Clinical trial results:
Natalizumabbehandling af progressiv multipel sklerose

Summary

EudraCT number	2009-016703-35
Trial protocol	DK
Global end of trial date	26 January 2012

Results information

Result version number	v1 (current)
This version publication date	26 June 2022
First version publication date	26 June 2022
Summary attachment (see zip file)	NAPMS summary (Natalizumab treatment of progressive multiple sclerosis reduces inflammation and tissue damage - results of a phase 2A proof-of-concept study_summary.docx)

Trial information

Trial identification

Sponsor protocol code	NAPMSv3.4

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01077466
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Danish Multiple Sclerosis Center, Rigshospitalet
Sponsor organisation address	Valdemar Hansens Vej 13, Glostrup, Denmark, 2600
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Scientific contact	Per Soelberg Sørensen Valdemar Hansens Vej 13 2600 Glostrup, Denmark, Danish Multiple Sclerosis Center, Rigshospitalet Valdemar Hansens Vej 13 2600 Glostrup, Denmark, 0045 38633406, pss@rh.dk

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	10 December 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 January 2012
Global end of trial reached?	Yes
Global end of trial date	26 January 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To study safety and efficacy of natalizumab treatment of primary and secondary progressive multiple sclerosis. This will be done by measuring the effect of treatment on inflammation in the CNS by means of osteopontin levels in the cerebrospinal fluid (CSF). Safety measures further includes physical and neurological exmination, blood samples and MRI measures of disease activity.

Protection of trial subjects:

Natalizumab is approved for the treatment of RRMS and is generally well tolerated. There is a known risk of 1:1000 for developing progressive multifocal leukoencephalopathy (PML). All patients will be observed for the known side effects throughout the course of the trial and all side effects are recorded. It has been previously shown that natalizumab may reduce some of the inflammation seen in progressive MS. It is not possible to say whether this effect is synonymous with a positive effect on the course of the disease. There is no placebo group in the study, so all patients will have the opportunity to achieve a beneficial effect. Since there are few or no effective treatments for progressive MS, a positive result of this study will have great significance for the development of new treatments for progressive MS.
No patient will be deprived of active treatment. There is no approved treatment for PPMS. All patients participating in the study will be informed about the risk of known side effects, including the risk of PML, as well as the risk of unforeseen side effects in connection with drug trials. Participants in the trial will at can withdraw from the study any time. The study will be performed in accordance with the Helsinki Declaration of Biomedical research involving human individuals and ICH GCP. The potential beneficial effects of natalizumab in the treatment of progressive MS are estimated to outweigh the possible side effects. The rationale for the study is emphasized by the fact that only a few or no effective treatments for progressive MS and the outcome will be of great importance for patients, regardless of the outcome. Based on the above considerations, it is assessed that ethically, there is not arguments against performing the experiment.

Background therapy:

Mitoxantrone and interferon-beta are approved for the treatment of SPMS. Before the patient beginning the study, these treatment options will be discussed with the patient.

Evidence for comparator: -

Actual start date of recruitment	01 March 2010
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	Denmark: 24

Worldwide total number of subjects	24
EEA total number of subjects	24

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)	24
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study Start Date : March 2010
Actual Primary Completion Date: January 2012
Actual Study Completion Date: January 2012

Pre-assignment

Screening details:

Inclusion Criteria:

Age between 19 and 55 years
Progressive disease course of multiple sclerosis (primary or secondary)
Duration of progressive phase of at least 1 year
Progression of > 1 EDSS point during the last 2 years (>½ EDSS point if EDSS > 5,5)
EDSS </= 6.5
Written and informed consent

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	Open label uncontrolled

Arm description:

300 mg Natalizumab IV for every 4 week for 56 weeks (15 doses for every patient).

Arm type	Experimental
Investigational medicinal product name	natalizumab
Investigational medicinal product code	AN100226
Other name	Tysabri
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

300 mg every 4 week

Number of subjects in period 1	Open label uncontrolled
Started	24
Completed	17
Not completed	7
Physician decision	4
Consent withdrawn by subject	3

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	24	24	
Age categorical			
Median (range) age was 44 (36-53) for SPMS and 48 (27-55) for PPMS.			
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)	24	24	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Female/male ratio was 7/5 for SPMS and 6/6 for PPMS.			
Units: Subjects			
Female	13	13	
Male	11	11	

Subject analysis sets

Subject analysis set title	NAPMS
Subject analysis set type	Full analysis

Subject analysis set description:

The included patients in the NAPMS trial were 12 secondary progressive MS patients (SPMS) and 12 primary progressive MS (PPMS) patients. Female/male ratio was 7/5 for SPMS and 6/6 for PPMS. Median (range) age was 44 (36-53) for SPMS and 48 (27-55) for PPMS. Disease duration 14 years for SPMS and 4 years for PPMS. Median EDSS was 5.25 for SPMS and 5.0 for PPMS.

Subject analysis set title	NAPMS completed
Subject analysis set type	Per protocol

Subject analysis set description:

17 patients completed the study

Reporting group values	NAPMS	NAPMS completed	
Number of subjects	24	17	
Age categorical			
Median (range) age was 44 (36-53) for SPMS and 48 (27-55) for PPMS.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	24		
From 65-84 years	0		
85 years and over	0		
Gender categorical			
Female/male ratio was 7/5 for SPMS and 6/6 for PPMS.			
Units: Subjects			
Female	13		
Male	11		

End points

End points reporting groups

Reporting group title	Open label uncontrolled
Reporting group description:	
300 mg Natalizumab IV for every 4 week for 56 weeks (15 doses for every patient).	
Subject analysis set title	NAPMS
Subject analysis set type	Full analysis
Subject analysis set description:	
The included patients in the NAPMS trial were 12 secondary progressive MS patients (SPMS) and 12 primary progressive MS (PPMS) patients. Female/male ratio was 7/5 for SPMS and 6/6 for PPMS. Median (range) age was 44 (36-53) for SPMS and 48 (27-55) for PPMS. Disease duration 14 years for SPMS and 4 years for PPMS. Median EDSS was 5.25 for SPMS and 5.0 for PPMS.	
Subject analysis set title	NAPMS completed
Subject analysis set type	Per protocol
Subject analysis set description:	
17 patients completed the study	

Primary: Cerebrospinal fluid osteopontin

End point title	Cerebrospinal fluid osteopontin
End point description:	
Mean change in CSF osteopontin from baseline to week 60	
End point type	Primary
End point timeframe:	
Baseline (week 0) to week 60	

End point values	Open label uncontrolled	NAPMS completed		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	17[1]	17		
Units: ng/mL				
arithmetic mean (confidence interval 95%)	65 (34 to 96)	65 (34 to 96)		

Notes:

[1] - Analysis made on the 17 patients completing the trial

Attachments (see zip file)	CSF endpoints/Figure 2_CSF biomarker endpoints_031213

Statistical analyses

Statistical analysis title	CSF osteopontin change
Comparison groups	Open label uncontrolled v NAPMS completed

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.0004
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	65
Confidence interval	
level	95 %
sides	2-sided
lower limit	34
upper limit	96
Variability estimate	Standard deviation
Dispersion value	60

Notes:

[2] - Single-arm longitudinal. Paired T-test.

Secondary: Cerebrospinal fluid CXCL13

End point title	Cerebrospinal fluid CXCL13
End point description:	
Mean change from baseline to week 60.	
End point type	Secondary
End point timeframe:	
Baseline to week 60	

End point values	Open label uncontrolled			
Subject group type	Reporting group			
Number of subjects analysed	17[3]			
Units: pg/mL				
arithmetic mean (confidence interval 95%)	28.6 (9.1 to 51.8)			

Notes:

[3] - Analysis made on the 17 patients who completed the study

Statistical analyses

No statistical analyses for this end point

Secondary: Cerebrospinal fluid MMP9

End point title	Cerebrospinal fluid MMP9
End point description:	
Mean change from baseline to week 60	
End point type	Secondary
End point timeframe:	
Baseline to week 60	

End point values	Open label uncontrolled			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: ng/mL				
arithmetic mean (confidence interval 95%)	0.28 (0.18 to 0.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cerebrospinal fluid neurofilament light chain

End point title	Cerebrospinal fluid neurofilament light chain
End point description: Mean change from baseline to week 60	
End point type	Secondary
End point timeframe: Baseline to week 60	

End point values	Open label uncontrolled			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: ng/mL				
arithmetic mean (confidence interval 95%)	243 (23 to 462)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cerebrospinal fluid myelin basic protein

End point title	Cerebrospinal fluid myelin basic protein
End point description: MEan change from baseline to week 60	
End point type	Secondary
End point timeframe: Baseline to week 60	

End point values	Open label uncontrolled			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: ng/mL				
arithmetic mean (confidence interval 95%)	0.21 (0.003 to 0.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage brain volume change

End point title	Percentage brain volume change
End point description:	
Change in percentage normalised brain volume from week 12 to week 60	
End point type	Secondary
End point timeframe:	
Week 12 to week 60	

End point values	Open label uncontrolled			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: percentage				
arithmetic mean (confidence interval 95%)	-0.55 (-0.83 to -0.26)			

Statistical analyses

No statistical analyses for this end point

Secondary: Normal apperaing white matter volume

End point title	Normal apperaing white matter volume
End point description:	
Change in normal appearing white matter volume from week 12 to week 60	
End point type	Secondary
End point timeframe:	
Week 12 to week 60	

End point values	Open label uncontrolled			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: mL				
arithmetic mean (confidence interval 95%)	-24.1 (-29.6 to -18.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Grey matter volume

End point title	Grey matter volume

End point description:

Change in grey matter volume (GMV) from week 12 to week 60

End point type	Secondary

End point timeframe:

Week 12 to week 60

End point values	Open label uncontrolled			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: mL				
arithmetic mean (confidence interval 95%)	2.3 (-2.8 to 7.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of new lesions on T2-weighted MRI images

End point title	Number of new lesions on T2-weighted MRI images

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 60

End point values	Open label uncontrolled			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: New T2 lesions	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of enlarging lesions on T2-weighted MRI images

End point title	Number of enlarging lesions on T2-weighted MRI images

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 60

End point values	Open label uncontrolled			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: enlarging lesions	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of lesions on T2-weighted MRI images

End point title	Volume of lesions on T2-weighted MRI images

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 60

End point values	Open label uncontrolled			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: mL				
arithmetic mean (confidence interval 95%)	-0.4 (-1.2 to 0.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Magnetization transfer ratio (MTR) in NAWM

End point title	Magnetization transfer ratio (MTR) in NAWM

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 60

End point values	Open label uncontrolled			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: ratio				
arithmetic mean (confidence interval 95%)	0.55 (0.11 to 0.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: Magnetization transfer ratio (MTR) in grey matter

End point title	Magnetization transfer ratio (MTR) in grey matter

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 60

End point values	Open label uncontrolled			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: ratio				
arithmetic mean (confidence interval 95%)	0.63 (0.13 to 1.14)			

Statistical analyses

No statistical analyses for this end point

Secondary: Magnetization transfer ratio (MTR) lesions

End point title	Magnetization transfer ratio (MTR) lesions

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 60

End point values	Open label uncontrolled			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: ratio				
arithmetic mean (confidence interval 95%)	0.39 (-0.13 to 0.91)			

Statistical analyses

No statistical analyses for this end point

Secondary: EDSS change

End point title	EDSS change

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 60

End point values	Open label uncontrolled			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: points				
arithmetic mean (confidence interval 95%)	-0.31 (-0.54 to -0.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Timed 25 foot walk

End point title	Timed 25 foot walk

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 60

End point values	Open label uncontrolled			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: seconds				
arithmetic mean (confidence interval 95%)	0.22 (-1.09 to 1.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: 9 hole peg test

End point title	9 hole peg test

End point description:

End point type	Secondary

End point timeframe:

Baseline to week 60

End point values	Open label uncontrolled			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: seconds				
arithmetic mean (confidence interval 95%)	-1.3 (-3.3 to 0.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline to week 60	
Assessment type	Systematic
Dictionary used	
Dictionary name	ICD10
Dictionary version	2010
Reporting groups	
Reporting group title	Open label uncontrolled
Reporting group description: 300 mg Natalizumab IV for every 4 week for 56 weeks (15 doses for every patient).	

Serious adverse events	Open label uncontrolled		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 24 (12.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Venous thrombosis limb			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
pneumonia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
ureteral stone			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Open label uncontrolled		
Total subjects affected by non-serious adverse events subjects affected / exposed	18 / 24 (75.00%)		
Nervous system disorders Tension headache subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 2 / 24 (8.33%) 2 1 / 24 (4.17%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 1 / 24 (4.17%) 1		
Ear and labyrinth disorders Pain in ear and jaw subjects affected / exposed occurrences (all)	 1 / 24 (4.17%) 1		
Gastrointestinal disorders nausea subjects affected / exposed occurrences (all)	 1 / 24 (4.17%) 1		
Reproductive system and breast disorders Postmenopausal bleeding subjects affected / exposed occurrences (all)	 1 / 24 (4.17%) 1		
Respiratory, thoracic and mediastinal disorders Upper respiratory tract infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all)	 5 / 24 (20.83%) 5 1 / 24 (4.17%) 1		
Skin and subcutaneous tissue disorders Hand dermatitis subjects affected / exposed occurrences (all)	 1 / 24 (4.17%) 1		

Urticaria			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Tension			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Wound infection			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Arthritis reactive			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Product issues			
Infusion related reaction			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Infections and infestations			
viral infection			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
herpes labialis			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Pneumonia			
subjects affected / exposed	18 / 24 (75.00%)		
occurrences (all)	29		
Urinary tract infection			
subjects affected / exposed	1 / 24 (4.17%)		
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/24682973