affected / exposed                       | 1 / 75 (1.33%)                                                                                              |  |  |
| occurrences causally related to treatment / all   | 0 / 1                                                                                                       |  |  |
| deaths causally related to treatment / all        | 0 / 0                                                                                                       |  |  |
| Psychiatric disorders                             |                                                                                                             |  |  |
| Suicidal attempt with intoxication                |                                                                                                             |  |  |
| subjects affected / exposed                       | 1 / 75 (1.33%)                                                                                              |  |  |
| occurrences causally related to treatment / all   | 0 / 1                                                                                                       |  |  |
| deaths causally related to treatment / all        | 0 / 0                                                                                                       |  |  |
| Infections and infestations                       |                                                                                                             |  |  |
| Influenza                                         | Additional description: This is reported as Upper respiratory infection in Appendix III, Safety assessment. |  |  |
| subjects affected / exposed                       | 1 / 75 (1.33%)                                                                                              |  |  |
| occurrences causally related to treatment / all   | 1 / 1                                                                                                       |  |  |
| deaths causally related to treatment / all        | 0 / 0                                                                                                       |  |  |
| Cholangitis                                       | Additional description: This is reported as Biliary tract infection in Appendix III, Safety assessment.     |  |  |
| subjects affected / exposed                       | 1 / 75 (1.33%)                                                                                              |  |  |
| occurrences causally related to treatment / all   | 0 / 1                                                                                                       |  |  |
| deaths causally related to treatment / all        | 0 / 0                                                                                                       |  |  |

|                                                 |                                                                                                  |  |  |
|-------------------------------------------------|--------------------------------------------------------------------------------------------------|--|--|
| Pyelonephritis                                  | Additional description: This is reported as Kidney infection in Appendix III, Safety assessment. |  |  |
| subjects affected / exposed                     | 2 / 75 (2.67%)                                                                                   |  |  |
| occurrences causally related to treatment / all | 1 / 2                                                                                            |  |  |
| deaths causally related to treatment / all      | 0 / 0                                                                                            |  |  |

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

| Non-serious adverse events                                                                           | Treatment period |  |  |
|------------------------------------------------------------------------------------------------------|------------------|--|--|
| Total subjects affected by non-serious adverse events                                                |                  |  |  |
| subjects affected / exposed                                                                          | 47 / 75 (62.67%) |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)                                  |                  |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps), other: Pituitary adenoma benign |                  |  |  |
| subjects affected / exposed                                                                          | 1 / 75 (1.33%)   |  |  |
| occurrences (all)                                                                                    | 1                |  |  |
| Vascular disorders                                                                                   |                  |  |  |
| Flushing                                                                                             |                  |  |  |
| subjects affected / exposed                                                                          | 2 / 75 (2.67%)   |  |  |
| occurrences (all)                                                                                    | 2                |  |  |
| Surgical and medical procedures                                                                      |                  |  |  |
| Surgical and medical procedures - other, Post LP headache/pains                                      |                  |  |  |
| subjects affected / exposed                                                                          | 13 / 75 (17.33%) |  |  |
| occurrences (all)                                                                                    | 13               |  |  |
| General disorders and administration site conditions                                                 |                  |  |  |
| Edema face                                                                                           |                  |  |  |
| subjects affected / exposed                                                                          | 1 / 75 (1.33%)   |  |  |
| occurrences (all)                                                                                    | 1                |  |  |
| Edema limbs                                                                                          |                  |  |  |
| subjects affected / exposed                                                                          | 3 / 75 (4.00%)   |  |  |
| occurrences (all)                                                                                    | 3                |  |  |
| Fatigue                                                                                              |                  |  |  |
| subjects affected / exposed                                                                          | 3 / 75 (4.00%)   |  |  |
| occurrences (all)                                                                                    | 3                |  |  |
| Fever                                                                                                |                  |  |  |

|                                                                               |                |  |  |
|-------------------------------------------------------------------------------|----------------|--|--|
| subjects affected / exposed                                                   | 1 / 75 (1.33%) |  |  |
| occurrences (all)                                                             | 1              |  |  |
| Infusion related reaction                                                     |                |  |  |
| subjects affected / exposed                                                   | 1 / 75 (1.33%) |  |  |
| occurrences (all)                                                             | 1              |  |  |
| Pain                                                                          |                |  |  |
| subjects affected / exposed                                                   | 2 / 75 (2.67%) |  |  |
| occurrences (all)                                                             | 2              |  |  |
| Immune system disorders                                                       |                |  |  |
| Immune system disorder - other, itching                                       |                |  |  |
| subjects affected / exposed                                                   | 1 / 75 (1.33%) |  |  |
| occurrences (all)                                                             | 1              |  |  |
| Reproductive system and breast disorders                                      |                |  |  |
| Menorrhagia                                                                   |                |  |  |
| subjects affected / exposed                                                   | 1 / 75 (1.33%) |  |  |
| occurrences (all)                                                             | 1              |  |  |
| Respiratory, thoracic and mediastinal disorders                               |                |  |  |
| Cough                                                                         |                |  |  |
| subjects affected / exposed                                                   | 2 / 75 (2.67%) |  |  |
| occurrences (all)                                                             | 2              |  |  |
| Dyspnea                                                                       |                |  |  |
| subjects affected / exposed                                                   | 2 / 75 (2.67%) |  |  |
| occurrences (all)                                                             | 2              |  |  |
| Respiratory, thoracic and mediastinal disorder - other, mycoplasma pneumoniae |                |  |  |
| subjects affected / exposed                                                   | 1 / 75 (1.33%) |  |  |
| occurrences (all)                                                             | 1              |  |  |
| Psychiatric disorders                                                         |                |  |  |
| Depression                                                                    |                |  |  |
| subjects affected / exposed                                                   | 2 / 75 (2.67%) |  |  |
| occurrences (all)                                                             | 2              |  |  |
| Investigations                                                                |                |  |  |
| Alanine aminotransferase increased                                            |                |  |  |
| subjects affected / exposed                                                   | 1 / 75 (1.33%) |  |  |
| occurrences (all)                                                             | 1              |  |  |
| Alanine aminotransferase increased,                                           |                |  |  |

|                                                                                     |                |  |  |
|-------------------------------------------------------------------------------------|----------------|--|--|
| Aspartate aminotransferase increased                                                |                |  |  |
| subjects affected / exposed                                                         | 1 / 75 (1.33%) |  |  |
| occurrences (all)                                                                   | 1              |  |  |
| Weight gain                                                                         |                |  |  |
| subjects affected / exposed                                                         | 1 / 75 (1.33%) |  |  |
| occurrences (all)                                                                   | 1              |  |  |
| Injury, poisoning and procedural complications                                      |                |  |  |
| Injury, poisoning and procedural complications - Other, Trauma shoulder due to fall |                |  |  |
| subjects affected / exposed                                                         | 1 / 75 (1.33%) |  |  |
| occurrences (all)                                                                   | 1              |  |  |
| Injury, poisoning and procedural complications - Other, Post traumatic knee pain    |                |  |  |
| subjects affected / exposed                                                         | 1 / 75 (1.33%) |  |  |
| occurrences (all)                                                                   | 1              |  |  |
| Injury, poisoning and procedural complications - Other, Cruciate ligament injury    |                |  |  |
| subjects affected / exposed                                                         | 1 / 75 (1.33%) |  |  |
| occurrences (all)                                                                   | 1              |  |  |
| Injury, poisoning and procedural complications - Other, Calf muscle rupture         |                |  |  |
| subjects affected / exposed                                                         | 1 / 75 (1.33%) |  |  |
| occurrences (all)                                                                   | 1              |  |  |
| Cardiac disorders                                                                   |                |  |  |
| Cardiac disorder - other, tachycardia                                               |                |  |  |
| subjects affected / exposed                                                         | 1 / 75 (1.33%) |  |  |
| occurrences (all)                                                                   | 1              |  |  |
| Nervous system disorders                                                            |                |  |  |
| Dizziness                                                                           |                |  |  |
| subjects affected / exposed                                                         | 1 / 75 (1.33%) |  |  |
| occurrences (all)                                                                   | 1              |  |  |
| Headache                                                                            |                |  |  |
| subjects affected / exposed                                                         | 1 / 75 (1.33%) |  |  |
| occurrences (all)                                                                   | 1              |  |  |
| Neuralgia                                                                           |                |  |  |

|                                                                                                                                                                                                                                                                                                                      |                                                                                                      |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                     | 1 / 75 (1.33%)<br>1                                                                                  |  |  |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                           | 1 / 75 (1.33%)<br>1                                                                                  |  |  |
| Eye disorders<br>Eye disorder - others, iritis, silent<br>subjects affected / exposed<br>occurrences (all)<br><br>Eye disorders - other, macula<br>hypertension with pigment<br>dispersion syndrome (PDS)<br>subjects affected / exposed<br>occurrences (all)                                                        | 1 / 75 (1.33%)<br>1<br><br>1 / 75 (1.33%)<br>1                                                       |  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspepsia<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br><br>Rectal hemorrhage<br>subjects affected / exposed<br>occurrences (all) | 1 / 75 (1.33%)<br>1<br><br>1 / 75 (1.33%)<br>1<br><br>1 / 75 (1.33%)<br>1<br><br>1 / 75 (1.33%)<br>1 |  |  |
| Skin and subcutaneous tissue disorders<br>Skin and subcutaneous tissue disorders<br>- other, hidradenitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Skin and subcutaneous tissue disorders<br>- other Rosacea<br>subjects affected / exposed<br>occurrences (all)                                   | 1 / 75 (1.33%)<br>1<br><br>1 / 75 (1.33%)<br>1                                                       |  |  |
| Endocrine disorders                                                                                                                                                                                                                                                                                                  |                                                                                                      |  |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                 |  |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|--|--|
| Endocrine disorder - other, B12 deficiency<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                                  | 1 / 75 (1.33%)<br>1                                                                                                             |  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Back pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Joint range of motion decreased<br>subjects affected / exposed<br>occurrences (all)<br><br>Myalgia, Fever<br>subjects affected / exposed<br>occurrences (all)<br><br>Musculoskeletal and connective tissue disorder - other, Hip pain<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 75 (1.33%)<br>1<br><br>6 / 75 (8.00%)<br>6<br><br>1 / 75 (1.33%)<br>1<br><br>1 / 75 (1.33%)<br>1<br><br>1 / 75 (1.33%)<br>1 |  |  |
| Infections and infestations<br>Cold<br>subjects affected / exposed<br>occurrences (all)<br><br>Infection and infestations - other, herpes zoster ophtalmicus<br>subjects affected / exposed<br>occurrences (all)<br><br>Infections and infestations - other, gastroenteritis<br>subjects affected / exposed<br>occurrences (all)<br><br>Infections and infestations - other, erythema infectiosum<br>subjects affected / exposed<br>occurrences (all)<br><br>Infections and infestations - other, herpes zoster | 6 / 75 (8.00%)<br>8<br><br>1 / 75 (1.33%)<br>1<br><br>3 / 75 (4.00%)<br>3<br><br>1 / 75 (1.33%)<br>1                            |  |  |

|                                                    |                  |  |  |
|----------------------------------------------------|------------------|--|--|
| subjects affected / exposed                        | 1 / 75 (1.33%)   |  |  |
| occurrences (all)                                  | 1                |  |  |
| Tooth infection                                    |                  |  |  |
| subjects affected / exposed                        | 2 / 75 (2.67%)   |  |  |
| occurrences (all)                                  | 2                |  |  |
| Upper respiratory infection                        |                  |  |  |
| subjects affected / exposed                        | 12 / 75 (16.00%) |  |  |
| occurrences (all)                                  | 12               |  |  |
| Upper respiratory infection, Cough,<br>Sore throat |                  |  |  |
| subjects affected / exposed                        | 1 / 75 (1.33%)   |  |  |
| occurrences (all)                                  | 1                |  |  |
| Upper respiratory infection, Fever                 |                  |  |  |
| subjects affected / exposed                        | 1 / 75 (1.33%)   |  |  |
| occurrences (all)                                  | 1                |  |  |
| Upper respiratory tract infection                  |                  |  |  |
| subjects affected / exposed                        | 1 / 75 (1.33%)   |  |  |
| occurrences (all)                                  | 1                |  |  |
| Urinary tract infection                            |                  |  |  |
| subjects affected / exposed                        | 5 / 75 (6.67%)   |  |  |
| occurrences (all)                                  | 5                |  |  |
| Wound infection                                    |                  |  |  |
| subjects affected / exposed                        | 1 / 75 (1.33%)   |  |  |
| occurrences (all)                                  | 1                |  |  |
| Vulval infection                                   |                  |  |  |
| subjects affected / exposed                        | 1 / 75 (1.33%)   |  |  |
| occurrences (all)                                  | 1                |  |  |
| Metabolism and nutrition disorders                 |                  |  |  |
| Hyperglycemia                                      |                  |  |  |
| subjects affected / exposed                        | 1 / 75 (1.33%)   |  |  |
| occurrences (all)                                  | 1                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27780912>

<http://www.ncbi.nlm.nih.gov/pubmed/27316241>