



## Clinical trial results:

### ITT-PMS Extension

## An extension study of intrathecal therapy with monoclonal antibodies in progressive multiple sclerosis

### Summary

EudraCT number	2012-000721-53
Trial protocol	SE
Global end of trial date	07 June 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	ITT-PMSExt
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#### 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, 46 702415852, 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	15 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 June 2018
Global end of trial reached?	Yes
Global end of trial date	07 June 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To assess long-term stabilising effects of on neurological symptoms by regular IT administered monoclonal antibodies in MS.

Protection of trial subjects:

1. Development of allergic and anaphylactic reactions.

Before each injection antihistamine and corticosteroids were administered to prevent any allergic reaction precipitated by the study drug. Continuous observations was done of the patient during the first hour after each injection of study drug and emergency equipment was available for immediate use in case of signs of allergic reactions. Standard treatm. with epinephrine, fluids, antihistamine and steroids were used; intensive care specialist was consulted when necessary.

2. Symptoms related to cytokine release from the lysis of B lymphocytes.

This was anticipated to demonstrate as increase in neurological symptoms and possibly also as diffuse cerebral symptoms. Our experience from the first study, this does not to appear as a problem in this population but rather belonged to treatment with Rituximab in CNS lymphoma patients.

3. Development of opportunistic CNS infections.

In the period immediately in relation with the intrahtecal injections, the major risk is contaminating bacterial infections. Precautions were taken to make the injections sterile. CSF samples were drawn for bacterial cultures at each Rituximab injection in the Rickham reservoir. If any sign of infection occurred, infectious disease specialist was consulted. In our first study (EudraCT number 2008-002626-11), one case of low virulent meningitis with propionebacteriae occurred which was treated successfully with standard antibiotics and removal of the Rickham reservoir. The patient recovered fully from the infection. In the longer perspective, special attention will be paid regarding PML. Any type of neurological deterioration that may raise the suspicion of PML will lead to emergent MRI and CSF examination regarding signs of PML/JC virus infectin. Further potential dosing of Retuximab will be halted until PML is ruled out

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 January 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: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

Notes:

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**Subjects enrolled per age group**

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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)	17
From 65 to 84 years	2
85 years and over	0

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## Subject disposition

### Recruitment

Recruitment details:

A total of 19 subjects were recruited for this study from two centres in Umeå and in Uppsala. The study population were subjects with secondary or primary progressive MS that had completed the first trial of intrathecal Rituximab with one year of follow-up (ITT-MS; EudraCT number 2008-002626-11) and signed consent to enrol in the extension study.

### Pre-assignment

Screening details:

Subject were eligible for inclusion in this study if all of the following criteria applied:

- Completed the ITT-MS trial (EudraCT number 2008-002626-11)
- Other therapy not indicated, contraindicated or failed
- Judged as compliant with the protocol
- In fertile females, willing to comply with effective contraceptive methods.

### Period 1

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

### Arms

<b>Arm title</b>	Active treatment with Rituximab
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Arm description:

After signing the informed consent for the extension study patients were treated with Rituximab (Mabthera®) as an intrathecal injection in a Rickham reservoir. A dose of 25 mg were given every 6 month for 2 years with a total of 5 doses.

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intrathecal use

Dosage and administration details:

Rituximab (Mabthera®) was given as an intrathecal injection in a Rickham reservoir. A dose of 25 mg were given every 6 month for 2 years with a total of 5 doses.

<b>Number of subjects in period 1</b>	Active treatment with Rituximab
Started	19
Completed	16
Not completed	3
Consent withdrawn by subject	1
Adverse event, non-fatal	1
Lack of efficacy	1



## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
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Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	19	19	
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)	17	17	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous			
Units: years			
median	47		
full range (min-max)	31 to 70	-	
Gender categorical			
Units: Subjects			
Female	13	13	
Male	6	6	

## End points

### End points reporting groups

Reporting group title	Active treatment with Rituximab
Reporting group description: After signing the informed consent for the extension study patients were treated with Rituximab (Mabthera®) as an intrathecal injection in a Rickham reservoir. A dose of 25 mg were given every 6 month for 2 years with a total of 5 doses.	

### Primary: The time to progression $\geq 1,0$ step on the EDSS scale (Expanded Disability Status Scale)

End point title	The time to progression $\geq 1,0$ step on the EDSS scale (Expanded Disability Status Scale) <sup>[1]</sup>
End point description: Assessments were done every 6 months during the study in conjunction with administration of study drug.	
End point type	Primary
End point timeframe: During the Active treatment	

#### 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: Statistical testing will be done as 2-sided on a 5 % level of significance, all confidence intervals (CI) will be 95 % intervals.

No specific procedure will be done for treating missing data and testing for multiplicity will not be considered.

Data analysis and presentation will be on a descriptive level

Each patient is it's own control. There is no comparison between groups.

Test of normality will be performed which will decide as to use parametric or non parametric statistics.

<b>End point values</b>	Active treatment with Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Number	16			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Tests of walking ability and hand function (6MWAT or 25 FWT)

End point title	Tests of walking ability and hand function (6MWAT or 25 FWT)
End point description: Assessments were done every 6 months during the study in conjunction with administration of study drug. 6 min walk test or 25 FWT and 9HPT (Ambulation, Arm function) were done at visit 0,6,12,18,24 month	
End point type	Secondary
End point timeframe: During active treatment	

## Statistical analyses

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No statistical analyses for this end point

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### **Secondary: Questionnaires regarding MS quality of life, symptom inventory and fatigue (SF12, FSMC)**

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End point title	Questionnaires regarding MS quality of life, symptom inventory and fatigue (SF12, FSMC)
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End point description:

Assessments were done every 6 months during the study in conjunction with administration of study drug.

SF12, SDMT and FSMC (Quality of Life, Cogn function andv Fatigue) were done at visit 0,6,12,18,24 month.

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End point type	Secondary
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End point timeframe:

During Active treatment

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## Statistical analyses

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No statistical analyses for this end point

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### **Secondary: Neurofilament levels in the CSF**

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End point title	Neurofilament levels in the CSF
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End point description:

Assessments were done every 6 months during the study in conjunction with administration of study drug.

LP (Biomarkers) were done at visit 0,12,24 month.

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End point type	Secondary
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End point timeframe:

During Active treatment

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## Statistical analyses

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No statistical analyses for this end point

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### **Secondary: Immunological markers in blood and CSF such as absolute numbers of major lym-phocyte subset as well as regulatory cell subset**

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End point title	Immunological markers in blood and CSF such as absolute numbers of major lym-phocyte subset as well as regulatory cell subset
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End point description:

Assessments were done every 6 months during the study in conjunction with administration of study drug.

LP and Immunology (Biomarkers and Lymphocyte subsets) were done at visit 0,12,24 month.

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End point type	Secondary
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End point timeframe:

During active treatment

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## Statistical analyses

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No statistical analyses for this end point

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### **Secondary: Safety assessment**

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End point title	Safety assessment
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End point description:

Assessments were done every 6 months during the study in conjunction with administration of study drug.

Blood chemistry, blood pressure and pulse were done at visit 0,6,12,18,24 month.

MRI was done at visit 0,12,24 month

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End point type	Secondary
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End point timeframe:

During Active treatment

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## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the time a patient consented to participate in the study until he/she completed the study all adverse events (AEs) and serious adverse events (SAEs) were collected, recorded and reported separately.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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### Reporting groups

Reporting group title	All patients
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Reporting group description:

All patients who consented to participate in the study.

<b>Serious adverse events</b>	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Meningitis bacterial	Additional description: Propionibacterium acne infection by the Rickham reservoir. Admitted to the hospital for an operation to take out the Rickham Reservoir. Treated with antibiotics intravenously for 10 days and additional 3-5 weeks with tablets. Fully recovered.		
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 19 (78.95%)		
Vascular disorders			
Deep venous thrombosis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nervous system disorders			

Double vision subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 3		
Tremor subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Dizziness subjects affected / exposed occurrences (all)	3 / 19 (15.79%) 4		
Vertigo subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Paresthesia subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 3		
Headache subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2		
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	3 / 19 (15.79%) 5		
Vomiting subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 3		
Constipation subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Skin and subcutaneous tissue disorders			
Basalioma subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Rash maculo-papular subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Rash			

subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2		
Pruritus subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2		
Renal and urinary disorders Calculus bladder subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Infections and infestations Small intestine infection subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	5 / 19 (26.32%) 13		
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Fever subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Sore throat subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Upper respiratory infection subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		

Vaginal fungal infection subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Pharyngitis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	Additional description: viral throat infection	
Metabolism and nutrition disorders Diabetes mellitus type 2 subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 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