



Clinical trial results:

Switch To RltuXimab in MS extension

An extension study of STRIX-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 | 2013-002378-26 |
| Trial protocol | SE |
| Global end of trial date | 12 April 2018 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 07 October 2018 |
| First version publication date | 07 October 2018 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | STRIX-MSext001 |
|-----------------------|----------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | County council of Västerbotten |
| Sponsor organisation address | University Hospital of Umeå, Umeå, Sweden, 90185 |
| Public contact | Anders Svenningsson, Dept of Neurology, University Hospital of Umeå, Umeå, Sweden, anders.svenningsson@ki.se |
| Scientific contact | Anders Svenningsson, Dept of Neurology, University Hospital of Umeå, Umeå, Sweden, +46 702415852, anders.svenningsson@ki.se |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 16 September 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 April 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 April 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study are

- To evaluate the efficiency on inflammatory parameters and the need of retreat-ment to keep a stable condition during long-term treatment with Rituximab in a co-hort of RRMS patients that otherwise would have been treated with first-line MS medications. The inflammatory parameters studied are new relapses and new T2- and Gd-enhancing lesions on MRI.
- To study the development of neurodegenerative processes during long-term treatment with Rituximab using quantitative MRI measurements and analysis of bi-omarkers for axonal damage in the cerebrospinal fluid (CSF). These values will be compared with age-matched healthy controls and, when applicable, with values before start of Rituximab treatment.

Protection of trial subjects:

MRI was be done every 12 months during the whole extension study.

Lumbar puncture was performed in close connection to the MRI examinations, as an optional exploratory study.

The Rituximab therapy was performed as on an outpatient basis and required approximately 6 hours per infusion.

In this extension study, two protocols was used for the long-term treatment of the patients based on patient age and possible inflammatory activity during the initial study (EudraCT 2010-023021-38).

Patients treatead according to Protocol no 1 was switched to Protocol no 2 if there was documented disease activity that fulfilled the criteria of "treatment failure" in the study proctol.

Patients treated according to Protocol no 2 was offered alternative treatment if there was documented disease activity that fulfilled the criteria of "treatment failure" in the study protocol.

Treatment failure definition, in this study, as occurrence of ANY of the below:

1. Any documented relapse activity during the extension study
2. Any documented Gd+ lesion on MRI during the extension study
3. More than one new or enlarging T2 lesion on MRI during the preceding year in the extension study

Tests during the study:

Blood chemistry (Safety)

Flow cytometry (Safety, exploratory)

MRI, standard + qMRI (Safety, neurodegeneration)

LP (optional exploratory) (Biomarkers, neurodegeneration)

Background therapy:

-

Evidence for comparator:

-

| | |
|---|------------------|
| Actual start date of recruitment | 04 November 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Sweden: 66 |
| Worldwide total number of subjects | 66 |
| EEA total number of subjects | 66 |

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) | 66 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Inclusion criteria for this extension study:

- Have completed the STRIX-MS trial (Eudra-CT 2010-023021-38).
- Willing to comply with study procedures
- In fertile females, willing to comply with effective contraceptive methods. These include birthcontrol pills, surgical sterilization

Pre-assignment

Screening details:

Patients included in the STRIX-MS trial were offered to continue with additional Rituximab courses in the form of this extension study.

Period 1

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

Arms

| | |
|-----------|---------------------------------|
| Arm title | Active treatment with Rituximab |
|-----------|---------------------------------|

Arm description:

Protocol no 1, assumed low inflammatory disease: Rituximab 500 mg at time 0, 6 and 12 months, thereafter only if indicated from the definition of "treatment failure" below.

Protocol no 2, assumed more active inflammatory disease:

Rituximab 1000 mg at time 0, 6 and 12 months, thereafter yearly (time 24 and 36 months)

| | |
|--|----------------------|
| 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:

Protocol no 1, assumed low inflammatory disease: Rituximab 500 mg at time 0, 6 and 12 months, thereafter only if indicated from the definition of "treatment failure".

Protocol no 2, assumed more active inflammatory disease: Rituximab 1000 mg at time 0, 6 and 12 months, thereafter yearly (time 24 and 36 months)

| Number of subjects in period 1 | Active treatment with Rituximab |
|--------------------------------|---------------------------------|
| Started | 66 |
| Completed | 59 |
| Not completed | 7 |
| Consent withdrawn by subject | 1 |
| Adverse event, non-fatal | 1 |
| Pregnancy | 1 |

| | |
|------------------|---|
| New diagnosis | 1 |
| Lack of efficacy | 3 |

Baseline characteristics

Reporting groups

Reporting group title

Overall trial

Reporting group description:

Each patient is its own control. There is no comparison between groups.

| Reporting group values | Overall trial | Total | |
|---|---------------|-------|--|
| Number of subjects | 66 | 66 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 66 | 66 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 44 | 44 | |
| Male | 22 | 22 | |

End points

End points reporting groups

| | |
|--|---------------------------------|
| Reporting group title | Active treatment with Rituximab |
| Reporting group description: | |
| Protocol no 1, assumed low inflammatory disease: Rituximab 500 mg at time 0, 6 and 12 months, thereafter only if indicated from the definition of "treatment failure" below. | |
| Protocol no 2, assumed more active inflammatory disease: | |
| Rituximab 1000 mg at time 0, 6 and 12 months, thereafter yearly (time 24 and 36 months) | |

Primary: The proportion of patients undergoing the predefined study protocols over three years that fulfils the criteria free from disease activity

| | |
|-----------------|---|
| End point title | The proportion of patients undergoing the predefined study protocols over three years that fulfils the criteria free from disease activity ^[1] |
|-----------------|---|

End point description:

The proportion of patients undergoing the predefined study protocols over three years that fulfils the criteria "free from disease activity" defined as:

- o Free from clinical relapse
- o Free from contrast-enhancing MRI lesions
- o No more than one new or enlarged MRI lesion visible on T2-weighted images during the previous 12 month period

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

The patients were followed up for a period of 3 years.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Each patient is its own control. There is no comparison between treatment groups.

All statistical testing will be done as two-sided on a 5 % level of significance, and in particular all confidence intervals (CI) will be 95 % intervals. Test of normality will be performed which will decide as to use parametric (eg Student's t-test) or non-parametric (eg Wilcoxon rank-sum test) statistic).

| End point values | Active treatment with Rituximab | | | |
|-----------------------------|---------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 59 | | | |
| Units: Numbers | 59 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of patients free from all signs of disease activity including, in addition to the primary endpoint, no new T2 lesions during the whole study period and no increase in EDSS.

| | |
|-----------------|--|
| End point title | The proportion of patients free from all signs of disease activity including, in addition to the primary endpoint, no new T2 |
|-----------------|--|

lesions during the whole study period and no increase in EDSS.

End point description:

The period included in this analysis is from month 0 in the original STRIX-MS study, ie when Rituximab was administered in the first time.

End point type Secondary

End point timeframe:

The patients were followed up for a period of 3 years.

| | | | | |
|-----------------------------|---------------------------------|--|--|--|
| End point values | Active treatment with Rituximab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 59 | | | |
| Units: Numbers | 59 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: • The degree of brain atrophy development over the course of the whole study peri-od measured as BPF as compared with age-matched healthy controls

End point title • The degree of brain atrophy development over the course of the whole study peri-od measured as BPF as compared with age-matched healthy controls

End point description:

End point type Secondary

End point timeframe:

The patients were followed for a period of 3 years.

| | | | | |
|-----------------------------|---------------------------------|--|--|--|
| End point values | Active treatment with Rituximab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 59 | | | |
| Units: Number | 59 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: • The levels of Neurofilament-light values in CSF analyses, which will be compared with age-matched healthy controls as well as before Rituximab treatment started.

| | |
|-------------------------------------|---|
| End point title | • The levels of Neurofilament-light values in CSF analyses, which will be compared with age-matched healthy controls as well as before Rituximab treatment started. |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| The patients were followed 3 years. | |

| | | | | |
|-----------------------------|---------------------------------|--|--|--|
| End point values | Active treatment with Rituximab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 59 | | | |
| Units: Numbers | 59 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: • The proportion of patients undergoing the predefined study protocol that because of disease activity will either change therapy or obtain additional Rituximab infu-sions.

| | |
|---|--|
| End point title | • The proportion of patients undergoing the predefined study protocol that because of disease activity will either change therapy or obtain additional Rituximab infu-sions. |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| The patients were followed for 3 years. | |

| | | | | |
|-----------------------------|---------------------------------|--|--|--|
| End point values | Active treatment with Rituximab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 59 | | | |
| Units: Numbers | 59 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: • To document the safety of Rituximab treatment during long-term

treatment of RRMS patients with Rituximab using a target based treatment protocol.

| | |
|-----------------|---|
| End point title | • To document the safety of Rituximab treatment during long-term treatment of RRMS patients with Rituximab using a target based treatment protocol. |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

The patients were followed for 3 years.

| | | | | |
|-----------------------------|---------------------------------|--|--|--|
| End point values | Active treatment with Rituximab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 59 | | | |
| Units: Numbers | 59 | | | |

Statistical analyses

No statistical analyses for this end point

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 | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Active treatment period |
|-----------------------|-------------------------|

Reporting group description:

Patients receiving Rituximab according to either protocol no 1 or protocol no 2 :

Protocol no 1, assumed low inflammatory disease: Rituximab 500 mg at time 0, 6 and 12 months, thereafter only if indicated from the definition of treatment failure.

Protocol no 2, assumed more active inflammatory disease: Rituximab 1000 mg at time 0, 6 and 12 months, thereafter yearly (time 24 and 36 months).

| Serious adverse events | Active treatment period | | |
|---|-------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 66 (7.58%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Nervous system disorders | | | |
| Migraine with aura | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Parkinson's disease | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulitis | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Active treatment period | | |
|---|--------------------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 50 / 66 (75.76%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | | |
| occurrences (all) | 2 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Pregnancy | Additional description: Healthy baby | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Swelling NOS | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 1 | | |
| Reproductive system and breast disorders | | | |
| Erectile dysfunction | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 1 | | |
| Ovarian function insufficiency | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |

| | | | |
|--|---------------------|--|--|
| Anxiety attack subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Insomnia subjects affected / exposed occurrences (all) | 2 / 66 (3.03%) 3 | | |
| Low mood subjects affected / exposed occurrences (all) | 2 / 66 (3.03%) 2 | | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Ferritin increased subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 2 / 66 (3.03%) 2 | | |
| Iron deficiency subjects affected / exposed occurrences (all) | 2 / 66 (3.03%) 2 | | |
| Lipids increased subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Injury, poisoning and procedural complications Fracture subjects affected / exposed occurrences (all) | 3 / 66 (4.55%) 4 | | |
| Headache post lumbar punction subjects affected / exposed occurrences (all) | 2 / 66 (3.03%) 2 | | |
| Itching subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Olekranon bursitis | | | |

| | | | |
|--------------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 1 | | |
| Pain due to intra-uterine coil | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 1 | | |
| Pain shoulder | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | | |
| occurrences (all) | 2 | | |
| Headache | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 1 | | |
| Parkinson's disease | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 1 | | |
| Speech impairment | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 1 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 1 | | |
| Visual phenomena | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 1 | | |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Dry eyes | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |

| | | | |
|--|--|--|--|
| Constipation subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Acid reflux subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Dry mouth subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Lymphocytic colitis subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 2 / 66 (3.03%) 2 | | |
| Skin sores subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Musculoskeletal and connective tissue disorders Arthritis subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Pain | Additional description: Pain preferred term for all AEs but lower level term: Pain, Pain hand/fingers, Pain joints, extremity, Pain joints/fingers/ankles, Pain knee, Pain leg, Pain neck/shoulder | | |
| subjects affected / exposed occurrences (all) | 5 / 66 (7.58%) 7 | | |
| Joint swelling subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Infections and infestations | | | |

| | | | |
|--|------------------------|--|--|
| Pharynx itching sensation of subjects affected / exposed occurrences (all) | 3 / 66 (4.55%) 3 | | |
| Borrelia infection subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Bronchial infection subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Cold subjects affected / exposed occurrences (all) | 10 / 66 (15.15%) 15 | | |
| Cough subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Eye infection subjects affected / exposed occurrences (all) | 2 / 66 (3.03%) 3 | | |
| Fever subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Herpes zoster ophthalmicus subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Influenza subjects affected / exposed occurrences (all) | 3 / 66 (4.55%) 3 | | |
| Otitis subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Otosalpingitis subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |
| Ringworm subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | | |

| | | | |
|------------------------------------|----------------|--|--|
| Sinusitis | | | |
| subjects affected / exposed | 5 / 66 (7.58%) | | |
| occurrences (all) | 5 | | |
| Sore throat | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | | |
| occurrences (all) | 2 | | |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 1 | | |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 2 | | |
| Upper respiratory infection | | | |
| subjects affected / exposed | 3 / 66 (4.55%) | | |
| occurrences (all) | 3 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 66 (6.06%) | | |
| occurrences (all) | 6 | | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 1 | | |
| Gout | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 1 | | |
| Vitamin B deficiency | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | | |
| occurrences (all) | 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