Clinical trial results:
Intrathecal therapy with monoclonal antibodies in severe progressive multiple sclerosis

Summary

EudraCT number	2008-002626-11
Trial protocol	SE
Global end of trial date	01 June 2016

Results information

Result version number	v1
This version publication date	12 July 2017
First version publication date	12 July 2017
Summary attachment (see zip file)	Clinical Study Report_Assessment of Safety_ITT-PMS (Clinical Study Report_Assessment of safety_ITT-PMS.pdf)

Trial information

Trial identification

Sponsor protocol code	ITT-PMS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01719159
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Umeå University
Sponsor organisation address	Dept of Neurology, Umeå, Sweden, 90185
Public contact	Anders Svenningsson, MD, PhD, Dept of Neurology, Umeå University , anders.svenningsson@umu.se
Scientific contact	Anders Svenningsson,MD, PhD, Dept of Neurology, Umeå University , anders.svenningsson@umu.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	22 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 June 2016
Global end of trial reached?	Yes
Global end of trial date	01 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Investigate tolerability and efficacy of intrathecally administered Mabthera in severe progressive MS where there is no available effective treatment

Protection of trial subjects:

1. Development of allergic and anaphylactic reactions
Before each injection, antihistamine and corticosteroids were administered in order to prevent any allergic reaction precipitated by the study drug. There was continuous observation of the patient during the first 4 hours after each injection of study drug and emergency equipment were available for immediate use in case of signs of allergic reactions. Standard treatment with epinephrine, fluids, antihistamine and steroids were available, intensive care specialist were available to be 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 diffuse cerebral symptoms. In case of signs of cytokine release symptom, further treatment with corticosteroids iv and/or was given as well as emergent MRI. Data from treatment of patients with CNS lymphoma indicate a relatively low risk of cytokine release syndrome since only one of the 24 studied cases de-veloped such symptoms which were rapidly reversible.
3. Development of opportunistic CNS infections.
In the period immediately in relation with the it injections, the major risk was contaminating bacterial infections. Precautions were done to make the injections sterile. CSF samples were drawn for bacterial cultures at each time Rituximab is given in the Rickham reservoir. If any sign of infection clinically, infectious disease specialist was consultated. In the longer perspective, special attention will be paid regarding PML. Any type of neurological deterioration that that may raise the suspicion of PML will lead to emergent MRI and CSF examination regarding signs of PML/JC virus infection. Further potential dosing of Rituximab will be halted until PML is safely ruled out.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 September 2009
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: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	22
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 23 subjects were recruited for the study from two centra in Umeå and Uppsala. Three patients (included in total 23) were initially treated and evaluated regarding side-effects and safety and reported to the Swedish Medical Products Agency as well as the local ethical committee before the remaining patients were recruited.

Pre-assignment

Screening details:

Screening details:
Subjects which fulfilled the inclusion criteria for the study.
Adults, males or non lactating females with progressive MS since at least three years, EDSS 4,0 - 7.0 and where conventional therapy not indicated, contraindicated or failed.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Baseline

Arm description:

The baseline values of the 23 patients fulfilling the inclusion criteria and enrolled in the study.

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

Dosage and administration details:

Rituximab (10 mg/mL; Roche AB, Stockholm, Sweden) was administered as 3 doses of 25 mg at weekly intervals. The first injection was performed approximately 3 weeks after implantation of the Ommaya reservoir in order to allow surgery-related subcutaneous swelling to subside. Patients were premedicated with 1 mg IV clemastine and 4 mg oral betamethasone 1 hour before the IT rituximab injection. In order to assess tolerance, the rituximab dose was titrated for the first 3 patients, with daily doses of 1 mg, 2.5 mg, 5 mg, 10 mg, and finally 25 mg. Daily monitoring of routine blood parameters and lymphocyte subpopulations by flow cytometry was performed to assess the safety and pharmacodynamic profile of IT treatment.

Number of subjects in period 1	Baseline
Started	23
Completed	23

Period 2

Period 2 title	Active treatment period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dose titration treatment with Rituximab

Arm description: -

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

Dosage and administration details:

In order to assess tolerance, the rituximab dose was titrated for the first 3 patients, with daily doses of 1 mg, 2.5 mg, 5 mg, 10 mg, and finally 25 mg. Repeated by 25 mg once weekly two times. Daily monitoring of routine blood parameters and lymphocyte subpopulations by flow cytometry was performed to assess the safety and pharmacodynamic profile of IT treatment.

Arm title	Active treatment with Rituximab

Arm description: -

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:

Before the dose was given 1 ml liquor was drawn and sent for routin culture analysis. Another 4 ml liquor was draw and saved. Rituximab (10 mg/mL; Roche AB, Stockholm, Sweden) was administered as 3 doses of 25 mg at weekly intervals. The first injection was performed approximately 3 weeks after implantation of the Ommaya reservoir in order to allow surgery-related subcutaneous swelling to subside. Patients were premedicated with 1 mg IV clemastine and 4 mg oral betamethasone 1 hour before the IT rituximab injection. 20 patients fulfilled this treatment period.

Number of subjects in period 2	Dose titration treatment with Rituximab	Active treatment with Rituximab
Started	3	20
Completed	3	20

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	23	23	
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)	22	22	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
median	45		
full range (min-max)	29 to 65	-	
Gender categorical Units: Subjects			
Female	16	16	
Male	7	7	

End points

End points reporting groups

Reporting group title	Baseline
Reporting group description:	
The baseline values of the 23 patients fulfilling the inclusion criteria and enrolled in the study.	
Reporting group title	Dose titration treatment with Rituximab
Reporting group description: -	
Reporting group title	Active treatment with Rituximab
Reporting group description: -	

Primary: Safety parameters during the study

End point title	Safety parameters during the study
End point description:	
Baseline assessments will be done twice with 2-4 weeks apart to have a baseline of criti-cal variables. LP and MRI will be performed once during this period. The therapy will be performed inpatient and require approximately 3 weeks hospital stay. Follow-up exami-nations will be performed at month 1, 3, 6, 9 an 12 after the last IT infusion.	
End point type	Primary
End point timeframe:	
During the active treatment.	

End point values	Baseline	Dose titration treatment with Rituximab	Active treatment with Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	3	20	
Units: Number of events	23	3	20	

Attachments (see zip file)	Endpoint AE disposition ITT-PMS/Endpoint AE disposition ITT-

Statistical analyses

Statistical analysis title	Key Elements of analysis plan
Statistical analysis description:	
All statistical testing will be done as 2-sided on a 5 % level of significance, and in particu-lar all confidence intervals (CI) will be 95 % intervals. In general, no specific procedure will be done for treating missing data and testing for multiplicity will not be considered. Most data analysis and presentation will be on a descriptive level	

Comparison groups	Dose titration treatment with Rituximab v Active treatment with Rituximab v Baseline

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.05 [1]
Method	Wilcoxon signed-rank test

Notes:

[1] - All statistical testing will be done as 2-sided on a 5 % level of significance, and in particu-lar all confidence intervals (CI) will be 95 % intervals.

Secondary: Clinical scoring

End point title	Clinical scoring

End point description:

End point type	Secondary

End point timeframe:

During active treatment

End point values	Baseline	Dose titration treatment with Rituximab	Active treatment with Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	3	20	
Units: Units				
number (not applicable)	23	3	20	

Statistical analyses

No statistical analyses for this end point

Secondary: Questionaires regarding MS quality of life, symptom inventory and fatigue

End point title	Questionaires regarding MS quality of life, symptom inventory and fatigue

End point description:

9HPT
SDMT
FSMC
SF12
25 FWT and 6 MWT if possible
EDSS

End point type	Secondary

End point timeframe:

During active treatment.

End point values	Baseline	Dose titration treatment with Rituximab	Active treatment with Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	3	20	
Units: Units				
number (not applicable)	23	3	20	

Statistical analyses

No statistical analyses for this end point

Secondary: Neurofilament levels in the CSF

End point title	Neurofilament levels in the CSF

End point description:

End point type	Secondary

End point timeframe:

During active treatment.

End point values	Baseline	Dose titration treatment with Rituximab	Active treatment with Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	3	20	
Units: Units				
number (not applicable)	23	3	20	

Statistical analyses

No statistical analyses for this end point

Secondary: Immunological markers in blood and CSF

End point title	Immunological markers in blood and CSF

End point description:

Immunologcal markers in blood and CSF such as absolute numbers of major lym-phocyte subset as well as regulatory cell subset.

End point type	Secondary

End point timeframe:

During active treatment.

End point values	Baseline	Dose titration treatment with Rituximab	Active treatment with Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	3	20	
Units: Units				
number (not applicable)	23	3	20	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are registered from the time point when the study participants sign the informed consent until their last visit.

Assessment type	Systematic

Dictionary used

Dictionary name	CTC AE
Dictionary version	4.0

Reporting groups

Reporting group title	All patients

Reporting group description: -

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 23 (17.39%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Viral infection			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 23 (4.35%)		
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	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 23 (78.26%)		
Injury, poisoning and procedural complications			
Injury, poisoning and procedural comlication -Other, tendon injury due to fall			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Injury, poisoning and procedural complication- Other: trauma to chest due to fall			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Nervous system disorders			
Paresthesia			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	5		
Nervous system disorders - Other, Vertigo			
subjects affected / exposed	10 / 23 (43.48%)		
occurrences (all)	15		
Headache			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Nystagmus			
subjects affected / exposed	4 / 23 (17.39%)		
occurrences (all)	5		
General disorders and administration site conditions			

Chills subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1		
Fatigue subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		
Fever subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2		
Flu like symptoms subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1		
Eye disorders Dry eye subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1		
Eye disorder - Other, Double vision subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 3		
Eye disorder - Other, Impaired vision subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 3		
Vomiting subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 3		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1		
Skin and subcutaneous tissue disorders - Other, Eczema in the scalp subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1		

Infections and infestations			
Lip infection, labial herpes simplex			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Upper respiratory infection			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	4		
Urinary tract infection			
subjects affected / exposed	5 / 23 (21.74%)		
occurrences (all)	5		
Vaginal infection, fungal			
subjects affected / exposed	1 / 23 (4.35%)		
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/25745637