Clinical Study Report – Assessment of Safety

Study title:

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

EudraCT number:
2010-023021-38

Study drug:
Rituximab

Report period:
2011 08 08 – 2015 04 30

Report date:
2015 10 15

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Summary and comments

The main purpose of the study was to compare the treatment of Rituximab with the present first line Disease-modifying drugs (DMD:s) regarding inflammatory activity and parameters reflecting neurodegeneration as measured via Magnetic resonance imaging (MRI), Cerebrospinal fluid (CSF) analysis and clinical investigation in patients with Relapsing-Remitting Multiple Sclerosis (RRMS). The study also analysed health economic, Quality of Life (QoL) and treatment satisfaction measures before and after therapy switch.

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 therapy switch. The MRI scans will be performed with double dose contrast and 15 minutes delay to maximize the sensitivity (18).
- 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 (19)

Secondary end points are:

- Estimation of societal costs per year to supply the different treatment regimens used before and after therapy switch
- Comparison of health related QoL and patient satisfaction before and after therapy switch, respectively

Tertiary endpoints are purely descriptive since there is no comparable period before therapy change to make comparative statistics with:

- The amount of retreatment needed within a two year period after one treatment cycle of Rituximab based on our treatment protocol
- The amount of patients that change to another therapy because of treatment failure within a two year period based on our treatment protocol
- The change in brain parenchymal fraction (BPF), total brain volume, total volume grey matter, total lesion volume and total myelin content between investigations before therapy switch and one and two years after therapy switch.

1. Introduction

The study population consists of subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) recruited from the standard Multiple sclerosis (MS) populations at the departments of Neurology at Norrlands University Hospital in Umeå, the University Hospital in Örebro and at the County Hospital in Östersund.

A total of 77 patients were enrolled in the study. Five patients did not complete the study. Two of the patients became pregnant during the study and were withdrawn from the study procedures but followed for the safety. Two patients took back their informed consent before the study treatment was started. One patient was discontinued with study medication due to lack of efficacy.

The study started to include patients 2011 08 08 (first subject first visit) and ended 2015 03 12 (last subject last visit).

2. Worldwide Marketing Approval Status

Not applicable in this investigator initiated clinical trial.

3. Actions Taken in the Reporting Period for Safety Reasons

Adverse Events have been followed for all patients enrolled in the study and reported in accordance with current regulations and approved protocol.

3.1 Study drug discontinued

The study medication was administered intravenously twice with 14 days apart. All the patients received two infusions. In some cases the patients experienced adverse events (non serious) which resulted in a temporarily stop of infusion of study medication, but as the event resolved, infusion continued after 15-30 minutes. The causality was assessed as related in those events.

4. Changes to Reference Safety Information

Not applicable when it is an investigator initiated clinical trial.

5. Inventory of Clinical Trials Ongoing and Completed during the Reporting Period

Not applicable.

6. Estimated Cumulative Exposure

6.1 Cumulative Subject Exposure in the Development Programme

Not applicable.

6.2 Patient Exposure from Marketing Experience

Not applicable.

7. Cumulative Summary Tabulations

7.1 Reference Information

Latest in Sweden approved summary of product characteristics for Mabthera (Rituximab) (FASS text).

7.2 Cumulative Listings of Serious Adverse Reactions during the Reporting Period

Reporting period: 2011 08 08 until 2015 04 30.
Six SAE reports (no SUSAR) have occurred in this study during the reporting period and none of them resulted in any change in study medication.

Patient number	**Study drug**	**Adverse Event**	**SAE**	**Causality assessment**
6264	Rituximab	Influensa	Yes	Possible
8499	Rituximab	Cholangitis	Yes	Not related
10727	Rituximab	Pyelonephritis	Yes	Not related
12750	Rituximab	Stroke	Yes	Not related
30-6486	Rituximab	Suicidal attempt with intoxication	Yes	Unlikely
30-9912	Rituximab	Pyelonephritis	Yes	Possible

1. SAE Influensa. The patient experienced severe headache, was hospitalised, and received intravenous hydration and injections with morphine. The patient recovered and causality was assessed as possible related to the study medication.
2. SAE Cholangitis. The patient was admitted to hospital for investigation, and if necessary, operation. The patient recovered from the SAE and the causality was assessed as not related to the study medication.
3. SAE Pyelonephritis. The patient was hospitalised and received intravenous antibiotics, followed by per oral antibiotics for 10 days. The patient recovered and the causality was assessed as not related to the study medication.
4. SAE Stroke. The patient had a stroke and was investigated at a stroke center. Ten days later the patient was discharged and was still recovering, now recovered. The causality was assessed as not related to the study medication.
5. SAE Suicidal attempt with intoxication. The patient felt low for a few days and took an overdose of antidepressants and sleeping pills. The event was assessed as an SAE and resulted in a short termed observation in the emergency room and later referral to a psychiatric consultant with subsequent follow-up. The patient recovered completely, and the contact with the psychiatric clinic was ended. The causality was assessed as unlikely related to the study medication.
6. SAE Pyelonephritis. The patient became ill with dysuria, fever and tenderness of the renal lobes and was hospitalised for one day. Diagnosis was pyelonephritis and treatment was initially i.v. and later p.o. antibiotics. The patient recovered completely and causality was assessed as possibly related to the study medication.

7.3 Cumulative AE (non serious) with causality related

Non-serious AE evaluated to be related to study drug were primarily of infectious type or infusion reactions. Although no control group was included in the study, the number of infections did not stand out as unusually high.
See appendix 1.

7.4 Cumulative AE (non serious) with causality not related

Non-serious AE evaluated not to be related to study drug appeared to conform well to the general population
See appendix 2.

7.5 Cumulative AE Number Observed and Rate with patient identifications

As expected, infections and infestations constituted the largest number of AE followed by general conditions and study-related procedures such as LP. It appears not deviating from what is expected that approximately 40% of individuals contracts at least one infection during a two-year period.
See appendix 3.

8. Significant Findings from Clinical Trials during the Reporting Period

Not applicable in a investigator initiated study

8.1 Completed Clinical Trials

Not applicable.

8.2 Ongoing Clinical Trials

Strix extension Eudra-CT: 2013-002378-26 is currently ongoing in the same sites as the initial study i.e Umeå, Örebro and Östersund neurologic clinics.
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

ITT-PMS Eudra CT: 2008-002626-11 is currently ongoing in Umeå and Uppsala neurologic clinics.
ITT-PMS is evaluating intrathecal therapy with monoclonal antibodies (Mabthera) in progressive multiple sclerosis.

8.3 Long-term Follow-up

Strix extension Eudra-CT: 2013-002378-26 (see 8.2)

8.4 Other Therapeutic Use of Investigational Drug

Not applicable.

8.5 New Safety Data Related to Combination Therapies

Not applicable.

9. Safety Findings from Non-interventional Studies

Not applicable.

10. Other Clinical Trial/Study Safety Information

Not applicable.

11. Safety Findings from Marketing Experience

Not applicable.

12. Non-clinical Data

Not applicable.

13. Literature

Not applicable.

14. Other DSURs

No previous DSUR but an annual report was sent to MPA in January 2013.

15. Lack of Efficacy

One patient was discontinued with study medication due to lack of efficacy (Patient 30-9927).

16. Region-Specific Information

Not applicable.

17. Late-Breaking Information

Not applicable.

18. Overall Safety Assessment

The Rituximab treatment given during the STRIX trial was associated with in total six serious adverse events out of which three were considered possibly related to the study drug. None of the serious side effects resulted in permanent harm. The remaining registered side effects that were judged possibly related were all known possible side-effects in conjunction with rituximab treatment. The overall safety of the investigated drug within the trial is therefore determined to be good.

18.1 Evaluation of the Risks

The rituximab treatment used within the trial is judged to have been of low risk for serious harm. There was an expected risk of known infusion-related reactions of mostly mild severity.

18.2 Benefit-risk Consideration

The benefit-risk from using rituximab as in the present study is evaluated to be favourable.

19. Summary of Important Risks

No important risks from using rituximab as in the present study were identified.

20. Conclusions

From the results of the present study, Rituximab appear to be safe and involving low risks as treatment for multiple sclerosis.

Appendix I

Cumulative AE (non serious) with causality related

Patient number	Study drug	Adverse Event	SAE	Causality assessment
5467	Rituximab	Menstrual bleeding, increased	No	Related
5538	Rituximab	Upper respiratory tract infection with fever	No	Possible
5538	Rituximab	Post lumbar headache	No	Possible
5754	Rituximab	Respiratory dyscomfort	No	Related
7604	Rituximab	Upper respiratory tract infection	No	Possible
7956	Rituximab	Shingles	No	Related
8803	Rituximab	Erythema infectiosum	No	Possible
10188	Rituximab	Cold	No	Possible
10188	Rituximab	Flushing, Dyspnea	No	Related
10188	Rituximab	Tachycardia	No	Related
10372	Rituximab	Edema face, Flushing	No	Related
10727	Rituximab	Urinary infection	No	Related
13481	Rituximab	Cold	No	Possible
13632	Rituximab	Cold	No	Possible
13632	Rituximab	Cough, Fever	No	Possible
13632	Rituximab	Cold with cough and sore throat	No	Related
13632	Rituximab	Swollen throat	No	Related
20-5376	Rituximab	Itching	No	Related
20-14169	Rituximab	Herpes zoster ophtalmicus	No	Related
30-5373	Rituximab	Urinary tract infection	No	Possible
30-5433	Rituximab	Tooth infection	No	Possible
30-5433	Rituximab	Perfusion related headache	No	Related
30-6486	Rituximab	Mycoplasmapneumonia	No	Possible
30-9663	Rituximab	Tooth infection	No	Possible
30-9663	Rituximab	Urinary tract infection	No	Possible
30-9663	Rituximab	Iritis, silent	No	Possible
30-9927	Rituximab	Nausea, vomiting	No	Possible
30-10364	Rituximab	Headache	No	Possible
30-10364	Rituximab	Elevated liver enzyme	No	Possible
30-10502	Rituximab	Urinary tract infection	No	Possible
30-10735	Rituximab	Elevated liver enzyme	No	Possible

Appendix II

Cumulative AE (non serious) with causality not related

Patient number	Study drug	Adverse Event	SAE	Causality assessment
5323	Rituximab	Pain and tenderness right shoulder, fever	No	Not related
5418	Rituximab	Joint pain MCP II bilaterally	No	No
6823	Rituximab	Post lumbar headache	No	Not related
6823	Rituximab	Disc Herniation	No	No
7604	Rituximab	Calf muscle rupture	No	Not related
7604	Rituximab	Joint range of motion decreased, Fatigue	No	No
7956	Rituximab	Post lumbar headache	No	Not related
7956	Rituximab	Cold prolonged	No	Not related
8499	Rituximab	Infection in finger	No	No
8789	Rituximab	Lumbago	No	Not related
10188	Rituximab	Dyspepsia	No	Not related
10240	Rituximab	Cough	No	No
12750	Rituximab	Positional vertigo benign	No	No
13474	Rituximab	Edema foot/ankle right foot	No	No
13632	Rituximab	Cruciate ligament injury	No	No
13632	Rituximab	Edema hands and feet	No	Not related
13806	Rituximab	Cold	No	Not related
20-5376	Rituximab	Trigeminal neuralgia?	No	Unlikely
20-5376	Rituximab	Upper respiratory infection with persisting cough	No	Unlikely
20-6034	Rituximab	Upper respiratory tract infection, fever, cough	No	Unlikely
20-7324	Rituximab	Upper respiratory tract infection	No	Unlikely
20-7324	Rituximab	Vulvovaginitis	No	Unlikely
20-7791	Rituximab	Upper respiratory infection	No	Unlikely
20-7791	Rituximab	Post LP headache	No	Unlikely
20-9169	Rituximab	Urinary tract infection	No	Unlikely
20-9169	Rituximab	Depression, fatigue	No	Unlikely
20-10323	Rituximab	Rosacea	No	Unlikely
20-10323	Rituximab	Upper respiratory infection with fever	No	Unlikely
20-10462	Rituximab	Post LP headache	No	Unlikely
20-10462	Rituximab	Cold symptoms with muscle aches	No	Unlikely
20-10538	Rituximab	Swollen foot/ leg	No	Unlikely
20-10538	Rituximab	Weight gain	No	Unlikely
20-11629	Rituximab	Pain left forefinger	No	Unlikely
20-11629	Rituximab	PostLP pains or due to hyperglycemia	No	Unlikely
20-12019	Rituximab	Hidradenitis	No	Unlikely
20-13847	Rituximab	Upper respiratory infection	No	Unlikely
20-13847	Rituximab	Depression? Fatigue? Shiftless?	No	Unlikely
20-14169	Rituximab	Pain left arm/shoulder	No	Unlikely
30-5306	Rituximab	Post LP headache	No	Not related
30-5306	Rituximab	Cold with cough and fever	No	Unlikely
30-5306	Rituximab	Dizziness	No	Unlikely

Patient number	Study drug	Adverse Event	SAE	Causality assessment
30-5373	Rituximab	Post traumatic knee pain	No	Not related
30-5373	Rituximab	Gastroenteritis	No	Unlikely
30-5433	Rituximab	Hip pain	No	Not related
30-5433	Rituximab	Maculahypertension	No	Unlikely
30-5433	Rituximab	Gastroenteritis	No	Unlikely
30-6874	Rituximab	Lumbago	No	Not related
30-6874	Rituximab	Rectal bleeding, mild	No	Not related
30-6874	Rituximab	Lumbago	No	Not related
30-6874	Rituximab	PostLP headache	No	Not related
30-8460	Rituximab	Lumbago	No	Not related
30-8460	Rituximab	Cold, mild	No	Unlikely
30-8460	Rituximab	Cold, mild	No	Unlikely
30-9486	Rituximab	Post LP headache	No	Not related
30-9663	Rituximab	Intervertebral disc displacement	No	Not related
30-9927	Rituximab	Post LP headache	No	Not related
30-9927	Rituximab	Respiratory tract infection	No	Unlikely
30-10364	Rituximab	Gastroenteritis	No	Unlikely
30-10502	Rituximab	Epigastralgia	No	Not related
30-10554	Rituximab	B12 deficiency	No	Not related
30-10554	Rituximab	Cold with fever and cough	No	Unlikely
30-10554	Rituximab	Cold without fever	No	Unlikely
30-10735	Rituximab	Post LP headache	No	Not related
30-10735	Rituximab	Cold with cough and fever	No	Unlikely
30-10817	Rituximab	Pituitary adenoma	No	Not related
30-10817	Rituximab	Trauma shoulder due to fall	No	Not related
30-10849	Rituximab	Post LP headache	No	Not related
30-10849	Rituximab	Cold mild, sore throat	No	Unlikely

Appendix III

Cumulative AE Number Observed and Rate with patient identifications

SOC	CTC AE	Related**	Not related***	Total cases
Cardiac disorder				
	Cardiac disorders - other, tachycardia	10188*		
	Total # (%)	**1 (0.9%)**		**1 (0.9%)**
Ear and labyrith disorders				
	Vertigo		12750*	
	Total # (%)		**1 (0.9%)**	**1 (0.9%)**
Endocrine disorders				
	Endocrine disorders, other: B12-deficiency		30-10554*	
	Total # (%)		**1 (0.9%)**	**1 (0.9%)**
Eye disorders				
	Eyes disorders, other: Iritis, silent	30-9663*		
	Eyes disorders, other: Maculahypertension with pigment dispersion syndrome (PDS)		30-5433*	
	Total # (%)	**1 (0.9%)**	**1 (0.9%)**	**2 (1.8%)**
Gastrointestinal disorders				
	Abdominal pain		30-10502*	
	Dyspepsia		10188*	
	Nausea	30-9927*		
	Rectal hemorrhage		30-6874*	
	Total # (%)	**1 (0.9%)**	**3 (2.7%)**	**4 (3.6%)**
General disorders and administration site conditions				
	Edema face	10372*		
	Edema limbs		20-10538*	
			13474*	
			13632*	
	Fatigue		7604*	
			20-9169*	
			20-13847*	

SOC	CTC AE		Related**	Not related***	Total cases
	Fever		13632*		
	Infusion related reaction		13632*		
	Pain			20-11629*	
				20-14169*	
		Total # (%)	**3 (2.7%)**	**8 (7.1%)**	**11 (9.8%)**
Immune system disorders					
	Immune system disorders - other, Itching		20-5376*		
		Total # (%)	**1 (0.9%)**		**1 (0.9%)**
Infections and infestations					
	Biliary tract infection			8499*	
	Cold			20-10462*	
				30-8460*	
				30-8460*	
				30-10735*	
				30-10849*	
				30-10554*	
				30-10554*	
				30-5306*	
	Infections and infestations - other, Herpes Zoster Ophtalmicus		20-14169*		
	Infections and infestations, other: gastroenteritis			30-10364*	
				30-5373*	
				30-5433*	
	Infections and infestations; other: Erythema infectiosum		8803*		
	Infections and infestations; other: Herpes Zoster		7956*		
	Kidney infection			10727*	
			30-9912*		
	Tooth infection		30-9663*		
			30-5433*		
	Upper respiratory infection			20-7324*	
				20-6034*	
				20-7791*	
				20-5376*	
				20-10323*	
				20-13847*	

SOC	CTC AE	Related**	Not related***	Total cases
	Upper respiratory infection	6264*		
		7604*		
			7956*	
		10188*		
		13481*		
		13632*		
			13806*	
	Upper respiratory infection, Cough, Sore throat	13632*		
	Upper respiratory infection, Fever	5538*		
	Upper respiratory tract infection		30-9927*	
	Urinary tract infection		20-9169*	
		10727*		
		30-9663*		
		30-5373*		
		30-10502*		
	Wound infection		8499*	
	Vulval infection		20-7324*	
	Total # (%)	**17 (15.2%)**	**25 (22.3%)**	**42 (37.5%)**
Injury, poisoning and procedural complications				
	Injury, poisoning and procedural complications, other: trauma shoulder due to fall		30-10817*	
	Injury, poisoning and procedural complications, other: post traumatic knee pain		30-5373*	
	Injury, poisoning and procedural complications; other: Cruciate ligament injury		13632*	
	Injury, poisoning and procedural complications - other, specify: calf muscle rupture		7604*	
	Total # (%)		**4 (3.6%)**	**4 (3.6%)**
Investigations				
	Alanine aminotransferase increased	30-10364*		
	Alanine aminotransferase increased, Aspartate aminotransferase increased	30-10735*		
	Weight gain		20-10538*	
	Total # (%)	**2 (1.8%)**	**1 (0.9%)**	**3 (2.7 %)**

SOC	CTC AE		Related**	Not related***	Total cases
Metabolism and nutrition disorders					
	Hyperglycemia			20-11629*	
		Total # (%)		**1 (0.9%)**	**1 (0.9%)**
Musculoskeletal and connective tissue disorders					
	Arthralgia			5418*	
	Back pain			6823*	
				8789*	
				30-6874*	
				30-9663*	
				30-8460*	
				30-6874*	
	Joint range of motion decreased			7604*	
	Myalgia, Fever			5323*	
	Muscoskeletal and connective tissue disorders, other: hip pain			30-5433*	
		Total # (%)		**10 (8.9%)**	**10 (8.9%)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
	Neoplasms benign, malignant and unspecified (incl cysts and polyps), other: Pituitary adenoma benign			30-10817*	
		Total # (%)		**1 (0.9%)**	**1 (0.9%)**
Nervous system disorders					
	Dizziness			30-5306*	
	Headache		30-10364*		
	Neuralgia			20-5376*	
	Stroke			12750*	
		Total # (%)	**1 (0.9%)**	**3 (2.7%)**	**4 (3.6%)**
Psychiatric disorders					
	Depression			20-9169*	
				20-13847*	
	Suicide attempt			30-6486*	
		Total # (%)		**3 (2.7%)**	**3 (2.7%)**

SOC	CTC AE	Related**	Not related***	Total cases
Reproductive system and breast disorders				
	Menorrhagia	5467*		
	Total # (%)	**1 (0.9%)**		**1 (0.9%)**
Respiratory, thoracic and mediastinal disorders				
	Cough		10240*	
	Cough	13632*		
	Dyspnea	5754*		
	Dyspnea	10188*		
	Respiratory, thoracic and mediastinal disorders; other: mycoplasma pneumoniae	30-6486*		
	Total # (%)	**4 (3.6%)**	**1 (0.9%)**	**5 (4.5%)**
Skin and subcutaneous tissue disorders				
	Skin and subcutaneous tissue disorders - other, Hidradenitis		20-12019*	
	Skin and subcutaneous tissue disorders - other, Rosacea		20-10323*	
	Total # (%)		**2 (1.8%)**	**2 (1.8%)**
Surgical and medical procedures				
	Surgical and medical procedures - other: Post LP headache / pains		20-10462*	
			20-11629*	
			20-7791*	
		5538*		
			6823*	
			7956*	
		30-5433*		
			30-9927*	
			30-9486*	
			30-10735*	
			30-5306*	
			30-10849*	
			30-6874*	
	Total # (%)	**2 (1.8%)**	**11 (9.8%)**	**13 (11.6%)**
Vascular disorders				
	Flushing	10372*		
		10188*		
	Total # (%)	**2 (1.8%)**		**2 (1.8%)**
	Total Events # (%)	**36 (32.1%)**	**76 (67.9%)**	**112 (100%)**

* Patient identification number
** Causal relationship to study medication Related = Assessment is Related or Possible
*** Causal relationship to study medication Not related = Assessment is Not related, No or Unlikely