Clinical trial results:
Switch To RItuXimab 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
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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 be-fore 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 procotol.
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 addi-tion 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 addi-tion 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 follwoed 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	1 / 66 (1.52%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	3		
Low mood			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Ferritin increased			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	2		
Iron deficiency			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	2		
Lipids increased			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	3 / 66 (4.55%)		
occurrences (all)	4		
Headache post lumbar punction			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	2		
Itching			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Olekranon bursitis			

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

Constipation			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Acid reflux			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Lymphocytic colitis			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 66 (3.03%)		
occurrences (all)	2		
Skin sores			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	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	5 / 66 (7.58%)		
occurrences (all)	7		
Joint swelling			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences (all)	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 occurrences (all)	5 / 66 (7.58%) 5		
Sore throat subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2		
Tonsillitis subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1		
Tooth infection subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 2		
Upper respiratory infection subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 3		
Urinary tract infection subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 6		
Metabolism and nutrition disorders Diabetes mellitus subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1		
Gout subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1		
Vitamin B deficiency subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 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