Clinical trial results:
Switch To RItuXimab 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	v2 (current)
This version publication date	07 March 2019
First version publication date	31 December 2017
Version creation reason	• Changes to summary attachments Full data set contains all information, there is no need for a summary attachment.

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:

Results analysis stage

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:

General information about the trial

Main objective of the trial:

To evaluate the feasability 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)

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 inflammato-ry parameters between first line DMD:s and Rituximab. Lumbar puncture will be per-formed once during this period in close connection with the second MRI, immediately be-fore 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 examina-tions 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, neurodegenereation
EDSS Disease progression
MSIS29 Social activity measure, QoL
SDMT Cognitive function
FSMC Fatigue

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:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 77

Worldwide total number of subjects	77
EEA total number of subjects	77

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)	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 injectible DMD:s, In fertile females, willing to comply with effective contraceptive methods. Clinically stable on first line injectible 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.

Number of subjects in period 1	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

Arm title	Treament 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.

Number of subjects in period 2	Treament 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 (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)	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	Treament 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
•To document the safety of Rituximab treatment in a non-selected population of RRMS patients using a new target based treatment protocol.
•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 thera-py switch. The MRI scans will be performed with double dose contrast and 15 minutes delay to maximize the sensitivity.
•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.

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	Treament period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75[1]	72[2]		
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.

Attachments (see zip file)	Published article/Improved treatment satisfaction after Published article/Reduced inflammation in relapsing-remitting

Statistical analyses

Statistical analysis title	Comparative statistics

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 Treament period
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority[3]
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	1 / 75 (1.33%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Eye disorders			
Eye disorder - others, iritis, silent			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Eye disorders - other, macula hypertension with pigment dispersion syndrome (PDS)			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Rectal hemorrhage			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Skin and sucutanous tissue disorders - other, hidradenitis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Skin and sucutanous tissue disorders - other Rosacea			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences (all)	1		
Endocrine disorders			

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

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, 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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

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

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