Clinical trial results:
An exploratory phase IIa study to evaluate the safety and immunological effects of intravenous interferon-1a (IFN-1a, Rebif®) therapy in the induction of tolerance to IFN in MS patients with neutralising antibodies (NAbs) to subcutaneous IFN-1a (Rebif® or Avonex®)

Summary

EudraCT number	2008-000256-26
Trial protocol	GB
Global end of trial date	12 February 2014

Results information

Result version number	v1 (current)
This version publication date	25 April 2019
First version publication date	25 April 2019
Summary attachment (see zip file)	NAb Anergy End of STudy Report Feb 2015 (NAb Anergy End of STudy Report Feb 2015.pdf)

Trial information

Trial identification

Sponsor protocol code	006114QM

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London
Sponsor organisation address	5 Walden Street, London, United Kingdom, E1 2EF
Public contact	Prof Gavin Giovannoni, Queen Mary University of London, +44 02078822579, g.giovannoni@qmul.ac.uk
Scientific contact	Prof Gavin Giovannoni, Queen Mary University of London, +44 02078822579, g.giovannoni@qmul.ac.uk

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	11 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 February 2014
Global end of trial reached?	Yes
Global end of trial date	12 February 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Perform a "proof-of-concept" phase IIa clinical trial to induce tolerance to IFNβ in subjects with NAbs to IFNβ-1a.

Protection of trial subjects:

AEs were monitored throughout the trial. Laboratory (haematology and biochemistry) tests, and physical examinations were performed at screening and thereafter at regular intervals throughout the trial.

Background therapy:

Investigational Medicinal Product (IMP)
Rebif® New Formulation EU/1/98/063/004, EU/1/98/063/005, EU/1/98/063/006
Mitoxantrone PL 04515/0127

Evidence for comparator: -	
Actual start date of recruitment	22 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	1
EEA total number of subjects	1

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)	1
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

One patient was consented and enrolled the study, out of the planned 15. It was difficult to recruit as new treatments were available once the trial started. This was an open label, UK study involving 1 site.

Pre-assignment

Screening details:

Male and female subjects with MS, aged 18 to 65 years (inclusive), who have been on IFNβ-1a for at least 12 months and have at least one significant relapse in the last 12 months and are considering switching therapy. Subjects with a positive NAb (neutralising antibody) titre of 20U will then be invited to continue in the study.

Pre-assignment period milestones

Number of subjects started	1
Number of subjects completed	1

Period 1

Period 1 title	Baseline - Visit 1 and Visit 2
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Arm title	Patient 1

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Interferon Rebif New Formulation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

(Rebif® New Formulation) 44mcg for injection. Rebif® New Formulation was administered via the IV route, under medical supervision, commencing with a dose of 44mcg. As this dose was tolerated, the subject received a further 88mcg IV on the same day followed by 132mcg IV daily for subsequent 4 days; the total intravenous dose administered will be 660mcg over 5 days.
As the patient developed neutropenia WHO grave 4, the 5th day of treatment was suspended and the total dose was 528mcg over 4 days.

Number of subjects in period 1	Patient 1
Started	1
Completed	1

Period 2	
Period 2 title	Visit 3
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Mitoxantrone infusion

Arms

Arm title	Patient 1

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Interferon Rebif New Formulation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

(Rebif® New Formulation) 44mcg for injection. Rebif® New Formulation was administered via the IV route, under medical supervision, commencing with a dose of 44mcg. As this dose was tolerated, the subject received a further 88mcg IV on the same day followed by 132mcg IV daily for subsequent 4 days; the total intravenous dose administered will be 660mcg over 5 days.
As the patient developed neutropenia WHO grave 4, the 5th day of treatment was suspended and the total dose was 528mcg over 4 days.

Number of subjects in period 2	Patient 1
Started	1
Completed	1

Period 3

Period 3 title	Visit 4
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Arm title	Patient 1

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Interferon Rebif New Formulation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

(Rebif® New Formulation) 44mcg for injection. Rebif® New Formulation was administered via the IV route, under medical supervision, commencing with a dose of 44mcg. As this dose was tolerated, the subject received a further 88mcg IV on the same day followed by 132mcg IV daily for subsequent 4 days; the total intravenous dose administered will be 660mcg over 5 days.
As the patient developed neutropenia WHO grave 4, the 5th day of treatment was suspended and the total dose was 528mcg over 4 days.

Number of subjects in period 3	Patient 1
Started	1
Completed	1

Period 4

Period 4 title	Visit 5 to Visit 9
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Patient 1

Arm description: -

Arm type	Experimental

Investigational medicinal product name	Interferon Rebif New Formulation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

(Rebif® New Formulation) 44mcg for injection. Rebif® New Formulation was administered via the IV route, under medical supervision, commencing with a dose of 44mcg. As this dose was tolerated, the subject received a further 88mcg IV on the same day followed by 132mcg IV daily for subsequent 4 days; the total intravenous dose administered will be 660mcg over 5 days.
As the patient developed neutropenia WHO grave 4, the 5th day of treatment was suspended and the total dose was 528mcg over 4 days.

Number of subjects in period 4	Patient 1
Started	1
Completed	1

Period 5	
Period 5 title	Visit 10 and Visit 11
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Patient 1

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Mitoxantrone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Mitoxantrone12mg/m2 /single dose

Number of subjects in period 5	Patient 1
Started	1
Completed	1

Period 6	
Period 6 title	Visit 12 to Visit 15
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Patient 1
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Interferon Rebif New Formulation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

(Rebif® New Formulation) 44mcg for injection. Rebif® New Formulation was administered via the IV route, under medical supervision, commencing with a dose of 44mcg. As this dose was tolerated, the subject received a further 88mcg IV on the same day followed by 132mcg IV daily for subsequent 4 days; the total intravenous dose administered will be 660mcg over 5 days.
As the patient developed neutropenia WHO grave 4, the 5th day of treatment was suspended and the total dose was 528mcg over 4 days.

Number of subjects in period 6	Patient 1
Started	1
Completed	1

Baseline characteristics

Reporting groups

Reporting group title	Baseline - Visit 1 and Visit 2

Reporting group description: -

Reporting group values	Baseline - Visit 1 and Visit 2	Total	
Number of subjects	1	1	
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)	1	1	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	42		
standard deviation	± 0	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	0	0	

Subject analysis sets

Subject analysis set title	patient 1
Subject analysis set type	Safety analysis

Subject analysis set description:

There was a SAE as for Grade 4 laboratory results that caused the last dose of interferon not to be injected, as per protocol. There were no other relevant safety issues with the trial’s only participant.

Reporting group values	patient 1		
Number of subjects	1		
Age categorical 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)	1		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	42		
standard deviation	± 0		
Gender categorical Units: Subjects			
Female	1		
Male	0		

End points

End points reporting groups

Reporting group title	Patient 1
Reporting group description: -	
Reporting group title	Patient 1
Reporting group description: -	
Reporting group title	Patient 1
Reporting group description: -	
Reporting group title	Patient 1
Reporting group description: -	
Reporting group title	Patient 1
Reporting group description: -	
Reporting group title	Patient 1
Reporting group description: -	
Subject analysis set title	patient 1
Subject analysis set type	Safety analysis

Subject analysis set description:

There was a SAE as for Grade 4 laboratory results that caused the last dose of interferon not to be injected, as per protocol. There were no other relevant safety issues with the trial's only participant.

Primary: Safety

End point title	Safety[1]

End point description:

There was a SAE as for Grade 4 laboratory results that caused the last dose of interferon not to be injected, as per protocol. There were no other relevant safety issues with the trial's only participant.

End point type	Primary

End point timeframe:

From Visit 5, when treatment starts, to Visit 15, last visit.

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: Descriptive statistics only

End point values	patient 1			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: Grade				
number (not applicable)	1			

Statistical analyses

No statistical analyses for this end point

Primary: NAb titre at 3, 6, 9 and 12 months post intravenous IFN -1a relative to baseline

End point title	NAb titre at 3, 6, 9 and 12 months post intravenous IFN -1a relative to baseline[2]

End point description:

NAb titre for Interferon-beta is a biological assay and reports in TRU/mL units
Visit 4. 171
Visit 12. 180
Visit 13. <20
Visit 14. <20
Visit 15. <20

End point type	Primary

End point timeframe:

NAb titre at 3 (Visit 12), 6 (Visit 13), 9 (Visit 14) and 12 (Visit 15) months post intravenous IFN -1a relative to baseline (Visit 4)

Notes:

[2] - 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: Descriptive statistics only

End point values	Patient 1	Patient 1	Patient 1	Patient 1
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	1	1
Units: TRU/mL				
number (not applicable)	1	1	1	1

End point values	Patient 1	Patient 1	patient 1	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1	1	1	
Units: TRU/mL				
number (not applicable)	1	1	1	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Immunological tests

End point title	Immunological tests

End point description:

T-cell proliferative response to rhuIFN -1a compared to baseline, change in T-and B-cell cytokine production in response to rhu-IFN -1a, as assessed using Elispot assays, intracellular cytokine staining, protein and mRNA levels, every 3 months post intravenous IFN-1a relative to baseline and the antigen-specific response will be compared to the changes in control antigen (tetanus toxoid) were not tested as only one patient was enrolled and completed and no significant value would be added with these analyses for one patient only.

End point type	Other pre-specified

End point timeframe:

Baseline and Visit 12, Visit 13, Visit 14 and Visit 15.

End point values	patient 1			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Number				
number (not applicable)	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From baseline Visit 4 to Visit 15	
Assessment type	Systematic

Dictionary used	
Dictionary name	SNOMED CT
Dictionary version	1

Reporting groups	
Reporting group title	Patient 1

Reporting group description:

AEs: neutropenia grade IV (1), lymphopenia grade III (1), hypotension moderate (1), mild alopecia (1), cold sores (1), back pain (1), numbness of fingers (1) and rigors (1)

Serious adverse events	Patient 1		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Neutropenia	Additional description: SAE with WHO grade IV neutropenia was detected pre Visit 9, so the 5th day of intravenous Rebif was not given. This was considered to be IMP related. This was reported to the sponsor, and discussed in the DSMB meeting.		
subjects affected / exposed	1 / 1 (100.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Patient 1		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Blood and lymphatic system disorders			
lymphopenia	Additional description: grade 3 lymphopenia		
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2011	(a)AMENDMENT - (b)DATE APPROVED BY ETHICS - (c)DATE APPROVED BY MHRA - (d)DATE APPROVED BY R&D - (e)Study Documents Included - (f)Comments (a1)Initial Submission - (b1)Rejected - (c1)Rejected - (d1)N/A - (e1)Protocol Version 1.0; PIS Version 1.0/Version 2.0; ICF Version 1.0; GP Letter Version 1.0; Investigators Brochure IFN-Beta- 1a; SmPC Mitoxantrone; SmPC Rebif-44mcg - (f1)Resubmission to MHRA made on 9 September as initial submission not valid. (a2)Resubmission - (b2)16 Feb 2009 - (c2)24 Nov 2008 - (d2)20 Feb 2009 - (e2)Protocol Version 2.0; GP Letter Version 2.0; PIS Version 3.0; ICF Version 1.0; Tissues for Future Use ICF 1.0; Investigators Brochure IFN-Beta- 1a; SmPC Mitoxantrone; SmPC Rebif-44mcg; IMP Labels - (f2)Updates based on rejection by both MHRA and REC (a3)Substantial Amendment 1 - (b3)Rejected 12 Mar 2010; Modified Amendment Sent Approved 26 Aug 2010 - (c3)Acknowledged 11 Mar 2010 - (d3)8 Apr 2011 - (e3)Protocol Version 3.0 and PIS Version 4.0 - (f3)Clarification of IMP name Rebif: New Formulation (RNF); Use of algorithm to calculate dose of IFNbeta; Introduction of ECG Monitoring at dosing; More study visits; PIS Updated with new Rebif algorithm for administration. (a4)Minor Amendment 1 - (b4)29 Jun 2013 - (c4)N/A Minor - (d4)12 Sep 2012 - (e4)ICF Version 2.0; Tissues for Future Use ICF 2.0 and PIS Version 5.0 - (f4)Update to Barts Health (a5)Minor Amendment 2 - (b5)11 Sep 2012 - (c5)N/A Minor - (d5)17 Sep 2012 - (e5)Protocol Version 4.0 - (f5)Update of mitoxantrone administration guidelines; Extension of trial to August 2014; Update to details of where patients are seen (a6)Amendment 3 - (b6)13 Nov 2013 - (e6)Protocol Version 5.0 - (f6)Update to DSMB charter as the previous charter had not been followed correctly and was not proportionate to the study risks

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 February 2014	End of trial because of difficulty in recruitment	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Only 1 out of 15 planned patients were recruited, which limits the analysis and conclusions

Notes: